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EDITORIAL

Cardiogenic Shock: ARGEN SHOCK 2 and the Hard Road of Knowing the Truth to Change Reality

Shock cardiogénico; ARGEN SHOCK 2 y el duro camino de conocer la verdad para modificar la realidad

RICARDO LEVÍN[1, MTSAC,]

...Truth? ... You can't handle the truth!
Colonel Nathan Jessup (Jack Nicholson).
"A few good men"

The fact that, besides the high associated morbidity, cardiogenic shock (CS) is the main cause of mortality in acute myocardial infarction (AMI), would be sufficient to consider it an issue of priority interest. Furthermore, except for early and adequate revascularization, the different treatments attempted to date, such as the use of vasoactive drugs, intra-aortic balloon pump (IABP) or the increasing use of venoarterial extracorporeal membrane oxygenation (VA-ECMO), have resulted ineffective in reducing the high mortality rate reported. (1-5)

The results of the ARGEN SHOCK 2 multicenter registry shed light on the dark territory of CS, and when the light shines bright and intense, it can result unpleasant and even annoying. (6)

Probably, the main result of the study, with all the mitigating circumstances applicable to a registry, is far from what is desirable or expected, as despite a revascularization rate of 91.1%, in-hospital mortality was 60.5% while 30-day mortality was 62.5%, figures that excluded patients with mechanical complications (presumably with higher mortality rate).

But facing a truth must teach us lessons and forces us to try to understand and explain the reasons; and although it may seem argumentative, something that we will call the "pandemic effect" could have occurred, as part of the time patients were recruited coexisted with COVID-19. This theory is supported by the fact that of the 54 "initial" centers willing to participate, only 23 managed to include at least one patient with AMI and CS during the 14 months of the study.

Supporting this "effect", we can add that two-thirds of patients entered the registry with CS, with a time from onset of symptoms of six hours (360 minutes). However, this does not allow us to determine the "effective" time course of CS, a fact that clearly may have influenced the results observed, highlighting the reluctance observed in many patients to timely attend medical institutions during the pandemic.

Besides this observation, and analyzing the positive data expressed in the high revascularization rate obtained, we could consider whether the classic paradigm of defining successful reperfusion in percutaneous coronary interventions in AMI patients with CS should be limited "only" to TIMI flow grade (although this is universally accepted and used) or whether it would be advisable to add other criteria expressing, on the one hand, the extent of tissue involvement and, on the other hand, its effective reversal after treatment.

A probable but common bias in our registries is a certain degree of "imbalance" in the geographical distribution of the centers where, in ARGEN SHOCK 2, of the 54 "initial" centers, 33 (61.1%) belonged to CABA and the province of Buenos Aires, with 14 (60.1%) of the 23 institutions effectively including patients.

Some considerations about the resources used.

It is clear that Swan-Ganz catheter (used in 33.3% of cases) is not a treatment, it does not "cure" per se, and, at most in expert hands, it will allow to confirm the diagnosis and will contribute to the management of CS providing information that, properly processed, could change strategies, and thus influence the prognosis. (7-8)

Intra-aortic balloon pump was used in 30.1%, which in view of the 66% of patients admitted with CS, almost all of them on vasoactive drugs, would raise the theoretical possibility that its use could have resulted in better outcomes, although its benefit has not been demonstrated in clinical practice (although this idea is physiologically reasonable). In addition, insertion of IABP is not necessarily an early procedure,

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and the high rate of complications (29.4%) deserves a separate analysis.

In the case of VA-ECMO, besides additional logistic requirements, its implementation has not yet demonstrated any influence on prognosis.

Finally, coincidentally, or not, the Council on Cardiovascular Emergency Care has completed the Consensus Statement on Cardiogenic Shock, which will be presented during the next SAC 2023 Congress. This consensus statement and the excellent contribution of Castillo Costa et al., as well as those usually made by the SAC Research Area, together with the LATIN SHOCK registry (NCT:05246683) currently under development, are intended to contribute to the understanding and subsequent change of a reality that, inevitably, needs to be modified.

Conflicts of interest

None declared.

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

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EDITORIAL

Discussion of Clinical Cases: from the Medical Board to the Heart Team

La evolución en la discusión de pacientes: de la junta médica al Heart Team

JOSÉ LUIS ZAMORANO[1,2,]

"The arrogance of success is to think that what you did yesterday will be sufficient for tomorrow."
W. Pollard 1828

For decades, surgical aortic valve replacement (SAVR) has been the only therapy to reduce mortality in patients with severe aortic stenosis. Short-, mid- and long-term results are indisputable. Among the countless revolutions in modern cardiology, one has been transcatheter aortic valve implantation (TAVI) for severe aortic stenosis. TAVI has been clearly beneficial for patients, with wonderful results in many aspects: clinical, mortality, hospitalization, cost-effectiveness, etc. However, it was also a new form of multidisciplinary treatment for this disease, with cardiac surgeons usually observing in their practice that the transcatheter technique was often selected regardless of the patient's opinion. This commonly resulted in the patient leaving the surgical environment only to remain within the cardiology department.

One of the thoughts implicit in the formidable data analysis performed over the years by Dr. Trivi et al. (1) is evidently the need to evaluate, discuss and agree on the best choice of treatment for each patient. This can be assessed only with an honest analysis, based on clinical practice guidelines, using dialogue, rather than confrontation, and including all stakeholders (i.e., the Heart Team).

Trivi et al. performed a retrospective analysis of the results from their patients over 10 years, with different therapeutic options being discussed by the Heart Team before any potential TAVI was conducted. On the one hand, we can see the results of their therapies are favorable and as expected, suggesting that the appropriate decision was made. On the other hand, while inclusion criteria included only analyzing patients who were initially eligible for TAVI, this procedure was not performed in many cases. The discussion is certainly well outlined, open and honest, although, in the end, the technique (TAVI) suggested at the beginning was performed in some patients but not in others.

However, there is room for further thoughts. Another interesting topic for analysis would be to explain what happened with patients who were initially selected for surgical treatment but who then underwent TAVI following discussion with the Heart Team.

Therefore, a relevant aspect for consideration is to decide which patients need to be evaluated by the Heart Team. TAVI is not a novel procedure and has perfectly fitted into the routine of therapy for aortic stenosis, as has surgery. Perhaps we should focus on patients where the decision is not so clear for reasons such as age, comorbidities, clinical condition, etc. Naturally, a 50-year-old patient with severe bicuspid aortic stenosis needs surgery, and thus, no deep discussion by the Heart Team is required. Likewise, an elderly patient in an experienced facility who is a suitable candidate for TAVI should not raise many questions.

A Heart Team is most beneficial for patients where therapy is not fully certain and where both techniques might be a good choice. Both pros and cons, as well as the results of the site, need to be considered before making the best choice in every case. In the same way as angiotensin-converting enzyme inhibitors are an obvious choice for ventricular dysfunction in heart failure, it is not worth arguing about obvious issues in the Heart Team. We need to focus on genuinely uncertain cases, assessing the best therapeutic option, and not just the technique or specialty. The Heart Team will be truly successful, beyond any right and wrong decisions, when focus is made only on the patient, evaluating their therapeutic options, excluding any futile therapies, and considering that sometimes both techniques are possible, while honestly selecting the

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best choice for that specific patient.

We congratulate Dr. Trivi et al. for their work, which has highlighted the importance of the Heart Team, for maintaining it for 10 years, and for paving the way for countless considerations. The aim of the Heart Team is not to confront fields of specialty or to identify an alpha male in discussions; it is rather a group of specialists (surgeons, cardiologists, anesthesiologists, and very often gerontologists) having an honest discussion on the best choice for every patient based on medical records, complementary tests, the site's experience, and factors affecting each individual, including any unbiased information provided to the patient and personal preferences. After all, this is one of the cornerstones of Medicine.

Conflicts of interest

None declared.

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ORIGINAL ARTICLE

Cardiogenic Shock in the Setting of Acute Coronary Syndromes in Argentina: Results from the ARGEN SHOCK 2 Registry

Shock cardiogénico en el contexto de los síndromes coronarios agudos en Argentina: resultados del Registro ARGEN SHOCK 2

YANINA CASTILLO COSTA[1, MTSAC], FLAVIO DELFINO[1, MTSAC], VÍCTOR MAURO[2, MTSAC], CARLOS M. BARRERO[2, MTSAC], MAURO GARCÍA AURELIO[2], HERALDO D´IMPERIO[1, MTSAC], STELLA MARIS MACÍN[2], RICARDO VILLARREAL[2, MTSAC], JUAN SOUTO[2], ESTEBAN FRONTERA[2]

ABSTRACT

Background: Cardiogenic shock (CS) is a life-threatening complication of acute myocardial infarction (AMI) and constitutes one of the leading causes of death.
Objective: The aim of this study was to investigate the clinical characteristics, treatment strategies, hospital outcome and 30-day mortality of CS in Argentina.
Methods: We conducted a prospective, and multicenter registry of patients with acute coronary syndromes (ACS) with and without ST-segment elevation complicated with CS that were hospitalized in 23 centers in Argentina for 14 months (between August 1, 2021, and September 30, 2022).
Results: The cohort was made up of 114 patients; median age was 64 years (58-73) and 72% were women; 76.3% corresponded to ST-segment elevation ACS, 12.3% to non-ST-segment elevation ACS, 7% had right ventricular infarction and 4.4% had mechanical complications. In 66.6% of cases CS was present on admission. Revascularization: 91.1%, use of inotropic agents: 98.2%, mechanical ventilation (MV): 59.6%, Swan-Ganz catheter: 33.3%, intra-aortic balloon pump: 30.1%. Overall in-hospital mortality was 60.5%, with no differences between ACS with or without ST-segment elevation, and was 62.6% at 30 days.
Conclusion: Morbidity and mortality of CS are high despite the high rate of reperfusion therapy used.

Key words: Cardiogenic Shock- Acute Coronary Syndromes- Registry

RESUMEN

El shock cardiogénico (SC) es una complicación grave del infarto agudo de miocardio (IAM) y constituye una de sus principales causas de muerte.
Objetivos: Conocer las características clínicas, estrategias de tratamiento, evolución intrahospitalaria y mortalidad a 30 días del SC en Argentina.
Material y métodos: Se trata de un registro prospectivo, multicéntrico, de pacientes internados con SC en el contexto de los síndromes coronarios agudos (SCA) con y sin elevación del segmento ST durante 14 meses (1 de agosto 2021 al 30 de septiembre 2022) en 23 centros de Argentina.
Resultados: Se incluyeron 114 pacientes, edad 64 (58-73) años, 72% hombres. El 76,3% de los casos corresponden a SCA con elevación del segmento ST, 12,3% a SCA sin elevación del segmento ST, el 7% a infarto de ventrículo derecho y el 4,4% a complicaciones mecánicas. El SC estuvo presente desde el ingreso en el 66,6% de los casos. Revascularización: 91,1%, uso de inotrópicos: 98,2%, asistencia respiratoria mecánica (ARM): 59,6%, SwanGanz: 33,3%, balón de contrapulsación intraaórtico: 30,1%. La mortalidad intrahospitalaria global fue 60,5%, sin diferencias entre los SCA con o sin elevación del segmento ST y a 30 días del 62,6%.
Conclusiones: La morbimortalidad del SC es muy elevada a pesar de la alta tasa de reperfusión empleada.

Palabras clave: Shock Cardiogénico- Síndromes Coronarios Agudos- Registro

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INTRODUCTION

Cardiogenic shock (CS) is an infrequent complication but remains the leading cause of death in patients hospitalized with acute myocardial infarction (AMI), (1) ranging from 40% to 55% depending on the populations analyzed. (2,3) In Argentina, the incidence of CS is 10%, and according to recent data from the ARGEN IAM ST Registry, CS mortality rate in the setting of ST-segment elevation MI is 57%. (4) Some recommendations of the guidelines for the treatment of CS in the setting of acute coronary syndromes have changed in recent years. (5) Moreover, as it has been more than 5 years since the first Argentine Registry of Cardiogenic Shock was published, (6) the Research Area of the Argentine Society of Cardiology (SAC) decided to carry out this study, the second National Registry of Cardiogenic Shock (ARGEN SHOCK), which was specially designed to determine the clinical characteristics, reperfusion strategies, treatments, in-hospital outcome and 30-day mortality of patients admitted to intensive care units with acute coronary syndromes (ACS) and CS on admission or who develop this complication during hospitalization.

METHODS

ARGEN SHOCK is a prospective, observational, and multicenter registry of consecutive patients with ACS complicated with CS conducted between August 1,2021, and September 30, 2022.

Cardiogenic shock was defined as systolic blood pressure (SBP) ≤ 90 mm Hg for at least 30 min or requirements of vasopressors or inotropic drugs to maintain a SBP ≥ 90 mm Hg, associated with clinical signs of hypoperfusion or pulmonary congestion.

Patients eligible for inclusion were > 18 years, admitted to coronary care units or multipurpose critical care units with ST-elevation ACS (STEACS) or non-ST-elevation ACS (non-STEACS) and with CS on admission or during hospitalization. Patients who developed mechanical complications were excluded for the analysis of mortality (n = 5).

Data were collected by the responsible investigators of the different centers in an ad hoc electronic worksheet designed on the RedCAP platform. In-hospital and 30-day events were analyzed.

The protocol was organized and conducted by the Research Area and the Council on Cardiovascular Emergency Care of the SAC. All the patients signed an informed consent form to be included. Follow-up at 30 days was reported by the principal investigators of the different participating centers.

Statistical analysis

The information obtained through RedCAP was exported to an Excel database and was analyzed using Epi-info 7 software package. Each variable was included in a frequency table. Continuous variables with normal distribution were presented as mean ± standard deviation, and those with non-normal distribution as median and interquartile range (IQR 25-75), and were compared using the Student's t test or the Wilcoxon rank sum test, as applicable. Discrete variables were expressed as percentages and were compared using the chi-square test with Yates correction or the Fisher's exact test, as applicable.

Contingency table analysis was used to compare the association or independence of the variables. The presence of associations or independent predictions between the different variables involved and mortality was analyzed using linear regression or multiple logistical regression analysis. Those variables with a p value <0.10 on univariate analysis were included in the different regression models. The value corresponding to each covariate was expressed as adjusted odds ratio (OR) with its corresponding 95% confidence interval. A two-tailed p value < 0.05 was considered statistically significant.

RESULTS

Fifty-four intensive care units from all over the country registered to participate in the registry: 17 from the city of Buenos Aires (CABA), 16 from the province of Buenos Aires (PBA) and the rest from other provinces of the country; 23 (10 in CABA, 4 in PBA and 9 in the rest of the country) included at least one patient. Of the participating centers, 74.5% were coronary care units, 18.2% were multipurpose units and 7.3% were intensive care units; 65.5 % of the centers had residents in cardiology. Doppler echocardiography was available in 98% of the centers and catheterization laboratory in 89%; 81.8% had cardiovascular surgery capabilities, 67.3% counted with intra-aortic balloon pump, 20% with extracorporeal membrane oxygenation (ECMO), 3.6% with Impella left ventricular assist device, and 23.6% with cardiac transplantation capabilities.

The registry included 114 patients with CS, 87 (76.3%) were STEACS and 14 (12.3%) non-STEACS, 5 had CS associated with mechanical complications and 8 had CS secondary to right ventricular (RV) infarction. Median age of the population was 64 years (58-73), 71.9% were men, 72.8% had hypertension, 35.1% had diabetes, 37.7% had dyslipidemia, and 35.1% were smokers. Almost all the patients (91.1%) underwent revascularization.

In 66.6% (74/114) of cases CS was present on admission. In the rest of the patients, 14,9% were admitted with Killip-Kimball class A, 13.2% with class B and 5.3% with class C, and 68.4% developed CS with 24 h.

Inotropic or vasoactive drugs were used in 98.2% of the patients (norepinephrine 86.6%, dopamine 20.5%, dobutamine 62.5% and levosimendan 11.6%); 59.6% required mechanical ventilation (MV). A Swan-Ganz catheter (SG) was inserted in 33.3% of the patients: 55.3% within the first day, 36.8% between 24 and 48 h and 7.9% after 48 h, and remained placed for a median time of 3 (2-4) days. The main indication for SG catheter was "treatment optimization" in 79%, for "diagnostic uncertainty" in 10.5% and as standard treatment of shock in the remaining 10.5%. Mortality rate in patients with a SG catheter inserted was 57.9%. There were no differences in the clinical characteristics and outcome of patients with or without insertion of a SG catheter.

Intra-aortic balloon pump (IABP) was used in

30.1% of cases and ECMO in 4 patients (who also required IABP); IABP remained placed for a median time of 2 (1-4) days. The complications associated with IABP occurred in 29.4% of the patients and included fever in 4 patients, acute lower limb ischemia in 3, and thrombocytopenia in 3. There were no cases of sepsis. In patients with IABP support, mortality was 67.6% (23/34 patients).

Patients receiving IABP were younger [60.5 years (56-66) vs. 65 (60-76.5), p < 0.01]; most of them were men (85.3% vs. 67.1%, p = 0.02) and had more requirement of MV (73.5% vs. 53.1%, p = 0.02). There were no significant differences in mortality according to the use of IABP: 67.6% vs 57%, p = 0.14.

The main events during hospitalization are presented in Table 1.

The incidence of bleeding events was 8.7%. A total of 12.3% of patients required transfusions: < 2 units in 21.4%, between 2 and 4 in 42.9% and > 4 in 35.7%.

In 92 patients without mechanical complications undergoing coronary angiography, significant one-vessel disease was observed in 19.6% of the cases, two-vessel disease in 33.7% and three-vessel-disease in 46.7%. In patients with more than one-vessel disease, 69.9% underwent culprit-only percutaneous coronary intervention (PCI), and 30.1% underwent multivessel intervention. The procedure was successful in 84% of the cases.

Overall, in-hospital mortality was 60.5% (53% within the first 48 h) and was due to persistent shock (62.3%), mechanical complications (11.6%), arrhythmias (11.6%), infections (7.3%) and others (7.2%).

After excluding those patients with mechanical complications, univariate analysis revealed that age, history of AMI, arrhythmias, absence of RV involvement and STEACS were associated with greater mortality (Table 2). On multivariate analysis, a history of AMI remained as an independent predictor (OR 4.58, 95% CI 1.09-19.22; p = 0.037).

Mortality at 30 days was 62.6%.

Patients with STEACS (n = 87) had a median age of 64 (RIC 58-74) years, 71.3% were men, 32.2% had diabetes, 40.2% had dyslipidemia, 34.5% smoked, and 16.1% had a history of previous infarction; 80.9% of STEACS were anterior wall infarctions. Median time from symptoms to admission was 360 (140 - 1080) minutes and 94.2% were managed with a reperfusion strategy: 83.8% received primary PCI and 9.7% received thrombolytic therapy (streptokinase in 81.8%). In 82.2% of the cases undergoing PCI the procedure was successful, with a median (IQR) door-to-balloon-time of 115 (60-180) minutes. In-hospital and 30-day mortality of STEACS was 64.4% and 65.5%, respectively. Mortality rate was 62.2% in patients reperfused and 100% in those without reperfusion (p = 0.051). Coronary angiography showed 2-3 vessel disease in 81.1% of the cases and revascularization of non-culprit stenoses were performed in 28.3% of the patients.

Table 1. In-hospital events and 30-day mortality

Event	n (%)
PIA/ReMI	4 (3.5%)
Arrhythmias	43 (37.7)
AF	15 (13.1)
VT/VF	18 (15.8)
ECV	15 (13.1)
AVB	10 (8.8)
Temporary pacing	9 (7.9)
Fever	24 (21)
Dialysis	9 (7.9)
Intra-aortic balloon pump	34 (30.1)
Heart transplantation	1 (0.88)
In-hospital mortality	69 (60.5)
30-day mortality	71 (62.6)

AF: atrial fibrillation; AVB: atrioventricular block; ECV: electric cardioversion; PIA: postinfarction angina; ReMI: reinfarction; VT/VF: ventricular tachycardia/ventricular fibrillation

DISCUSSION

Cardiogenic shock is the most life-threatening complication of MI and remains the leading cause of MI-related mortality. Historically, the incidence of CS was 5 to 15%, but has been decreasing worldwide across the years. (7-9). This is not the situation in our environment, where mortality remains between 8% and 10%. (1,4)

As in other contemporary registries, STEACS was the most common cause of cardiogenic shock. (10) Although in our population the prevalence of men was higher than that of women, the proportion of women affected was greater compared with populations with ACS and without shock, as in many registries available. (3,4,7,11,12) The age of our patients with shock is like that of international registries. (4)

In the setting of an ACS, CS may be present since hospital admission or may develop during hospitalization, but most cases occur within the first 24 hours; (3,4) in our registry, 66.6% of patients had CS since admission, similar to other experiences. (3,13)

Adequate reperfusion in AMI decreases overall mortality and the incidence of shock by limiting the size of the myocardium involved; (14,15) likewise, its use in the setting of CS also decreases mortality, as demonstrated in the SHOCK trial.(13) Therefore, all the clinical practice guidelines strongly recommend emergency revascularization in patients with shock, independently of the time since infarction occurred. (16-18) In our study, reperfusion rate was close to 90%, as observed in experiences in more developed countries. The prevalence of severe multivessel disease in the setting of CS ranges from 60% to 78%, (4,19) similar to that found in our study. As in the ReNa Shock registry, (20) culprit-only revascularization was the strategy most used, following current guidelines.

Table 2. Univariate analysis for predictors of mortality Population: 109 patients (excluding the 5 patients with mechanical complications)

	Dead n= 64	Alive n= 45	p
Age, years, (median, IQR)	65 (59-76)	62 (56-68)	0.04
Male sex, (%)	71	71	0.46
Diabetes (%)	34	35	0.44
Hypertension (%)	72	73	0.43
Current smoker (%)	30	38	0.19
CKD (%)	4.7	0	0.09
Previous stroke (%)	3	0	0.17
Previous MI (%)	23.5	6.7	0.01
K-K class D on admission (%)	71.9	62.2	0.14
PIA/ReMI (%)	1.5	6.6	0.11
VF/VT (%)	20.3	11.1	0.12
AF (%)	9.4	15.5	0.17
ECV (%)	17.2	6.7	0.06
Failed PCI (%)	18.9	13.5	0.26
Time from symptoms onset at admission, min (median, IQR)	360 (120-1176)	360 (140-1080)	0.93
Anterior infarction (%)	48.4	57.8	0.17
STEACS (%)	87.5	68.9	0.01
RV involvement (%)	3.1	13.3	0.02
Reperfused (%)	90.5	93.3	0.31
Mutivessel disease (2 or greater), (%)	78.2	83.8	0.26

AF: atrial fibrillation; CKD: chronic kidney disease; ECV: electric cardioversion; IQR: interquartile range; K-K: Killip-Kimball; PCI: percutaneous coronary intervention; PIA: post-infarction angina; ReMI: reinfarction; RV: right ventricular; STEACS: ST-segment elevation acute coronary syndrome; VF: ventricular fibrillation; VT: ventricular tachycardia.

The use of IABP, a strategy not systematically recommended by the guidelines, (21-23) was 30.1%, like that of the ReNa SHOCK and other international registries (4,7), and its use did not imply differences in mortality. (24) The indication of other support devices was low, 3.5%, but higher than in the previous registry (2.4%).

Although some studies have reported a decline in mortality associated with CS throughout the years, (25, 26), it is still high, with figures between 40 and 60%. (10,18,19) Our overall in-hospital mortality was 60.5%, similar to that of the ReNa Shock (54%) registry and of the patients with CS in the ARGEN-IAM-ST registry (58%). (27)

The history of AMI was the only independent predictor of in-hospital mortality found in our study.

We found a 30-day mortality rate of 62.6%. Compared with international studies, mortality rate was 40.2% in the IABP-SHOCK II study (24) and 47.6% in the CULPRIT SHOCK study. (28) In our study, 30-day mortality is significantly higher than the one reported by the international literature (10) and even higher than that of patients in the SHOCK trial (51.5%) (13), which was conducted more than two decades ago. The differences found are not easy to interpret, since most of our patients were reperfused within a reasonable time course, comparable to that of other experiences. Unfortunately, this registry does not include the percentage of patients who developed cardiac arrest with successful cardiopulmonary resuscitation, because when the registry started, the new classification of the SCAI (29), which describes the significant adverse prognostic value of cardiac arrest, had not been validated yet. (30) Nevertheless, in a recent study by our group (in patients with ST-segment elevation myocardial infarction) we have found that the prevalence of cardiac arrest in the setting of CS is high (44.8%) and that patients presenting cardiac arrest and CS had a mortality rate of 79.3% compared with 39% in patients without cardiac arrest on admission. (31)

The disparity in the outcome of patients highlights the importance of updated local data since our reality (and probably that of the rest of Latin America) does not seem to be the same as in the United States or Europe. The Argentine Society of Cardiology is currently recruiting patients for the LATIN SHOCK registry (NCT:05246683), which will provide information on the situation in Latin America in this area for the first time.

Perhaps at some future time mortality may de-

crease if cardiogenic shock patients are managed with a much broader multidisciplinary approach, as is currently recommended. (32)

Limitations

The present registry represents the actual treatment of patients with CS in Argentina who were mostly recruited in high complexity centers with residents in cardiology; thus, these results cannot be extrapolated to patients with CS on admission or developed during hospitalization in other type of centers.

CONCLUSIONS

The characteristics of cardiogenic shock in Argentina do not differ much from other populations worldwide; however, mortality in our environment is very high (despite high reperfusion) and has remained stable over the last years.

Conflicts of interest

None declared.

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

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Appendix

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Hospital Álvarez	CABA	
Hospital Cullen	Santa Fe	Perello Leonel
Hospital de Alta Complejidad El Cruce	Buenos Aires	Adamowski Mariano Alejandro
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Hospital Español de Mendoza	Mendoza	Valentina Rodríguez
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Hospital Italiano Regional del Sur	Buenos Aires	Verónica Heredia
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ORIGINAL ARTICLE

Impact of a Heart Team in patients with aortic stenosis who are candidates for transcatheter aortic valve replacement

Impacto de un Heart Team en pacientes con estenosis aórtica candidatos a reemplazo percutáneo

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ABSTRACT

As transcatheter aortic valve implantation (TAVI) for aortic stenosis (AS) became widespread, the need for a Heart Team (HT) arose to choose the best treatment. There are few reports regarding its usefulness.

Objectives: To analyze treatment outcomes in patients with AS evaluated by a HT for 10 years.

Methods: Consecutive enrollment of all patients with AS who were candidates for TAVI between January 2012 and July 2021 to choose the best treatment, including surgical aortic valve replacement (SAVR) and conservative medical management (CMM).

Results: Out of 841 patients, 455 were assigned to TAVI (53%), 213 to SAVR (24%), and 183 to CMM (23%). The percentage assigned to TAVI has increased from 48% to 62% over time (p<0.05). Patients who underwent TAVI versus those who underwent SAVR were older (86 ± 7 vs. 83 ± 7 years), had a higher EUROSCORE II (6.2, 95% CI 5.7-6.6 vs. 5.6; 95% CI 4.4-6.5) and were frailer (1.62 ± 1 vs. 0.91 ± 1), in all cases p<0.01. Actuarial survival (95% CI) at 1 and 2 years was 88% (84-91%) and 82% (77-86%) for TAVI, 83% (76-88%) and 78% (70-84%) for SAVR, and 70% (60-87%) and 59% (48-68%) for CMM, respectively (p<0.001).

Conclusions: For the first 10 years after a Heart Team was established for AS decision-making, approximately half of the patients were assigned to TAVI, and the rest were equally assigned in halves to either surgery or observation. Survival for patients who received interventions was similar at 2 years and higher than in those who did not.

Keywords: Aortic stenosis - Transcatheter aortic valve implantation - Prosthetic heart valves.

RESUMEN

La difusión del reemplazo valvular aórtico percutáneo (TAVI) en la estenosis aórtica (EAo) generó la creación de un *Heart Team* (HT), para elegir el mejor tratamiento. Existen pocos reportes sobre su utilidad.

Objetivos: analizar los resultados del tratamiento de los pacientes con EAo evaluados por un HT durante 10 años

Material y métodos: Inclusión consecutiva de todos los pacientes con EAo candidatos a TAVI entre enero del 2012 y julio del 2021 para seleccionar el mejor tratamiento, incluyendo además Cirugía de Reemplazo Valvular Aórtico (CRVA) y Tratamiento Médico Conservador (TMC).

Resultados: De 841 pacientes, se asignaron a: TAVI 455 (53%), CRVA 213 (24%) y TMC 183 (23%). El porcentaje asignado a TAVI aumentó con el tiempo de 48 a 62% (p<0,05). Los pacientes que fueron a TAVI, con respecto a los enviados a CRVA eran mayores (86±7 vs 83±7 años), con mayor EUROSCORE II (6,2, IC95% 5,7-6,6 vs 5,6, IC95% 4,4-6,5) y más frágiles (1,62±1 vs 0,91±1), en todos los casos p<0,01. La sobrevida actuarial (IC 95%) a 1 y a 2 años fue, para TAVI 88% (84-91%) y 82% (77-86%), para CRVA 83% (76-88%) y 78% (70-84%) y para TMC 70% (60-87%) y 59% (48-68%) respectivamente (p<0,001).

Conclusiones: Durante los primeros 10 años de establecido un *Heart Team* para la toma de decisiones en EAo, se asignaron a TAVI aproximadamente la mitad y el resto se asignó por mitades a cirugía u observación. La sobrevida de los pacientes intervenidos fue similar a 2 años y mayor que la de los no intervenidos.

Palabras clave: Estenosis aórtica - Reemplazo de la Válvula Aórtica Transcatéter - Prótesis valvulares cardíacas

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INTRODUCTION

Degenerative aortic stenosis (AS) is a disease with an incidence and prevalence that increase at the same rate as life expectancy in the population. (1) In fact, the degenerative etiology has become the most common, replacing rheumatic heart valve disease. (2)

As the population over 80 years old has been increasing, the problem of how to treat degenerative AS in the elderly has increased as well.

Typically considered to be an end-of-life disease and usually associated with other heart and non-cardiovascular (CV) diseases, the emergence and popularization of transcatheter aortic valve implantation (TAVI) has put the focus on a new therapeutic option for these patients, previously left to the natural progression of the disease. (3)

As in many other cases, appearance of a new treatment led to reconsider the usefulness and selection of candidates for traditional treatment i.e., surgical aortic valve replacement (SAVR). The need to select patients for one treatment or the other derived in multidisciplinary team discussions about the best treatment for different conditions. Thus, a Heart Team (HT) or a Valve Team for AS was created (with no equivalent term in Spanish).

HT discussion about the choice of treatment for degenerative AS was quickly incorporated by clinical practice guidelines, (4,5) though with little evidence due to the lack of large and controlled studies that might show its usefulness. However, the need to discuss the best treatment for these complex patients immediately led to its implementation, and it soon became unavoidable and required when planning a TAVI. (6)

Our site has had a Heart Team for 10 years, so we felt the need to analyze its results and compare the characteristics of the patients assigned to each treatment.

METHODS

Design: A retrospective and single site study with consecutive enrollment of all patients with severe AS evaluated by the HT from January 2012 to July 2021. HT referral criteria were the following: 1) cases already selected for TAVI, and 2) uncertain cases when choosing between TAVI, SAVR and conservative medical management (CMM) as the best strategy. TAVI was recommended for symptomatic patients with known severe AS and variables warranting indication, such as increased surgical risk, old age, frailty, and suitability for the procedure, while SAVR was advised in patients with a lower surgical risk, unsuitable for TAVI, or requiring another intervention. Patients who failed to meet intervention criteria, patients for whom invasive treatment was considered futile, patients with a life expectancy of less than 1 year, or patients who refused to receive the procedure continued with CMM.

Severe AS was defined as a valve area ≤1 cm^2 (or ≤0.6 cm^2/m^2), based on the definition of the ESC (European Society of Cardiology) guidelines on valvular heart disease. (4) When in doubt, especially in cases of low-flow, low-gradient AS, the Agatston aortic valve calcium score by computed tomography (CT) was used, where a score over 2000 in men and 1300 in women was considered as severe. (5) All patients under intervention were evaluated by catheter coronary angiography, and a vast majority were also assessed using multi-layer contrast CT.

Members of the HT: The HT was composed of, at least, one cardiovascular surgeon, one interventional cardiologist, one CV imaging specialist, and one clinical cardiologist specialized in valve disease. The HT held weekly meetings (online during the pandemic). In case of disagreement, agreement was reached via a new discussion. The number of evaluated patients, recommended management, and interventions were annually compared over 10 years. Patients under intervention were followed up via personal, telephone or e-mail contact.

Frailty score: The degree of frailty was measured using Fried 1-5 scale assessing mobility, autonomy, handgrip response, etc. (7). A patient with a score ≥ 2 was considered frail according to median values.

Statistical analysis

Quantitative variables were reported as mean ± standard deviation (SD) or median and interquartile range (IQR) based on distribution and were compared using the Kruskal Wallis multiple comparisons test; categorical variables were reported as percentages and compared using the multiple chi-square test. A p value <0.05 was considered to be statistically significant. The STATA 13 statistical package was used.

Ethical considerations

The protocol was sent to the PRIISA platform and approved by the institutional Ethics Committee.

RESULTS

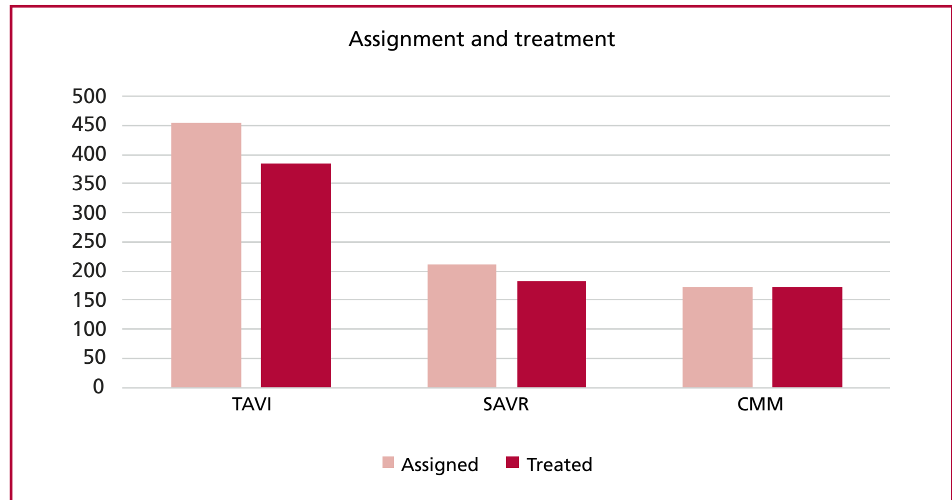
Of 841 evaluated patients, 455 (54%) were assigned to TAVI, of which 385 (85% of those assigned) received treatment; 213 (25%) were assigned to SAVR, of which 183 (86% of those assigned) underwent surgery and 173 (22%) received CMM (Figure 1).

The number of patients evaluated by the HT increased every year, with a marked reduction associated with the COVID-19 pandemic (see Figure 2). The proportion of patients under TAVI also increased from 48% in the first half of the assessed patients to 65% in the most recent half ($p <0.05$).

The baseline characteristics of the patients assigned to every treatment are summarized in Table 1: the mean age was 85 ± 5 years, 46% were female, the aortic valve area determined by ultrasound was 0.67 ± 0.2 cm^2, the left ventricular ejection fraction (LVEF) was 55 ± 13%, 53% had coronary artery disease, and 46% had comorbidities. Patients assigned to TAVI were older than those assigned to SAVR, had a smaller valve area, had a higher EuroSCORE II, and were frailer. Those assigned to CMM were similar to those who underwent TAVI, except for the larger valve area.

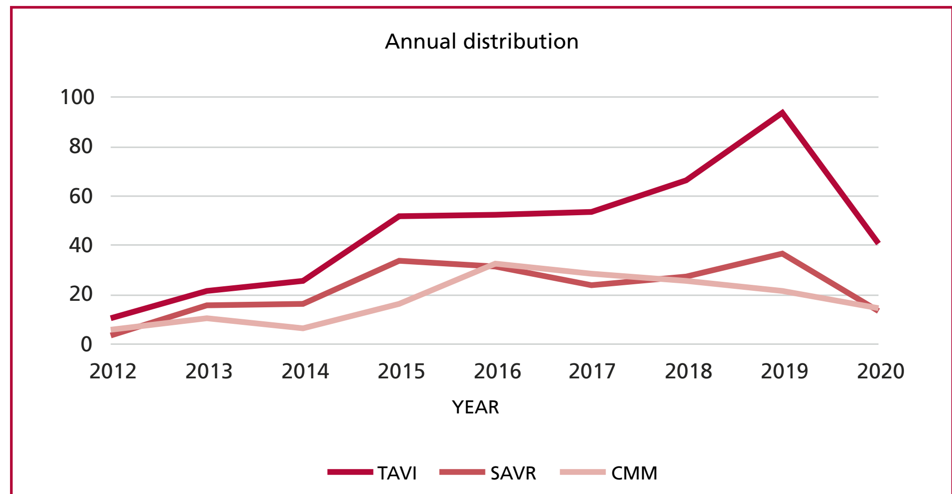
Actuarial survival (95% CI) at 1 and 2 years was 88% (84-91%) and 82% (77-86%) for TAVI, 83% (76-88%) and 78% (70-84%) for SAVR, and 70% (60-87%) and 59% (48-68%) for CMM, respectively, ($p <0.001$, Figure 3).

The independent predictors of actuarial mortality are detailed in Table 2.



CMM: conservative medical management; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

Fig. 1. Heart Team assignment and actual treatment received.



CMM: conservative medical management; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

Fig. 2. Number of patients evaluated by the HT and recommended management. The proportion assigned to TAVI increased significantly over the years. The decrease in 2020 is related to the COVID-19 pandemic.

Table 1. Comparison of patients assigned to TAVI, SAVR and CMM by the HT

	TOTAL: 841	TAVI: 455	SAVR: 213	CMM: 173	p
Age (years), mean + SD	85 ± 5	87 ± 6	83 ± 8	86 ± 8	<0.001*
Male sex (%)	54	54	61	57	<0.05 **
Valve area, cm^2, median (IQR)	0.67 (0.5-0.8)	0.65 (0.5-0.8)	0.69 (0.6-0.9)	0.70 (0.5-0.8)	<0.05***
LVEF (%), mean + SD	55 ± 13	55 ± 11	55 ± 12	54 ± 12	NS
Comorbidities (%)	46	46	44	49	NS
Coronary artery disease (%)	53	55	57	44	NS
EuroSCORE II, median (IQR)	6.0 (4.2-7.0)	6.1 (3.8-7.8)	5.6 (2.6-6.2)	6.1 (3.8-6.4)	<0.05*
Frailty score, mean ± SD	1.49 ± 1	1.62 ± 1	0.91 ± 1	1.74 ± 1	<0.05*

*SAVR vs. TAVI and CMM; **CMM vs. SAVR and TAVI; ***TAVI vs. SAVR and CMM
CMM: conservative medical management
IQR: interquartile range
LVEF: left ventricular ejection fraction
SAVR: surgical aortic valve replacement
SD: standard deviation
TAVI: transcatheter aortic valve implantation

DISCUSSION

The emergence of a new therapeutic option like TAVI in patients with severe AS –which to a large extent supplements the treatment of patients with high surgical risk– also requires a multidisciplinary approach in the cardiovascular team in charge of these patients.

Thus, there emerged the need to discuss the most appropriate management for each case by interventionists, surgeons, imaging specialists, valve disease specialists, etc. (8)

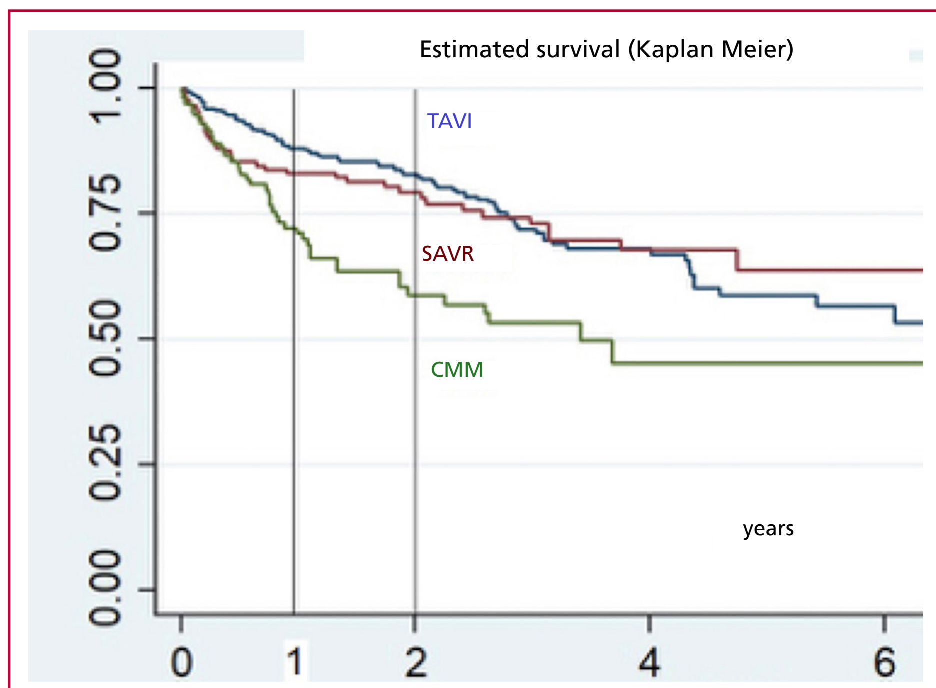
Though recommendations by the scientific societies are unanimous and often required by procedure funders, the lack of publications on the results of the Heart Team (HT) is remarkable both nationally and globally. (9-12).

Therefore, the objective of this study was to analyze the results of treatment in patients with AS evaluated by the HT over the first 10 years of its creation.

Notably, during this period some changes occurred both in the prostheses and in the implantation techniques, and experience was gained in terms of diagnosis, patient selection, and therapy. (13) In addition, the acceptance of a new therapeutic approach allowed us to evaluate more patients with no prior intervention. In fact, the annual analysis showed sustained increase in evaluated patients, as well as a larger number of TAVIs, with an average of half the patients under assessment, and there was a significant decrease associated with the COVID-19 pandemic, which reflects the side effect suffered by this population with severe cardiovascular conditions. (14)

About half of the patients were assigned to TAVI (this percentage increased to 60% in the last few years due to the increased acceptance of the procedure), and the rest were equally assigned to surgery or conservative management. These percentages are remarkably similar to those recently presented by the HT from the Italian group of Burzotta et al., for patients with valvular heart disease, with 77% experiencing AS. (15)

Evaluated patients were mostly in their eighties,



CMM: conservative medical management; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation

Fig. 3. Actuarial survival for patients under TAVI (transcatheter aortic valve implantation), SAVR (surgical aortic valve replacement) or CMM (conservative medical management) as recommended by the HT.

Table 2. Independent predictors of actuarial mortality.

	RR	95% CI	p
Age	1.04	1.01–1.06	0.002
LVEF	0.98	0.97–0.99	0.015
Renal failure	1.58	1.16–2.17	0.004
Diabetes	1.52	1.07–2.15	0.018
CMM	1.99	1.41–2.81	0.001

CMM: conservative medical management; LVEF: left ventricular ejection fraction; RR: relative risk

had severe AS (reconfirmed by the HT, a major task of this team), were mostly asymptomatic, had comorbidities and an estimated surgical risk that was at least intermediate, and an EuroSCORE II around 6, on average. The LVEF was near the lower limit of normal, and at least half of the patients had coronary artery disease.

Patients selected for TAVI were comparable to those selected for SAVR, except for a higher estimated surgical risk in the former, who were older and frailer. Actuarial survival at 1 and 2 years (88% and 82% with TAVI, 83% and 78% with SAVR, p = NS) seems to be reasonable with both strategies and suggests an adequate choice of treatment in a setting where access to transcatheter valve implantations is limited by high costs.

Focus should be made on the group under CMM: this is a heterogenous group ranging from a subgroup with less severe valve disease and absence of symptoms i.e., with no intervention indicated at the time of assessment, to a subgroup with no intervention required due to the lack of severe comorbidities, futility or end stage, also including patients who refuse to have the intervention, thus making a comparison difficult.

As observed virtually in every set, patients without intervention show significantly poorer survival (70% and 59% at 1 and 2 years), which supports intervention in candidates. In fact, CMM was the main mortality predictor in a multivariate analysis (see Table 2), with a relative risk near 2: patients under (non-interventional) medical management had twice the mortality rate of those under intervention (either with TAVI or surgery) during the follow-up, beyond other risk predictors.

Notably, patients evaluated by the HT were not all patients with AS but those considered for TAVI. Patients with an indication of conventional surgery or patients for whom no intervention was considered were not evaluated. This is the most common strategy at present and seems to be the future in terms of the HT. (16)

Our study showed 12% mortality at 1 year for TAVI, 17% for SAVR, and 30% for CMM. The Portuguese group from Catia Costa et al. (10) published a similar study of 473 patients evaluated by their HT over 8 years: mortality after a year was 16% for TAVI, 11% for surgery, and 20% for medical management. For the Spanish group from Diego Iglesias et al. (11), mortality at 1 year was 20% for TAVI and 18% for surgery. In addition, this study analyzed the prognostic value of the HT decision in the long term and found that such decision was an independent predictor of long-term mortality. The results from our study can also be compared to those from large studies, such as PARTNER and SURTAVI. (17,18) In our setting, the only publication referring to the usefulness of the HT for AS is the work by Garmendia et al. on new hospitalization predictors. (19)

Limitations

As cited above, our study has a selection bias, as it includes only patients considered to be candidates for TAVI. (20,21) Another limitation is the retrospective nature of data collection, the involvement of only one site (making it difficult to generalize findings), and major financial restrictions in terms of percutaneous valves availability in our setting, especially in the first half of the decade under analysis.

CONCLUSIONS

Ten years after creation of the Heart Team to select patients with AS who are candidates for TAVI, about half of them have been assigned to TAVI, while the rest were divided in two to undergo either surgery or observation. Patients under intervention seem to follow the selection pattern suggested by the team. Survival in patients under intervention seems to be similar up to 2 years with TAVI or SAVR, and is reasonable for both strategies, which suggests an adequate choice of treatment. Worse progression in patients under no intervention supports an invasive strategy in those who are candidates for intervention.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Non-conventional Determinants of Cardiovascular Health in Latin American Women

Determinantes no convencionales de la salud cardiovascular de la mujer en Latinoamérica

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ABSTRACT

Background: Besides traditional risk factors (RF), non-conventional determinants (NCD) of cardiovascular (CV) health are additional risk factors in women. Therefore, they should be explored to establish their prevalence and association with the female gender.
Objective: The aim of this study is to know the prevalence of socioeconomic (SE) and psychosocial (PS) factors as NCD in CV health in Latin American (LATAM) women.
Methods: We conducted an observational, cross-sectional study using an anonymous survey distributed among LATAM women between May and June 2022. The information gathered included SE and PS NCD, traditional RF and cardiovascular disease (CVD).
Results: A total of 4915 women participated; mean age was 49 ± 13 years. Most respondents (49.6%) lived in Argentina, 55.8% in large cities; 94.4% reported adequate access to healthcare services and 89% had access to some level of education. Although 79.9% had a paid job, more than half reported their salary was not commensurate (59.5%) and 26.7% reported exposure to violence at the workplace. The most prevalent PS factors were low to moderate level of satisfaction (68.3%), anxiety or irritability (51.9%), apathy, negative thoughts, or unhappiness (41.7%). Age > 45 years was significantly associated with overweight, obesity, unemployment, and violence at the workplace.
On multivariate analysis, sleep disorders (OR 1.7; p = 0.001), living in a city with low population density (OR 0.5; p < 0.001), violence at the workplace (OR 1.8; p = 0.001), anxiety (OR 1.5; p = 0.001) and a history of pregnancy complications (OR 1.6; p = 0.022) were independently associated with CVD.
Conclusion: The prevalence of PS and SE factors affecting the CV health of LATAM women was significant. Variables such as violence at the workplace, anxiety, or irritability, living in cities with low population density, sleep disorders and pregnancy complications were independently associated with CVD. This survey shows the impact of SE and PS factors as NCD on the cardiometabolic burden and CV health of women in LATAM, mainly in those > 45 years.

Key words: Cardiovascular Diseases - Women - Latin America - Risk Factors - Psychosocial Factors - Socioeconomic Factors

RESUMEN

Introducción: Más allá de los factores de riesgo (FR) tradicionales, hay determinantes no convencionales (DnoC) de la salud cardiovascular (CV) que operan en las mujeres como factores de riesgo adicional. Es por ello necesario explorarlos y establecer su prevalencia y vínculo con el género femenino.
Objetivo: conocer la prevalencia de los DnoC socioeconómicos (SE) y psicosociales (PS) y su impacto en la salud CV de la mujer en Latinoamérica (LATAM).
Material y métodos: estudio observacional, de corte transversal realizado a través de una encuesta anónima en mujeres de LATAM entre mayo y junio de 2022. Se recabaron datos sobre DnoC (SE y PS), FR convencionales y enfermedad cardiovascular (ECV).
Resultados: participaron 4915 mujeres con edad media de 49 ±13 años. El 49,6 % residía en Argentina, el 55,8 % en grandes ciudades, el 94,4 % declaró acceso adecuado a la salud y el 89 % tuvo acceso a algún nivel de educación. Si bien el 79,9 % expresó tener trabajo remunerado, más de la mitad refirió percibir un salario no acorde (59,5 %) y una exposición a la violencia en el ámbito laboral (26,7 %). Los determinantes PS más prevalentes fueron el bajo a moderado nivel de satisfacción (68,3 %), la ansiedad o irritabilidad (51,9 %), el desinterés, los pensamientos negativos o la infelicidad (41,7 %). El grupo de edad mayor de 45 años se asoció significativamente a más sobrepeso, obesidad, desempleo y violencia laboral.
En el análisis multivariado se encontró asociación independiente con ECV para el trastorno del sueño (OR 1,7; p = 0,001), residir en una ciudad de baja densidad poblacional (OR 0,5; p < 0,001), la violencia laboral (OR 1,8; p = 0,001), la ansiedad (OR 1,5; p = 0,001) y al haber padecido complicaciones del embarazo (OR 1,6; p = 0,022).

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Conclusión: se demostró una importante prevalencia de factores PS y SE que impactan en la salud CV de las mujeres en LATAM. Variables como la violencia laboral, la ansiedad o la irritabilidad, residir en ciudades de baja densidad poblacional, así como los trastornos del sueño y complicaciones del embarazo se asociaron de forma independiente con la ECV. Esta encuesta muestra el impacto de los DnoC SE y PS en la carga cardiometabólica (CCM) y la salud CV de las mujeres en LATAM, principalmente en aquellas mayores de 45 años.

Palabras clave: Enfermedades Cardiovasculares - Mujeres - Latinoamérica - Factores de Riesgo - Factores Psicosociales - Factores Socioeconómicos

INTRODUCTION

The idea that the differences between men and women are exclusively due to biological differences is a reductionist concept, since there are emotional and sociocultural differences between both genders. In the emotional and psychological sphere, women are not only affected by hormonal fluctuations throughout their lives, but also by the complexity of their neurocognitive functions, shaped by the culture of different societies throughout history. (1)

Belonging to certain sociodemographic groups may have additional adverse health effects; many of these groups are underrepresented in randomized or observational studies. The factors contributing to this reality include problems with access to healthcare, low per capita income, educational level, assignment of multiple tasks and roles, and gender-based violence. Underrepresentation of women in clinical trials contributes to the lack of evidence of the impact of cardiovascular disease (CVD) on them. This could partly explain why CVD continues to disproportionately affect women, both in those conditions they share with men and in disorders that are more prevalent in women, as stroke, heart failure (HF) with preserved left ventricular ejection fraction, and myocardial infarction (MI) and nonobstructive coronary arteries. (2)

The Pan American Health Organization (PAHO) states that 80% of worldwide cardiovascular deaths occur especially in low- and middle-income countries and indicates that the incidence is the same in men and women. (3)

Poverty and the resulting impact on the psychosocial sphere have a greater impact on women, who are more likely to suffer a heart attack than their male counterparts. (4-8) The most marginalized and poorest populations are at greater risk for CVD, and among these populations, women are the most prone to suffer such episodes. (4)

In Latin America, unfavorable socioeconomic conditions have a major impact on female gender, affecting quality of life and access to decent housing, healthy diet or scheduled physical exercise, together with poor access to education since childhood, with unsatisfied basic needs. (9)

Nowadays we count with evidence about the impact of stressful triggers, as acute-chronic stress, anger-hostility complex, depression, vital exhaustion, anxiety, and gender-based violence at home and at the workplace. Low sociocultural, economic, and demographic level, and even harmful environmental exposures, are associated with higher risk of developing physical and mental diseases. (4,10-19) Other pollutants, as tropospheric ozone, nitrogen dioxide and volatile organic compounds, play a role in the development of diseases,. More than 90 percent of the world's population lives in areas where pollution levels exceed World Health Organization guidelines. The effects of air pollution are associated with large urban centers, manufacturing centers and areas with heavy traffic. In addition, we must add "indoor" air pollution that mainly affects the population of low to middle-income countries who still cook and heat their homes with firewood or coal. (10,11) All these factors have different effects according to gender, as in coronary syndromes, ischemia without obstructive coronary arteries (MINOCA/INOCA), takotsubo syndrome, and X syndrome. The latter are not associated with traditional risk factors, and adverse psychological and sociodemographic profiles seem to play a determining role. We now know that these conditions have a less benign course than was previously thought. (20,21)

In this context, it is necessary to implement a gender mainstreaming approach in trials, research, and medical practice. The lack of attention in this regard constitutes a gender bias or gap that has had a negative impact on the diagnosis and prognosis of a disease considered not prevalent in women, when in fact it has been disregarded or ignored. (22)

OBJECTIVE

The aim of this study is to know the prevalence of SE and PS factors as NCD in CV health in a population of Latin American (LATAM) women.

METHODS

We conducted an observational, cross-sectional study using an anonymous survey with closed questions developed in REDCap. The participation was voluntary. The survey was distributed among women >18 years between May and June 2022 through social networks (WhatsApp, e-mail, Facebook, and others) of members and district leaders of the Heart and Women Area of the Argentine Society of Cardiology (SAC) in different geographic regions of Argentina. The participation of the Council of Cardiovascular Disease in Women of the South American and Interamerican Society of Cardiology (SSC-SIAC) made it possible to distribute the survey in different LATAM countries. The survey is published in the Appendix. The questions dealt with personal

and occupational psychosocial sphere, gender-based violence (23), and conventional risk factors and CVD.

Statistical analysis

The population was divided into two groups: the first group was made up of women aged ≤ 45 years and the second group of those respondents > 45 years, to explore differences in the main variables in two different generations. Mean age of onset menopausal transition (WHO), when estrogen levels decline and cardiometabolic changes begin to occur, was used to define the cut-off point (Figure 1). The association between non-conventional and traditional factors was also explored.

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

Discrete variables were analyzed using the chi square test or Fisher's exact test, as applicable. For continuous variables, the t test or the Mann-Wihtney test were used, as applicable, and in case of 3 groups or greater, ANOVA or the Kruskall-Wallis test were used, as applicable. A p value < 0.05 was considered statistically significant.

All the calculations were performed with the software package R.

Ethical considerations

The survey was approved by the Committee on Ethics of the Argentine Society of Cardiology. An informed consent was not required due to the design of the study.

RESULTS

A total of 4915 women responded the survey. Mean age was 49 ±13 years.

Fourteen women (0.3%) identified themselves as belonging to the LGTBIQ+ (acronym for lesbian, gay, bisexual, transgender, intersex and queer; the plus sign represents people with diverse sexual orientation and gender identity) community.

Most respondents (49.6%) lived in Argentina, followed by Uruguay (15.5%), Chile (4.3%) and Peru (3.8%), among other countries (Figure 1).

Of those surveyed, 55.8% lived in large cities and 10.5% in towns. Quick and easy healthcare access was reported by 94.4% of respondents, and mostly in the private sector (83.6%). Lower population density (< 500 000 inhabitants) was associated with higher body mass index (BMI, 26 vs. 25 kg/m2, p = 0.002) and CVD (9% vs. 5%; p = 0.046).

Most survey respondents have access to basic services, such as public water system (90.2%), electrical grid (97.9%) and sewage system (82.5%); only 57% had access to pipe gas.

In terms of marital status, most respondents were married or had a partner (65.3%) or were cohabiting with a partner or children (66.9%). Hypertension (HTN) and tobacco use were more common in those without a partner (24% vs. 20%, p = 0.002, and 13% vs. 9%, p < 0.001, respectively).

Eighty-nine percent received some level of education and 4.1% did not complete compulsory education. (24) Educational level less than secondary school graduation was significantly associated with HTN (30% vs. 2%), diabetes (DM, 9% vs. 5%) and CVD (10% vs. 5%), in all cases with p < 0.001.

A total of 79.9% had a paid job, half of them were professionals (51.2%) and most of them were employees (68.7%). Forty-five percent reported working more than 44 hours per week, mainly those < 45 years (51% vs 40%, p < 0.001); 38.7% considered the workload was excessive and 85.7% reported their physical and emotional health was compromised. The variable "salary not commensurate with workload" (59.5%) was associated with HTN, higher BMI and CVD, in all cases with statistical significance. Labor inequity in terms of hierarchical positions or remuneration was reported by 33.8%.

Unemployment was associated with HTN, DM, smoking habits and CVD (p < 0.001).

Gender-based violence (physical, psychological, sexual, and institutional violence based on sexual orientation or gender identity, UN) occurred at the workplace (26.7%) and at home (22.4%). Violence at the workplace was associated with CVD (8% vs. 5%, p < 0.001), while violence at home was associated with dyslipidemia (DLP, 40.5% vs. 37%, p = 0.047], higher BMI (26.4 vs. 25.7 kg/m^2, p < 0.001) and smoking

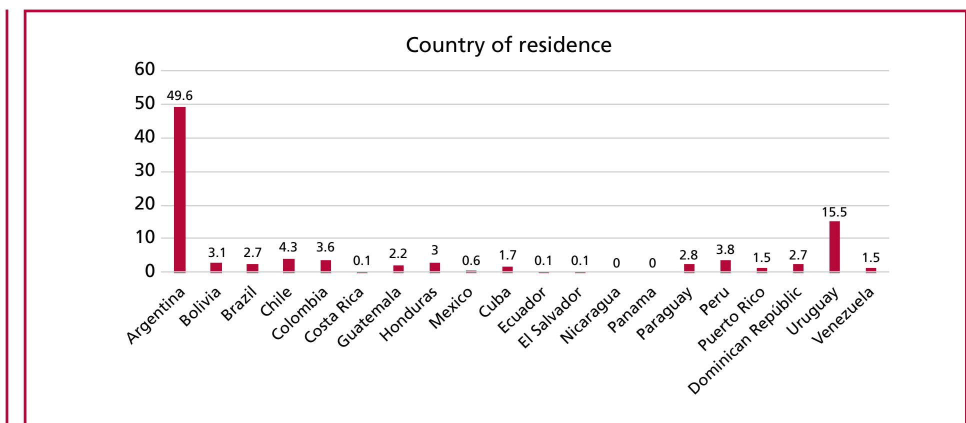

Fig. 1. Proportion of participant from the different Latin American countries

habits (15% vs. 9%, $p < 0.001$, respectively).

A total of 25.4% of the respondents had experienced sexual violence or sexual abuse during their lifetime, associated with higher BMI (26.3 vs. 25.7 kg/m2, $p < 0.001$) and smoking habits (13% vs. 9%, $p < 0.001$, respectively).

Only 31.7% reported high level of satisfaction in their personal life. Low to moderate level of satisfaction (68.3%) was significantly associated with higher cardiometabolic burden, and higher rates of DBT, DLP, higher BMI, smoking habits, and CVD. Social discrimination was reported by 19.8%, mainly due to physical appearance; this variable was associated with higher BMI ($p < 0.001$), smoking habits (12% vs. 10%, $p = 0.043$) and CVD (15% vs. 9%, $p < 0.001$).

Mood disorders (apathy, negative thoughts, or unhappiness) in the last two weeks (41.7%), were associated with higher rates of DLP (40% vs. 36%) and smoking habits (13% vs. 9%), while irritability or anxiety (51.9%) were associated with higher rates of smoking habits, higher BMI, and CVD (7% vs. 5%, $p < 0.001$). Sleep disorders (57%) were associated with DLP (40% vs. 34%) and CVD (7% vs. 4.5%, $p < 0.001$).

Regarding conventional RF, 21.6% had hypertension and were taking antihypertensive drugs, 5.2% were diabetics, 10.4% were current smokers and 30% were former smokers. Tobacco exposure was higher in transgender respondents ($p = 0.026$).

More than half of the respondents (54.1%) reported cholesterol levels > 200 mg/dL, and 48% reported a waist circumference > or equal to 88 cm.

Forty-six percent had a BMI below 25 kg/m2, 34% had overweight (between 25 and 30 kg/m2), mainly those > 45 years (36% vs. 31%, $p < 0.001$) and 20% had obesity (BMI > 30 kg/m2), which was also more common in those > 45 years (22% vs. 17%, $p < 0.001$).

Less than half (46.4%) of the women surveyed perform at least 150 minutes of physical exercise per week; 63.9% mentioned having little or no time for personal leisure activities. A total of 58.8% did not follow a balanced and healthy diet; 9.5% drank more than 100 g of alcohol per week and 5.3% took drugs; both variables were associated with a higher prevalence of smoking habits.

Annual heart health check was reported by 43.4% and 77.5 % underwent an annual gynecological exam.

Cardiovascular disease was reported by 6.6%: arrhythmias (50.3%), coronary artery disease (21.8%), heart failure (21.5%), cerebrovascular disease (9.7%), aortic and peripheral artery disease (6.7%) and renal artery disease (0.7%). Regarding coronary artery disease, 46.8% reported a history of angina, 35.5% myocardial infarction, 30.6% percutaneous coronary intervention with or without stenting, and 19.4% myocardial revascularization surgery.

Half of the respondents (50.3%) were taking some type of medication on a regular basis. The most commonly used drugs were antihypertensive agents (34.6%), lipid-lowering agents (21.7%) and anxiolytics/antidepressants (25.2%).

When asked about the obstetric history, 72.8% responded having at least one pregnancy and 15.6% of them reported one or more of the following complications: hypertension (44.9%), premature delivery (58.6%), miscarriage (2.9%), voluntary termination (1.1%) and gestational diabetes (16.9%). An adverse obstetric history was associated with HTN (32 % vs. 23 %, $p < 0.001$), DM (10 % vs. 5 %, $p < 0.001$), higher BMI (27 vs. 26 kg/m2, $p < 0.001$) and current CVD (9 % vs. 5 %, $p = 0.022$).

Cancer was considered the leading cause of death in women by 44.4% of respondents, followed by CVD (38.1%) and feminicide (14.4%).

On multivariate analysis, sleep disorders (OR 1.7, $p = 0.001$), living in a city with low population density (OR 0.5, $p < 0.001$), violence at the workplace (OR 1.8, $p = 0.001$), anxiety (OR 1.5, $p = 0.001$) and a history of pregnancy complications (OR 1.6, $p = 0.022$) were independently associated with CVD.

Age > 45 years was significantly associated with overweight, obesity, unemployment, and violence at the workplace, while sexual violence, higher workload with commensurate salary and higher educational level were related with age < or equal to 45 years (Figure 2).

DISCUSSION

This survey shows the impact of self-referred PS and SE determinants on the cardiometabolic burden (CMB) and CV health of women in LATAM, mainly in those > 45 years.

In Latin America, the proportion of overweight and obese adults has significantly increased in recent decades, (25) and this epidemic has spread to low- and middle-income countries. Malnutrition in all its forms, whether overweight, obesity or undernutrition, is associated with poverty. (26) In Argentina, the prevalence of overweight and obesity over the years has shown a clear upward trend, particularly in the most socially vulnerable groups. (27)

A multinational South American cohort examined variations in the incidence and mortality rates of CVD and analyzed the contribution of modifiable risk factors to the development of CVD and to all-cause death. Deaths were higher in rural areas compared to urban areas, and low educational level ranked as the third risk factor. (28) In addition, exposure to an excessive workload associated with dissatisfaction with the salary earned in relation to workload, together with inequity, constitute chronic stress factors that affect mental and physical health (85.7%), a situation that was exacerbated during the COVID-19 pandemic (the prevalence of depression and anxiety in Argentina reached 36.4%). (29,30) Mood disorders as apathy, negative thoughts or unhappiness in the last two weeks, and irritability or anxiety were significantly associated with higher CMB and CVD.

In 2021, the American Heart Association (AHA)

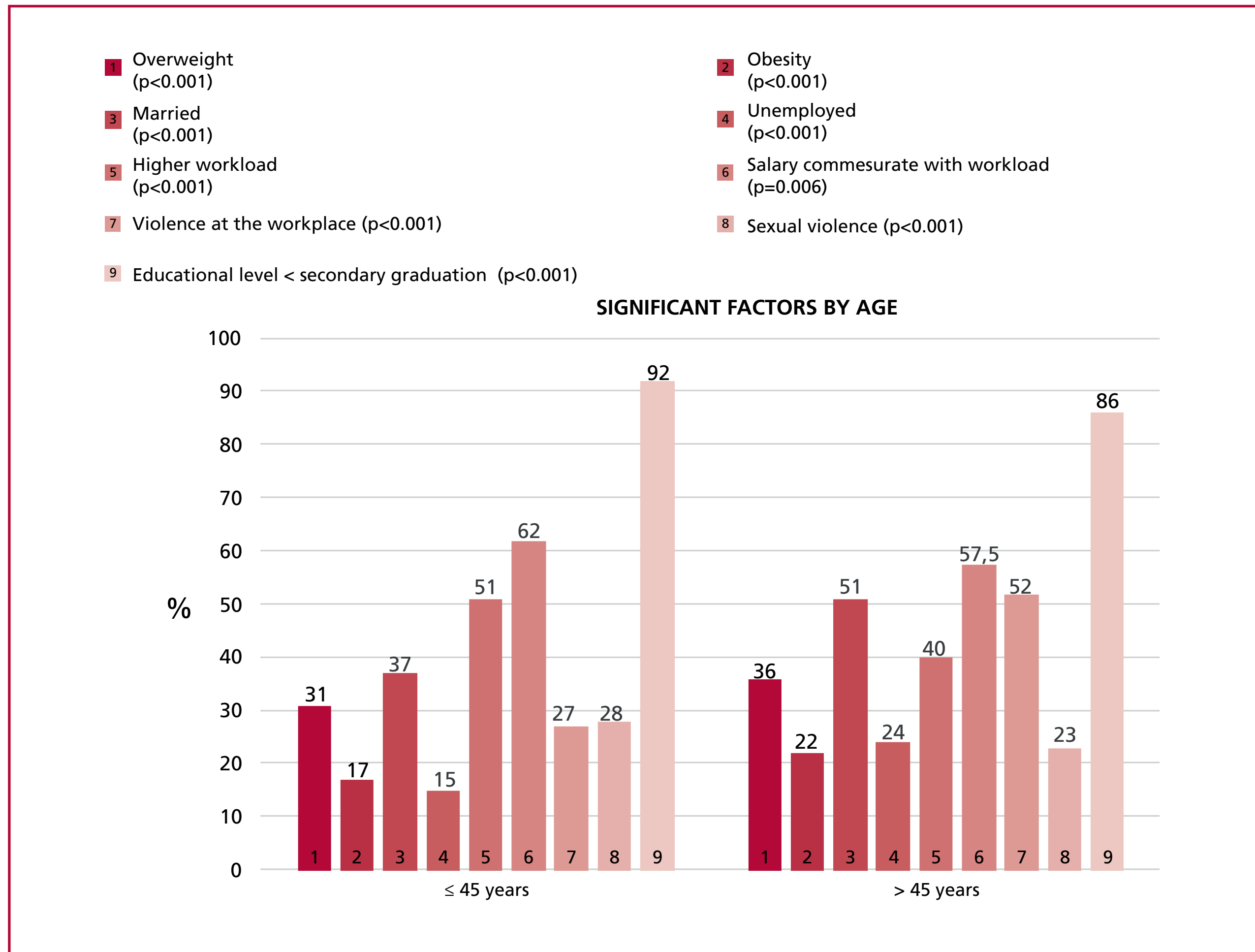

Fig. 2. Significant factors by age

published a scientific statement associating certain positive psychological factors (e.g., optimism, sense of purpose, happiness) and negative psychological factors (e.g., stress, depression, anxiety) to CV health and CV risk, respectively. (31) Emotional distress is considered a risk factor associated with increased CMB and CVD with increased platelet reactivity, risk of coronary heart disease, and incidence of depression, anxiety, and suicide. (32-34)

Gender-based violence is an emerging risk factor that begins early, affects adolescents and young women, and is more prevalent in low-income countries over lifetime. (35) In the population surveyed, gender-based violence occurred both at the workplace (26.7%) and at home (22.4%) representing a global public health problem and a violation of human rights. (36) Even cardiometabolic disorders developed after a childhood marked by abuse can lead to unhealthy lifestyle habits (sedentary lifestyle, unhealthy diet, sleep disorders, use of toxic substances and smoking) and psychological disorders (post-traumatic stress) with an impact on the immune, metabolic, neuroendocrine, and autonomic nervous systems. (37)

Sleep disorders were associated with CVD in the surveyed population. During 2022, the AHA published "Life's Essential 8" (LE8). (38) This update document included "quality of sleep" as an essential factor. The evidence demonstrates that fragmented sleep and inappropriate sleep duration (short duration, < 6 h, or long duration, > 9 h) is associated with increased morbidity and mortality, primarily from cardiovascular disorders and increased risk of type 2 diabetes. (39) Furthermore, short and fragmented sleep patterns are independently associated with higher atherosclerotic plaque burden in middle-aged individuals in multiple territories. (40)

CONCLUSION

We demonstrated a significant prevalence of PS and SE factors affecting the CV health of women in LATAM, where variables such as violence at the workplace, anxiety, or irritability, living in cities with low population density, sleep disorders and pregnancy complications were independently associated with CVD. This is the most extensive survey to date showing the impact of SE and PS factors as NCDs on the

CMB and CV health of women in LATAM, mainly in those > 45 years.

In this context, it is necessary to implement a gender mainstreaming approach in trials, research, and medical practice. The lack of attention in this regard constitutes a gender bias or gap that has had a negative impact on the diagnosis and prognosis of CVD in women.

Changes in policies, education and training, innovations in health care delivery, and diversification of cardiology are essential to overcome disparities that affect cardiovascular health in LATAM women. It is necessary to think of women as part of a whole rather than a simple part of a whole.

Study limitations

As this study is based on a non-probabilistic sample, it is difficult to accurately establish the prevalence of RFs in the target population. There is also a disproportion among respondents, with high participation of Argentine women and low representation of the rest of LATAM countries. The information gathered was self-reported by the participants, without corroborating the answers.

Conflicts of interest

None declared.

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

Financing

None.

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APPENDIX

1) Analysis of variables

	Without partner (n=1692)	With partner (n = 3177)	p
HTN, %	24	20	0.002
Diabetes, %	5.7	5	NS
Dyslipidemia, %	39	37	NS
BMI, mean (SD)	26 (6)	25 (6)	NS
Current smoking, %	13	9	<0.001
Cardiovascular disease, %	7	6	NS

	Educational level less than secondary school graduation (n=550)	Secondary education or higher (n=4327)	p
HTN, %	30	2	<0.001
Diabetes, %	9	5	<0.001
Dyslipidemia, %	41	37	NS
Current smoking, %	16	9	<0.001
BMI, mean (SD)	25 (3)	25 (5)	NS
Cardiovascular disease, %	9.5	6	0.001

	Unemployed (n = 919)	Employed (n = 3862)	p
HTN, %	30	19	<0.001
Diabetes, %	7.25	4.75	<0.001
Dyslipidemia, %	39.5	37	NS
Current smoking, %	10	10	NS
BMI, mean (SD)	25 (3)	25 (5)	NS
Cardiovascular disease, %	10	5	<0.001

	Violence at the workplace (n = 1300)	No violence at the workplace (n = 3562)	p
HTN, %	20	16.5	0.003
Diabetes, %	5	4	NS
Dyslipidemia, %	39.5	33	0.001
BMI, mean (SD)	25 (5)	26 (6)	0.003
Current smoking, %	10	11	NS
Cardiovascular disease, %	5.5	5	NS

	Workload < 44 h/week (n= 2051)	Workload 44 h/week or more (n=1681)	p
HTN, %	20	16.5	0.003
Diabetes, %	5	4	NS
Dyslipidemia, %	39.5	33	0.001
BMI, mean (SD)	25 (5)	26 (6)	0.003
Current smoking, %	10	11	NS
Cardiovascular disease, %	5.5	5	NS

	Violence at home (n = 1088)	No violence at home (n = 3769)	p
HTN, %	20	22	NS
Diabetes, %	5	5	NS
Dyslipidemia, %	40.5	37	0.047
BMI, mean (SD)	26.4 (6)	25.7 (6)	<0.001
Current smoking, %	15	9	<0.001
Cardiovascular disease, %	7	6	NS
	Sexual abuse (n = 1229)	**No sexual abuse (n = 3618)**	**p**
HTN, %	18	22.5	0.001
Diabetes, %	4.5	5.5	NS
Dyslipidemia, %	39	37	NS
BMI, mean (SD)	26.3 (6)	25.7 (6)	<0.001
Current smoking, %	13	9	<0.001
Cardiovascular disease, %	6	6	NS
	Discrimination (n = 962)	**No discrimination (n = 3894)**	**p**
HTN, %	19	22	NS
Diabetes, %	6	5	NS
Dyslipidemia, %	36	38	NS
BMI, mean (SD)	27 (6)	25.6 (6)	<0.001
Current smoking, %	12	10	0.043
Cardiovascular disease, %	9	5	<0.001
	Psychotherapy (n = 918)	**No psychotherapy (n = 3937)**	**p**
HTN, %	16	23	<0.001
Diabetes, %	4	6	0.029
Dyslipidemia, %	38	38	NS
BMI, mean (SD)	25 (6)	26 (6)	<0.001
Current smoking, %	12	10	0.042
Cardiovascular disease, %	6	6	NS
	High satisfaction level (n = 1543)	**Moderate and low satisfaction level (n = 3331)**	**p**
HTN, %	20	22	NS
Diabetes, %	3	6	<0.001
Dyslipidemia, %	35	38	0.045
BMI, mean (SD)	25 (5)	26 (6)	<0.001
Current smoking, %	7	12	<0.001
Cardiovascular disease, %	5	7	0.004
	Alcohol intake (n = 462)	**No alcohol intake (n = 4412)**	**p**
HTN, %	20	22	NS
Diabetes, %	5	5	NS
Dyslipidemia, %	40	37	NS
BMI, mean (SD)	26 (6)	25 (6)	NS
Current smoking, %	20	9	<0.001
Cardiovascular disease, %	5	6	NS

	Drug abuse (n = 257)	No drug abuse (n = 4618)	p
HTN, %	7	22	<0.001
Diabetes, %	3	5	NS
Dyslipidemia, %	37	37	NS
BMI, mean (SD)	25 (5.6)	26 (6)	0.020
Current smoking, %	28	9	<0.001
Cardiovascular disease, %	4	6	NS
	Sleep disorders (n = 2781)	**No sleep disorders (n = 2093)**	**p**
HTN, %	22	21	NS
Diabetes, %	6	5	NS
Dyslipidemia, %	40	34	<0.001
BMI, mean (SD)	26 (5.9)	25.7 (5.7)	0.26
Current smoking, %	10	10	NS
Cardiovascular disease, %	7	4.5	<0.001
	Apathy and unhappiness (n = 2028)	**No apathy or unhappiness (n = 2840)**	**p**
HTN, %	20	23	0.003
Diabetes, %	5	5	NS
Dyslipidemia, %	40	36	0.019
BMI, mean (SD)	26 (6)	25 (5.5)	NS
Current smoking, %	13	9	<0.001
Cardiovascular disease, %	7	6	NS
	Anxiety and irritability (n = 2528)	**No anxiety and irritability (n = 2343)**	**p**
HTN, %	20	23	0.018
Diabetes, %	5	5	NS
Dyslipidemia, %	39	36	NS
BMI, mean (SD)	26 (6)	25 (5.5)	0.017
Current smoking, %	12	8	<0.001
Cardiovascular disease, %	7	5	<0.001
	Pregnancy complications (n = 562)	**No pregnancy complications (n = 3052)**	**p**
HTN, %	32	23	<0.001
Diabetes, %	10	5	<0.001
Dyslipidemia, %	40	37	
BMI, mean (SD)	27 (6.4)	26 (6)	<0.001
Current smoking, %	7	11	0.007
Cardiovascular disease, %	9	6	0.022
	Cardiovascular disease (n = 298)	**Without cardiovascular disease (n = 4617)**	**p**
HTN, %	57	19	<0.001
Diabetes, %	14	5	<0.001
Dyslipidemia, %	39	37	NS
BMI, mean (SD)	27 (5.8)	25.8 (5.8)	<0.001
Current smoking, %	8	9	NS

BMI: body mass index; HTN: hypertension; SD: standard deviation

2) Questionnaire of non-conventional determinants in Latin American women

Questions	Options	Results
Age		49 (13)
Marital status	-Single/Not cohabiting with partner	(857; 17.6%)
	-Married	(2218; 45.6%)
	-With partner	(959; 19.7%)
	-Separated/Divorced/Widow	(835; 17.1%)
Gender	-Biologically female	(4682; 99.7%)
	_Transgender	(12; 0.3%)
	-Transsexual	(2; 0.0%)
Educational level (choose the highest level achieved)	-Incomplete primary level	(16; 0.3%)
	-Complete primary level	(40; 0.8%)
	-Incomplete secondary level	(147; 3.0%)
	-Complete secondary level	(347; 7.1%)
	-Incomplete tertiary level	(214; 4.4%)
	-Complete tertiary level	(711; 14.6%)
	-Incomplete university level	(495; 10.1%)
	-Complete university level	(2907; 59.6%)
Country of residence	Argentina	(2388; 49.6%)
	Bolivia	(147; 3.1%)
	Brazil	(128; 2.7%)
	Chile	(208; 4.3%)
	Colombia	(175; 3.6%)
	Costa Rica	(3; 0.1%)
	Cuba	(82; 1.7%)
	Ecuador	(5; 0.1%)
	El Salvador	(5; 0.1%)
	Guatemala	(107; 2.2%)
	Honduras	(143; 3.0%)
	México	(28; 0.6%)
	Nicaragua	(2; 0.0%)
	Panama	(0; 0.0%)
	Paraguay	(134; 2.8%)
	Peru	(182; 3.8%)
	Puerto Rico	(73; 1.5%)
	Dominican Republic	(129; 2.7%)
	Uruguay	(744; 15.5%)
	Venezuela	(71; 1.5%)
	Other	(56; 1.2%)
Which other country?		
Population density of the place where you live?	-Small town up to 1999 inhabitants	(136; 2.8%)
	-Large town from 2000 to 19 999 inhab.	(374; 7.7%)
	-Small city from 20 000 to 49 999 inhab.	(574; 11.9%)
	Intermediate city from 50 000 to 499 999 inhab.	(1053; 21.8%)
	-Large city > 500 000 inhab.	(2697; 55.8%)
Do you have easy and rapid healthcare access?	-Yes	(4580; 94.4%)
	-No	(272; 5.6%)
Regularly accesses medical care	-Public	(793; 16.4%)
	-Private	(4055; 83.6%)

(Continue)

(Continuation)

Housing domain		
How do you get access to water?	-Public water system (running water)	(4372; 90.2%)
	-Water supply from a well/borehole with pump or hand pump	(389; 8.0%)
	-Other	(87; 1.8%)
Do you have electricity?	-No	(16; 0.3%)
	-Yes, electrical grid	(4739; 97.9%)
	-Yes, from generator (combustion engine)	(45; 0.9%)
	-Others	(42; 0.9%)
What type of sewage system do you have?	-Connected to public sewer network	(3862; 82.5%)
	-Connected to septic tank	(427; 9.1%)
	-Connected to drywell	(349; 7.5%)
	-Others	(42; 0.9%)
What do you use to cook or heat your house? (You can choose several options)	-Piped gas	(2700; 57.0%)
	-Bottled gas (tank or cylinder)	(1458; 30.8%)
	-Firewood	(281; 5.9%)
	-Coal	(20; 0.4%)
	-Electricity	(1456; 30.7%)
	-Others	(67; 1.4%)
Cohabitants (You can choose several options)	-Single	(692; 14.6%)
	-With partner	(985; 20.8%)
	-Partner and children	(2180; 46.1%)
	-Other persons	(982; 20.8%)
	-Pets	(1010; 21.4%)
Workplace domain		
Do you have a paid job?	-Yes	(3862; 79.9%)
	-No	(969; 20.1%)
You are	-Self-employed	(1165; 31.3%)
	-An employee	(2558; 68.7%)
You work as:	-Domestic worker/caregiver	(51; 1.4%)
	-Industry or factory worker	(49; 1.3%)
	-Retail clerk	(93; 2.5%)
	-Administrative employee	(522; 13.9%)
	-Teacher/professor	(384; 10.2%)
	-Professional	(1928; 51.2%)
	-Entrepreneur	(166; 4.4%)
	-Retired	(224; 5.9%)
	-Others	(348; 9.2%)
Do you work more than 44 hours per week?	-Yes	(1681; 45.0%)
	-No	(2051; 55.0%)
Do you find your workload excessive?	-Yes	(1445; 38.7%)
	-No	(2286; 61.3%)
Do you consider your workload has affected your physical or emotional health?	-Yes	(1237; 85.7%)
	-No	(207; 14.3%)
Do you consider your salary commensurate with your workload?	-Yes	(1511; 40.5%)
	-No	(2222; 59.5%)

(Continue)

(Continuation)

Have you suffered gender-based violence at the workplace? (Physical, psychological, sexual and institutional violence based on sexual orientation or gender identity)	-No, never	(3562; 73.3%)
	-Yes, in the past	(1169; 24.0%)
	-Yes, at present	(131; 2.7%)
Is there gender equity (equality) at your workplace in terms of hierarchical positions or remuneration?	-Yes	(2462; 66.2%)
	-No	(1259; 33.8%)
Personal matters domain		
Have you ever suffered sexual violence or sexual abuse?	-Yes	(1229; 25.4%)
	-No	(3618; 74.6%)
Have you suffered gender-based violence at home? (Physical, psychological, sexual and institutional violence based on sexual orientation or gender identity)	-No, never	(3769; 77.6%)
	-Yes, in the past	(1028; 21.2%)
	-Yes, at present	(60; 1.2%)
Have you ever been socially discriminated against?	-Yes	(962; 19.8%)
	-No	(3894; 80.2%)
The social discrimination was related to:	-Your ethnic/racial status	(151; 16.1%)
	-Your physical appearance	(443; 47.3%)
	-Your culture	(74; 7.9%)
	-Your religion	(85; 9.1%)
	-Your socioeconomic situation	(321; 34.3%)
	-Your gender	(269; 28.7%)
	-Your disability	(25; 2.7%)
Do you have time for personal leisure activities?	-No	(450; 9.3%)
	-Yes, sometimes	(2652; 54.6%)
	-Sí, regularly	(1755; 36.1%)
Do you consider that the current health situation (COVID-19 pandemic) has resulted in excessive workload?	-No	(1136; 30.3%)
	-Yes, a little	(1281; 34.2%)
	-Yes, to a large extent	(1328; 35.5%)
Do you consider that the current healthcare situation has resulted in excessive demands on yourself?	-No	(1355; 28.0%)
	-Yes, a little	(2079; 43.0%)
	-Yes, to a large extent	(1399; 28.9%)
Weight (kg)		
Height (cm)		
Waist circumference	-< 88 cm	(2520; 52.0%)
	≥ to 88 cm	(2324; 48.0%)
Do you have hypertension? (high blood pressure)	-Yes	(1052; 21.6%)
	-No	(3816; 78.4%)
Are you taking any medication for your blood pressure?	-Yes	(1054; 21.7%)
	-No	(3808; 78.3%)
Do you check your blood pressure regularly? (each month)	-Yes	(2270; 46.7%)
	-No	(2594; 53.3%)
Do you know your total cholesterol levels?	-< 200 mg/dL	(2234; 45.9%)
	-Between 201 and 240 mg/dL	(1140; 23.4%)
	-> 240 mg/dL	(202; 4.2%)
	-Don't know	(1289; 26.5%)
Are you diabetic? High blood sugar levels	-Yes	(255; 5.2%)
	-No	(4609; 94.8%)
Do you smoke?	-Yes	(509; 10.4%)
	-No, never	(2910; 59.6%)
	-I used to smoke but don't smoke now	(1463; 30.0%

(Continue)

(Continuation)

Are you taking any medication?	-Yes	(2445; 50.3%)
	-No	(2415; 49.7%)
Which medication?	-Antihypertensive agents (for blood pressure control)	(827; 34.6%)
	-Lipid lowering agents (for blood cholesterol control)	(520; 21.7%)
	-Hypoglycemic agent (for blood sugar control)	(252; 10.5%).
	-Aspirin	(246; 10.3%)
	-OC/HRT (oral contraceptives/hormone replacement therapy)	(237; 9.9%)
	-Anxiolytics/antidepressants	(603; 25.2%)
	-Antiarrhythmic drugs	(162; 6.8%)
	-Diuretics (for HF control)	(152; 6.4%)
	-Others	(1203; 50.3%)
Are you now on psychotherapy?	-Yes	(918; 18.9%)
	-No	(3937; 81.1%)
Do you do at least 150 minutes a week of physical activity?	-Yes	(2262; 46.5%)
	-No	(2599; 53.5%)
Do you get an annual heart health check?	-Yes	(2110; 43.4%)
	-No	(2755; 56.6%)
Do you get an annual gynecological exam?	-Yes	(3770; 77.5%)
	-No	(1097; 22.5%)
Do you have any cardiovascular disease?	-Yes	(321; 6.6%)
	-No	(4540; 93.4%)
Which cardiovascular disease?	-Coronary artery disease	(65; 21.8%)
	Carotid artery disease (stroke-TIA transient ischemic attack)	(29; 9.7%)
	-Peripheral artery disease (abdominal aorta and lower extremity arteries)	(20; 6.7%)
	Renal artery disease	(2; 0.7%)
	-Arrhythmias	(150; 50.3%)
	-Heart failure	(64; 21.5%)
Which coronary artery disease?	-Infarction	(22; 35.5%)
	-Angina	(29; 46.8%)
	_Angioplasty/stent	(19; 30.6%)
	-MRS	(12; 19.4%)
Which is your level of satisfaction with your personal life?	-Low	(430; 8.8%)
	-Moderate	(2901; 59.5%)
	-High	(1543; 31.7%)
Do you drink more than 100 g of alcohol per week? (More than 1 liter of wine, more than 3 liters of beer, more than 300 ml of liquor per week).	-Yes	(462; 9.5%)
	-No	(4412; 90.5%)
		(4618; 94.7%)
Do you take drugs?	-No, never	(178; 3.7%)
	-Yes, in the past	(79; 1.6%)
	-Yes, at present	(1011; 20.7%)
Have you ever gotten pregnant?	-No	(3551; 72.8%)
	-Yes	(123; 2.5%)
	-Yes, with fertility treatment	(140; 2.9%)
	-Yes, I miscarried it/them (miscarriage/recurrent)	
	-Yes, I voluntarily terminated pregnancy	(55; 1.1%)

(Continue)

(Continuation)

Did you have pregnancy complications?	-Yes	(562; 15.6%)
	-No	(3052; 84.4%)
Which complication?	-Hypertension	(244; 44.9%)
	-Diabetes	(92; 16.9%)
	_Premature delivery (less than 37 weeks)	(318; 58.6%)
Do you feel motherhood limited your professional growth?	-Yes, to a large extent	(358; 10.1%)
	-Yes, slightly	(1115; 31.4%)
	-No	(2075; 58.5%)
Do you consider having a balanced and healthy diet?	-No	(751; 15.4%)
	-Yes, slightly	(2115; 43.4%)
	-Yes, regularly	(2012; 41.2%)
Have you recently had trouble to fall asleep or to stay asleep?	-No	(2093; 42.9%)
	-Yes, sometimes	(1453; 29.8%)
	-Yes, regularly	(1328; 27.2%)
Have you felt apathy or had negative thoughts or been unhappy in the last 2 weeks?	-Yes	(2028; 41.7%)
	-No	(2840; 58.3%)
Do you feel anxious or irritable?	-Yes	(2528; 51.9%)
	-No	(2343; 48.1%)
Which do you consider is the leading cause of death in women?	-Cardiovascular diseases	(1856; 38.1%)
	-Infections	(39; 0.8%)
	-Respiratory diseases	(42; 0.9%)
	-Cancer	(2164; 44.4%)
	-Feminicide	(709; 14.6%)
	-Other	(62; 1.3%)

ORIGINAL ARTICLE

Endovascular Treatment of Aneurysms with Complex Aortic Anatomy

Tratamiento endovascular de aneurismas con anatomía aórtica compleja

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ABSTRACT

Background: Arterial anatomy is the main limiting factor for standard endovascular aortic (EVAR) approach. We present our experience for endovascular repair of complex aortic aneurysms.
Methods: This is a retrospective observational study in patients with complex aneurysms (juxta/pararenal and thoracoabdominal) treated consecutively with: fenestrated (FEVAR), branched (BEVAR), EndoAnchors (ESAR), or chimney (ChEVAR) stents. The decision of the technique was determined based on the arterial anatomy.
Results: The last 50 procedures were evaluated (6 women; mean age 71.3 years; diameter 69.6 mm; and 3 patients with complicated aneurysms), among whom 22 received FEVAR (2.8 fenestrated stents/patient), 11 BEVAR, 11 ESAR and 6 ChEVAR (1.8 chimney stents/patient). Technical success rate was 100% (absence of type I or III endoleak with adequate patency of the visceral vessels). Three patients died within the first 30 days (6%). During follow-up, 5 patients presented with renal artery occlusion, treated successfully in 4 cases. Four patients developed type IA endoleak (3 secondary ESAR and one ChEVAR), one patient IC endoleak and almost a quarter of cases type IIIB endoleak (22%, 3 out of 11 patients receiving ESAR, none of the industrial FEVAR group). Overall survival was 88.6% at one year, and 86.5% of cases were free from reoperation.
Conclusions: This is the first publication in our setting that shows a global approach to the patient with complex aortic aneurysm, according to the anatomical characteristics. These technologies already play a primary role in the treatment of these patients.

Keywords: Abdominal Aortic Aneurysm - Endovascular repair - Device modification - Durability - Long-term follow-up - Thoracoabdominal aneurysms - Juxtarenal aneurysms - Complex Aorta

RESUMEN

Introducción: la anatomía arterial es la principal limitante para el abordaje aórtico endovascular estándar. Presentamos nuestra experiencia para la reparación endovascular de aneurismas aórticos complejos.
Material y métodos: estudio observacional retrospectivo en pacientes con aneurismas complejos (yuxta/pararrenales y toracoabdominales) tratados en forma consecutiva mediante: endoprótesis fenestradas (*FEVAR*), ramificadas (*BEVAR*), con *EndoAnchors* (*ESAR*), o en chimenea (ChEVAR). La decisión de la técnica fue determinada con base en la anatomía arterial.
Resultados: se evaluaron los últimos 50 procedimientos (6 mujeres; edad promedio 71,3 años; diámetro 69,6mm; 3 pacientes con aneurismas complicados), de los cuales 22 recibieron FEVAR (2,8 fenestraciones / paciente), 11 BEVAR, 11 ESAR y 6 ChEVAR (1,8 chimeneas /paciente). La tasa de éxito técnico fue del 100% (ausencia de endoleak I o III con permeabilidad adecuada de los vasos viscerales). A 30 días 3 pacientes fallecieron (6%). Durante el seguimiento, 5 pacientes presentaron oclusión de la arteria renal, repermeabilizada en 4. Cuatro pacientes desarrollaron un *endoleak* tipo IA (3 ESAR secundarios y un ChEVAR), un paciente un *endoleak* IC y un cuarto uno IIIB (22%, 3 de los 11 ESAR, ninguno de los FEVAR industriales). En el análisis de supervivencia, la supervivencia global fue del 88,6% al año, y libre de reoperación del 86,5%.
Conclusiones: se trata de la primera publicación en nuestro medio que muestra un enfoque global del paciente con un aneurisma de aorta complejo, de acuerdo con sus características anatómicas. Estas tecnologías ya desempeñan un papel primario en el tratamiento de estos pacientes.

Palabras clave: Aneurisma de Aorta Abdominal - Tratamiento Endovascular - Modificar dispositivo – Durabilidad - Seguimiento a largo plazo - Aneurismas toracoabdominales - Aneurismas Yuxtarrenales - Aorta Compleja

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INTRODUCTION

More than 80% of infrarenal abdominal aortic aneurysms with an indication for treatment are currently excluded using an endovascular approach. (1) For this purpose, two technical alternatives have been developed: standard and complex techniques. The arterial anatomy, especially that corresponding to the visceral segment of the aorta, is the decisive factor. Endovascular repair must be sealed in a healthy aorta to provide a durable repair. Therefore, when the aneurysm has a healthy segment for infrarenal sealing, a standard approach is used, which is accompanied by a low complication rate. (2-3)

On the contrary, the development of endovascular methods for patients with visceral aortic involvement has brought about a radical change. The complex approach, indicated when the sealing zone compromises or is in contact with the segment of the aorta from which the mesenteric or renal arteries emerge, implies the use of devices that make it possible to respect the origin of these arteries. It is especially in these procedures where the results are specifically related to an advanced diagnostic and therapeutic algorithm.

We present our experience with a global technical approach (therapeutic algorithm) in endovascular repair of patients with complex aortic aneurysms.

METHODS

Patient Selection

This is a retrospective observational study that evaluated the 30-day and 3-year outcome in patients with complex aneurysms treated using an endovascular approach to place fenestrated (Fenestrated Endovascular Aneurysm Repair, FEVAR) or branched (Branched Endovascular Aneurysm Repair, BEVAR) endografts, standard endografts reinforced with EndoAnchors (EndoSuture Aneurysm Repair, ESAR), or standard endografts with parallel or chimney stents to preserve the visceral arteries (Chimney Endovascular Aneurysm Repair, ChE-VAR). The decision of the technique was determined based fundamentally on arterial anatomy. Emergency patients were excluded.

Definitions and End Points

Aortic aneurysm with complex anatomy is a juxtarenal, pararenal, paravisceral, or thoracoabdominal aortic aneurysm (TAAA), which, per instructions for use of a standard endovascular graft, is not a candidate for exclusion by placement of only a standard infrarenal bifurcated endograft (EVAR).

Three fundamental algorithms have been used for the diagnosis and treatment of these patients.

Patients were evaluated by CT angiography with intravenous injection of contrast, except in those with creatinine clearance less than 30 ml/min, in whom the intra-arterial route with an aortic catheter was preferred to reduce the amount of contrast in -injected (less than 60 ml for thoracoabdominal studies).Various imaging tools were also used during surgery to reduce the amount of contrast and radiation: image fusion (Vessel Navigator, Azurion/Allura Xper FD20, Philips Healthcare), intraoperative cone beam tomography (Xpert-CT, Philips) and intravascular ultrasound (IVUS Vulcano, Philips).

Patients were evaluated with CT angiography before discharge to verify aneurysm exclusion, device integrity, and aortic collateral vessel patency. Doppler and CT scan without contrast were performed only in those with renal failure.

In the absence of endoleak, follow-up controls were performed by CT angiography and Doppler at 6 and 12 months and then annually, whereas in the presence of endoleak, follow-up was carried out according to the type of endoleak, characteristics of the patient and behavior of the aneurysmal sac.

Therapeutic algorithm

FEVAR includes a series of aortic devices that can be custom-made by a technology manufacturer (Custom Made Devices, CMD, Cook Medical, Bloomington, Ind) or by a physician in the operating room (Physician Modified Stent Graft, PMSG). Fenestrations are holes in the prosthetic material of the device that correspond to a visceral aortic branch (celiac trunk, superior mesenteric, or renal arteries), thus allowing the graft to lie more proximally than a standard configuration would admit. The orifice/fenestration of the endograft is then made to coincide with the origin of the artery to be preserved. To seal and specifically anchor the fenestration, stents are placed inside it towards the preserved artery. FEVAR was indicated in patients with a short infrarenal neck, less than 5mm in length, and visceral aortic diameter less than 36 mm. (Fig.1)

BEVAR. Standard branched graft (Zenith t-BRANCH, Cook Medical, Denmark) consists of a tubular endograft with four caudal branches, located in the standard longitudinal and axial axes, based on CT files of patients with thoracoabdominal aneurysms. It also requires an additional stent, a bridge, to connect and seal the stent branch with the visceral vessel. It was indicated in patients with type IV thoracoabdominal aneurysms (Fig. 2).

ESAR. EndoAnchors (Heli-FX™ EndoAnchor™ system, Medtronic Inc, Minneapolis, USA), are endosutures that reinforce the contact between the endograft and the arterial wall at the neck level. The procedure involves the endovascular screwing of small helical clips, simulating the force of a hand-sewn surgical anastomosis. This approach was used in patients with the possibility of a correct apposition (contact) between the endograft and the infrarenal aorta of at least 10 mm, but with a neck over 30 mm in diameter, and conical, teardrop- or hourglass-shaped necks, all tomographic characteristics that are associated with an increased risk of mid-term dilation of the proximal neck. It was also used in previously operated patients, with growth of the aneurysmal sac due to type II endoleak and neck dilation of more than 10% or more than 32 mm in diameter.

CHEVAR. Chimney stents ensure inflow through a covered stent placed in the visceral branch parallel to the endograft. It was indicated in patients with a short neck, 5 to 10 mm but less than 28 mm in diameter, especially in high-risk patients not only for aneurysm rupture (pain or more than 70 mm) but also at high surgical risk (ASA IV).

Statistical analysis

Continuous data are presented as mean and standard deviation (SD) and categorical data as percentages. Continuous data were compared using Student's t-test or Wilcoxon's test according to their distribution. Paired data tests were used to compare the dimensions before and after the intervention. Categorical data were compared with the chi-square test or Fisher's exact test, as appropriate. Event-free survival was defined by survival analysis, with the creation of Kaplan Meier curves. Statistical analysis was performed using SPSS 25.0 software for Windows. (SPSS, Inc., Chicago, IL).

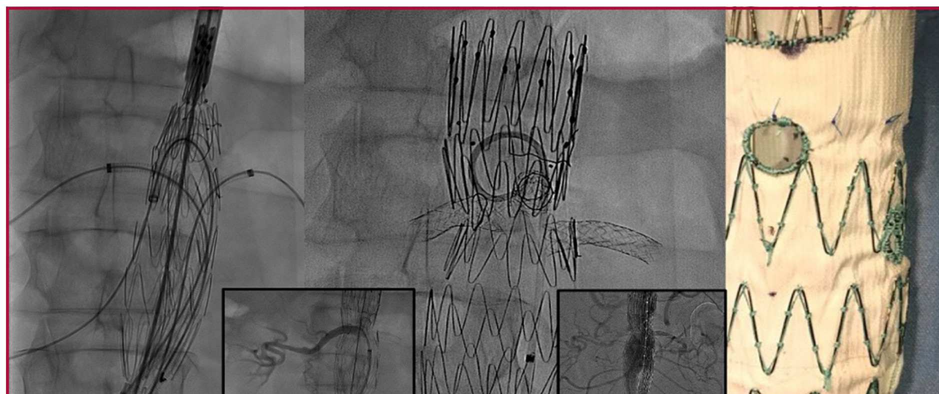

Fig. 1. From left to right. Angiographic image showing fenestrated endograft in position with introducers and guidewires placed in the renal and superior mesenteric arteries. Bottom left: Cannulation of the right renal artery. Middle: Fenestrated endograft (FEVAR) with deployed stents in the renal and mesenteric arteries. Bottom right: Final angiography. Right: Photograph of fenestrated endograft manufactured in the operation room with a central fenestration for the superior mesenteric artery.

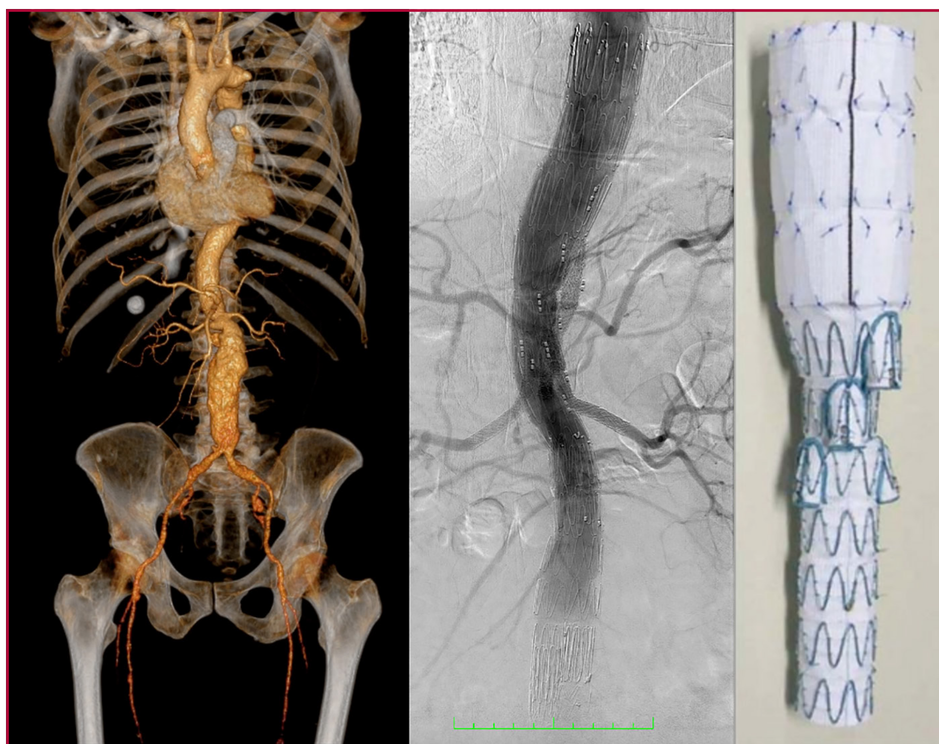

Fig. 2. Left: Computed tomography angiography of a patient with juxta-visceral aneurysm. Center: Final angiography with branched endograft towards the celiac trunk, the superior mesenteric artery and both renal arteries. Right: Protograph of the branched endograft.

RESULTS

The last 50 patients who underwent endovascular procedures for complex aortic disease, were consecutively evaluated; 44 were men (88%) and 3 (6%) had complications at the time of presentation (symptomatic or ruptured and contained aneurysm). Mean age was 71.3 ± 11.6 years, and mean aneurysmal diameter was 69.6 ± 16.6 mm (FEVAR 68.5 mm, BEVAR 66.4 mm, ESAR 72.3 mm, and ChEVAR 79, 8 mm p=0.418). Twelve patients (24%) presented with a previous EVAR. In this subgroup, the indication for treatment was due to type IA endoleak (n=4, 33.3%), migration (n=2, 16.7%), and proximal neck dilation (n=6, 50%).

Procedures performed included: 22 FEVAR (17 PMSG and 5 CMD), 11 BEVAR, 6 ChEVAR, and 11 ESAR.

Technical success rate was 100% without the presence of type I or III endoleak, with adequate branch patency. Three patients died during the first 30 perioperative days, one in the immediate postoperative period due to mesenteric atheroembolism (BEVAR), a second patient on day 22 due to pneumonia (patient with ruptured and contained aneurysm) and another due to ventricular tachycardia on day 8, the last two deaths secondary to ChEVAR.

Complications during follow-up

During an average follow-up of 17 months (range 1-48 months), four patients presented with type IA endoleak, three of whom received a FEVAR (all with a prior secondary ESAR, treated during follow-up for proximal neck dilation), and a fourth, with a previous ChEVAR, which was corrected by gutter embolization

and EndoAnchors placement.

Renal artery occlusion occurred in five patients (3 BEVAR and 2 PMSG). Three were corrected, a fourth high-risk patient remained asymptomatic without treatment and the fifth patient presented renal artery occlusion in an already atrophic kidney, so he also received no treatment.

In the Kaplan-Meier analysis, overall survival was 88.6% at 1 year and 77.3% at 3 years; 86.5% of cases were free of reoperation at 1 year and 61.3% at 3 years, while primary vessel patency was 91.3% at one year and 79.9% at three years.

Behavior of the aneurysmal sac

Overall, the aneurysmal sac underwent a non-significant reduction from 68.3 mm±15.6 mm to 66.9 mm±17.6 mm (p=0.69). However, knowing the small number of patients in the series, the tomographic information was disaggregated by procedure. Patients with BEVAR developed sac narrowing from 64.9 mm±8.12mm to 59 mm±8.2mm (p=0.14) and those with FEVAR from 60.17 mm±11.1 mm to 54.17 mm±9.9 mm (p= 0.31). Specifically, aneurysmal sac enlargements developed in type IA endoleak patients who were repaired and three in type II endoleak patients currently under observation.

DISCUSSION

This series shows the experience of a center specialized in the treatment of patients with aortic aneurysms. Supported by a selection based on anatomical and clinical-surgical criteria, it is the first publication in our setting that shows a global approach to the patient with complex aortic aneurysm. The application of a well-established protocol made it possible to treat this group of patients at high surgical risk, even during the pandemic, with a perioperative morbidity and mortality rate similar to international standards.

It is estimated that 50% of patients with abdominal aortic aneurysms are not candidates for endovascular repair with the devices currently available on the market due to their unfavorable anatomy. (4) This includes patients with short or angled necks, aneurysmal extension to the internal iliac artery, or aneurysmatic involvement of the juxtarenal, paravisceral, and thoracoabdominal aorta (complex aorta). Good surgical candidates can tolerate conventional open surgery.(5,6) However, in a recent presentation at the Charing Cross International Symposium in London on April 27, 2023, the surgical team from the University of Brescia, after matching covariates from 204 patients with thoracoabdominal aneurysms, determined that 30-day mortality after open surgery was 13% vs. 5% for complex endovascular treatment; paraplegia was 10% vs. 3%, severe respiratory complications 18% vs. 7%, cardiac complications 42% vs. 26% and severe renal 27% vs. 6% for endovascular treatment. This shows a real world with current statistics, advanced technology and a surgical team with experience in both approaches.

Complex endovascular aortic techniques were designed to extend the proximal sealing zone from the infrarenal segment to the juxta or suprarenal aorta, thus avoiding the limitation of the absence or short length of the infrarenal aortic segment. From the moment we started in 2011 the first option for these patients has been and remains the placement of a fenestrated endograft (FEVAR). Since then, evolution has meant better patient selection, innovative changes in endograft design, significant developments in imaging technology, and the application of standardized protocols for perioperative care. It is clear that care for these patients does not begin or end in the operating room; hence the importance of multidisciplinary care, on which the overall success of the procedure depends.

Fenestrated grafts specifically need to be custom assembled. Arterial anatomy is unique for each patient, and precise contact between graft orifice and the origin of the artery to be preserved is required. That information is obtained from the CT scan and must be transferred to a design to build the endograft. The industrial production of these devices (*Cook Medical* in our case) implies a certain delay in their availability (authorization time, production, and transfer) that may be too long for patients with urgent needs (aneurysms of more than 7 cm, symptomatic or ruptured). The way to respond to this problem was to train in endograft manufacturing, but fenestrated in the operating room, which has the enormous advantage of the almost immediate availability of a custom-made endograft. (7) For this purpose, two members of the team were trained at the Mayo Clinic (Rochester, Minnesota). This allowed us to design these endografts with variables such as number, location, and fenestration size or to design them to be cannulated for a femoral or subclavian approach. Thus, we can access from the cranium to caudally oriented vessels, and also avoid placing a bulky introducer in a femoral artery, which could cause limb ischemia. (8) However, published evidence and our own experience determine that this type of endografts modified in the operating room should be indicated in exceptional cases. The study presented by Dr. Oderich of the Mayo Clinic determined that the current approach has evolved from devices built in the operating room to almost exclusively company manufactured devices (CMD). These have been manufactured with greater technical success, with no mortality and with fewer serious adverse events. (9) In our series, none of the patients who received a CMD developed complications.

It is also important to emphasize the strict follow-up that these patients require. As shown in the results section, this approach is accompanied by a not negligible rate of reoperations: almost 10% of patients received a second procedure due to branch instability (occlusion or endoleak). But, most were minor surgeries and did not affect survival. (10-13)

A goal of the division was also to try to decrease the need for FEVAR in a specific group of patients.

Patients with proximal necks excluded from the instructions for use, but in whom the CT scan analysis allowed us to predict that we had a contact zone of 10 mm, were not treated with FEVAR as the first option. (14) The experience obtained with EndoAnchors allowed us an adequate seal, with no mid-term mortality or type IA endoleak, when EndoAnchors were implanted in the primary procedure. Same as in the ANCHOR registry, these results remain promising. (15) On the other hand, when they were placed before a proximal neck dilation, in some cases, the consequent dilation ended in a proximal endoleak, which had to be repaired by FEVAR.

ChEVAR was relegated to a strict anatomical and clinical indication. We are aware of the higher incidence of type IA endoleak associated with this technique, and for this reason we are very selective in its use. (16)

Finally, BEVAR was not performed in the context of dilated necks but in those evidently aneurysmal, juxta/pararenal aneurysms, where the dilated visceral aorta implied more than 5 mm of distance between the endograft and the origin of the visceral artery. (17)

Spinal cord ischemia is a devastating complication, with a known association between its incidence and mortality. (18) In 2019, we published our protocol for its prevention, analyzing 29 patients. (19) Since then, we have had no cases of early or late paraplegia.

Although current international guidelines do not directly translate into recommendations for complex treatment, it is logical and reasonable to assume that the benefits of an endovascular approach will be even greater when applied to patients with juxta, pararenal, or thoracoabdominal aneurysms. (20,21) It is well known that, due to their age and comorbidities, especially these patients have a limited life expectancy beyond surgery. It could be argued, then, that quality of life is a better metric for evaluating outcomes than survival.

Ethical considerations

The protocol was approved by the Ethics Institutional Board.

Limitations

As limitations, this was a mid-term follow-up study and in the context of a pandemic, which partially hindered patient follow-up. It is also worth highlighting the number of patients analyzed (50 patients) which, while being a representative value for our country, does not allow us to arrive to robust recommendations, but to demonstrate the possible advantages of centralizing pathologies based on experience and applied technology.

CONCLUSIONS

In conclusion, this presentation shows a global approach in which different techniques do not oppose but rather complement each other to achieve mid-term effective and long-lasting treatment in patients with complex aortic aneurysms. The goal is not to compare the techniques, since they have different indications, but rather to seek a final result, which is the minimally invasive treatment of patients with great technical complexity.

Conflicts of interest

None declared.

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

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REVIEW ARTICLE

What Are We Talking About When We Talk About Palliative Care in Heart Failure?

¿De qué hablamos cuando hablamos de cuidados paliativos en insuficiencia cardíaca?

MARIÁNGEL SÁNCHEZ[1], FRANCISCO PROASI[2], LUIS AHUALLI[1], CLAUDIO HIGA[1, MTSAC]

ABSTRACT

Background: Heart failure is a chronic, complex and progressive disease, with high morbidity and mortality, and growing prevalence. Despite advances in therapeutic strategies to improve survival and reduce hospitalizations, heart failure still generates a negative impact on the patients' quality of life, making it necessary to develop health policies based not only on their physical but also on their psychosocial integrity. Palliative care refers to specialized, interdisciplinary care focused on improving the quality of life of patients who suffer a disease with elevated morbidity and mortality. The aim of this review is to assess the impact of the implementation of palliative care in the multidisciplinary treatment of heart failure throughout all the stages of the disease, and to determine the feasibility of its application in clinical practice.

Key words: Heart failure - Palliative care - Prognosis

RESUMEN

La insuficiencia cardíaca (IC) es una enfermedad crónica, compleja y progresiva, con elevada morbimortalidad y creciente prevalencia. Pese al avance en las estrategias terapéuticas, destinadas a mejorar la sobrevida y reducir hospitalizaciones, la IC continúa generando un impacto negativo en la calidad de vida de los pacientes. Surge ante este reto la necesidad de desarrollar políticas de salud basadas no solo en la integridad física, sino también en la integridad psicosocial. Los cuidados paliativos (CP) hacen referencia a un cuidado especializado, interdisciplinario, enfocado en mejorar y mantener la calidad de vida de los pacientes que se enfrentan a una enfermedad con elevada morbimortalidad como lo es la IC. El propósito de la presente revisión es evaluar el impacto de la integración de los CP en el tratamiento multidisciplinario de la IC en todas las fases de la enfermedad y determinar la factibilidad de su aplicación en la práctica clínica.

Palabras clave: Insuficiencia cardíaca - Cuidados paliativos - Pronóstico

INTRODUCTION

Heart failure (HF) is a complex syndrome whose prevalence has increased in the last years as a result of population aging, the presence of multiple comorbidities and the higher survival of cardiovascular diseases. (1-3) Despite the development of therapeutic strategies destined to reduce mortality, HF is associated with elevated morbidity and progressive functional impairment. (4) Moreover, decompensations represent one of the main causes of hospitalization in adults over 65 years of age, with a high rate of rehospitalizations. (5)

Several authors have demonstrated a negative impact on the quality of life of patients with HF due to the limitation in functional class (FC), loss of independence in daily life activities and presence of physical symptoms and mood changes (comparable or greater to those of oncological patients) that are occasionally underdiagnosed and undertreated. (6-8)

The World Health Organization (WHO) acknowledges palliative care (PC) as "an approach to improve the quality of life of patients and their relatives facing problems associated with a potentially mortal disease. It includes the prevention and the relief of suffering through the early identification, assessment and cor-

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rective treatment of pain and other problems, whether physical, psychosocial or spiritual. (9) In oncological patients, the early intervention of PC teams has been shown to improve the quality of life and reduce costs and hospital admissions. It is therefore interesting to evaluate if patients with HF could also benefit from the care provided by the different PC levels.

The aim of the present review is to assess the existing evidence on the impact of incorporating PC to the multidisciplinary treatment of HF, the limiting factors in its application and its feasibility in daily clinical practice.

PALLIATIVE CARE

Originally, PC was developed within the frame of care of end-stage oncological patients, with the purpose of achieving symptomatic end-of-life control. (10) The growing prevalence of chronic, non-communicable diseases and the morbidity and mortality they generate has led to a transition from the classical model of care in which PC was administered in end-stage patients, towards a model of integral care which emphasizes the early onset of PC together with the active treatment of the disease. In this last model, as the disease progresses and the needs of the patient increase, PC is intensified to accompany the patient and his/her relatives, even contemplating the care of the family during the mourning process after the patient's death. This organizational model generates a paradigm in the care of the chronic patient, in which both the curative and palliative treatments are similarly rated, allowing a dynamic and integral care that leaves behind the original concept of PC focused on end-of-life treatment (11-13) (Figure 1).

In patients with chronic diseases, PC has shown a consistent benefit in terms of quality-of-life improvement, symptomatic control, reduction of hospitalizations and increase in anticipated measures that prioritize comfort over invasive measures at the end of life, with the consequent reduction in health costs, which avoids futility. (14,15)

Three levels of care are identified in PC. (16,17)

- First level or primary PC: it involves the application of basic PC competencies by first level of care professionals to provide symptomatic control in patients.
- Second level or secondary PC: it consists of interdisciplinary care in which the PC teams are consulted and deliver complementary support. The specific structure of each team varies according to the patient's needs. (11)
- Third level or tertiary PC: care is carried out in healthcare centers with specialized PC teams. It provides care to very complex patients who need hospitalization.

Access to PC has been declared a universal human right. (18) According to WHO, Argentina is among the countries with active growth in PC. (11) However, there is inequity in its access. The National Palliative Care Law was enacted in 2022 to guarantee PC access in all the care settings.

Application of palliative care in heart failure: let´s go to the evidence

In the prospective, randomized and open-label PREFER study, an integral PC home monitoring model together with cardiologists specialized in HF was compared with only the latter monitoring strategy in NYHA FC III-IV HF patients (36 patients per group). The Edmonton symptoms assessment scale (ESAS) and the Kansas City Cardiomyopathy Questionnaire (KVCQ) were used to analyze results. The first refers to a tool evaluating the average intensity of symptoms such as pain, dyspnea, asthenia, nausea, depression, anxiety, welfare, poor appetite and insomnia during a period of time. The second corresponds to a self-administered questionnaire specific for HF, consisting of 23 items that involve 5 self-perceived dimensions regarding the patient's health condition: physical limitation, symptoms (frequency, severity and stability), self-care, quality of life and social limitation. The PC strategy together with HF specialists demonstrated a statistically significant improvement in the quality of life compared with the control group (p=0.05)

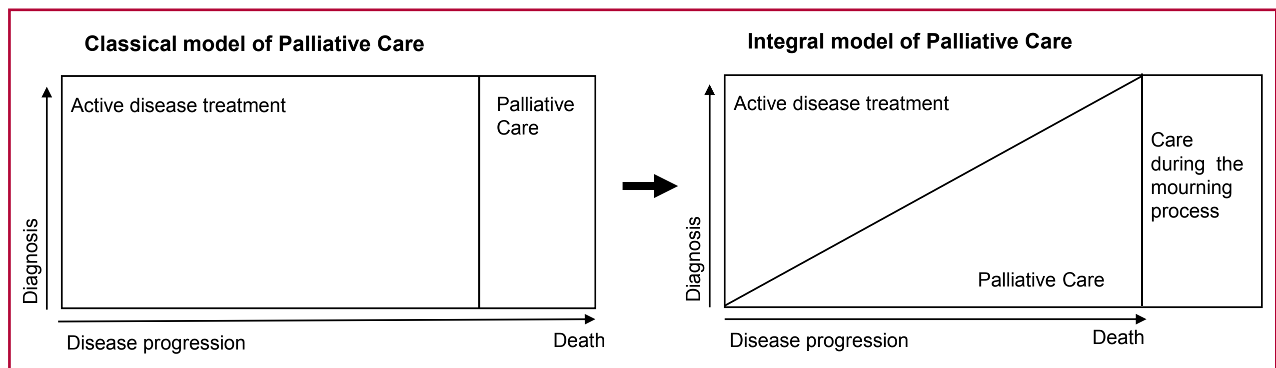

Fig. 1. Transition from the classical model of palliative care towards an integral care model, which emphasizes the early onset of palliative care, together with an active treatment of the disease. Modified from Lynn J, Adamson DM. Living well at the end of life; adapting health care to serious chronic illness in old age. WHO regional office for Europe. 2004.

as well as improved symptom burden (p=0.035). The implementation of integral care evidenced a significant change in FC at 6 months compared with control (39% vs. 10%, p=0.012). Additionally, the intervention group reduced hospitalizations (p=0.009). (19). These findings are consistent with those reported by Wong et al. who showed a reduction in the number of readmissions and symptomatic improvement with a PC strategy in patients discharged after a hospitalization for HF. (20)

In the PAL-HF study, 150 patients with advanced HF (AdHF) were randomly allocated to receive standard medical care, vs. the latter together with PC monitoring. Mean age was 71 years and more than 70% were in NYHA FC III, with an average of 2.2 hospitalizations in the year prior to enrollment. KCCQ scores evidenced poor quality of life, with a high symptom burden. The KCCQ and the Functional Assessment of Chronic Illness Therapy Palliative Care scale (FACIT-Pal) were used to analyze the results. The latter refers to a 46-item self-administered questionnaire evaluating quality of life in the physical, socio-familial, emotional and functional domains and also includes specific PC aspects. A change in favor of patients assigned to the PC interdisciplinary monitoring arm was observed with a KCCQ difference of 9.49 points (95% CI 0.94-18.05; p=0.030) and a difference in the FACIT-Pal scale of 11.77 points (95% CI 0.84-22.71; p=0.035) compared with patients undergoing conventional monitoring at 6 months of follow-up. In addition, a significant benefit was observed in the degree of anxiety (p=0.048) and depression (p=0.020), also in favor of interdisciplinary monitoring. (21)

In a systematic review of randomized controlled clinical trials including 1050 AdHF patients, the implementation of PC plus standard care was compared with standard care alone. The integral PC monitoring combined with standard care was associated with improved quality of life, reduced number of hospitalizations (OR 0.56; 95% CI 0.33-0.94) and decreased symptom burden compared with the usual care. (22)

These findings indicate a consistent benefit in terms of quality of life and symptom burden improvement in patients with AdHF. However, it is necessary to emphasize the difficulty posed by the incorporation and permanence of end-stage patients in research studies, as reflected by the low number of patients they include. Moreover, since most studies evaluate subjective endpoints, the potential risk of bias should be considered when interpreting the results.

Barriers in the implementation of palliative care in patients with heart failure

Heart failure clinical practice guidelines recommend considering the addition of PC to patient care. (23,24) However, one third of the patients are bed-ridden at the time of PC monitoring onset. (25,26) This exposes existing barriers that promote inequity in the access to PC among HF patients.

For some professionals, PC monitoring together with the active treatment of the disease involves contradictory actions, as they consider that PC is exclusively reserved for end stages of the disease, as a resource when the therapeutic objectives are not met and there are no other alternatives. (27) This reveals the existing conceptual error at the population level regarding the palliative term, as well as the limited training in PC that healthcare professionals have. (28, 29)

On the other hand, several authors agree about the lack of communication between physicians and HF patients. Only 12% of professionals annually discuss the prognosis with their patients (30,31) hampering advanced care planning, as the consultation with the GP in an ambulatory patient constitutes a favorable context to consider anticipated directives. These directives represent a willful declaration that the patient makes in full use of his/her mental faculties, with the aim of their becoming effective when he/she cannot express them. Thus, it ensures that the future healthcare is carried out according to the patient's preferences, guaranteeing the fulfillment of the principle of autonomy and a better quality of end-of-life care. (32,34)

Another important aspect to consider is the difficulty that presents the detection of the right moment for inclusion in PC monitoring. It is frequently found that after an acute decompensation, and following the administration of adequate treatment, the patient can recover and be discharged. However, the patient does not return to his/her previous state. These repeated decompensation episodes with subsequent recovery may cast doubt in the treating physicians, delaying the inclusion in PC programs. A systematic review evaluating the criteria of referral to PC revealed that 50% was carried out due to persistent physical symptoms and mood disorders, 45% for advanced NYHA FC and 37% for frequent hospitalizations. (35) Several scores have been postulated to approach this problem, such as the Heart Failure Survival Score (HFSC) and the Seattle Heart Failure Score (SHFS), (36) as well as the use of the surprise question "would you be surprised if this patient died next year?", to identify HF patients near the end of life and thus promote the consultation with PC. Straw et el. evidenced a statistically significant association between the answer "not surprised" and all-cause death at one year (p=0.046). (37) It is important to emphasize that, unfortunately, these tools expose the idea of referral to PC in advanced stages of the disease. Nevertheless, they could be useful for an objective assessment of the patient's prognosis, guiding advanced care planning.

Palliative care in heart failures: guidelines and recommendations

The European Society of Cardiology HF Association has published several recommendations acknowledging the value of early PC implementation for the multidisciplinary management of HF. (38) The last edition

of the Diagnosis and Treatment Guideline establishes that HF patients could benefit from the integration of PC during follow-up, independently of the stage in which they are, even if its incorporation is posed from the moment of diagnosis and its requirements increase as the disease progresses and advances. This organizational model generates a change in the paradigm for the HF patient, categorizing both the curative and palliative treatments, thus allowing a dynamic and integral care that leaves behind the original concept of PC focused on end-of-life treatment. (13) Moreover, it invites healthcare professionals to apply a palliative approach since the first level of care, detecting the patients' needs and enabling the referral to specialized teams for a more specific management when this is necessary (Figure 2).

The early implementation PC model has shown to be beneficial in oncological patients. (15) However, no objective evidence analyzing the impact of PC onset since diagnosis in HF patients has been found, since most studies include patients in advanced stages of the disease. Currently, the randomized, controlled, prospective, open-label, multicenter Early Palliative Care in Heart Failure Trial is being developed, including 200 HF patients with preserved or impaired left ventricular ejection fraction in NYHA FC ≥2. Participants have been randomly assigned to receive standard care by specialized cardiologists or by these physicians associated with PC. The primary outcome will evaluate quality of life at 12 months. (39) The conclusions of this work could provide the necessary impulse to overcome the current challenges related with the limited use of PC and allow a greater application from early stages in patients with HF.

FINAL REFLECTION

Heart failure is a complex and with increasing prevalence disease, which causes progressive functional capacity impairment and elevated associated morbidity and mortality. The existent analogy with oncological patients when evaluating the high symptom burden and the benefits demonstrated by PC carried out since the early stages of the disease invite to consider a paradigmatic change in the care of HF patients.

The progressive implementation of PC since diagnosis and as part of a multidisciplinary management of HF from the first moment has the main purpose of detecting and contributing to the specific needs of each patient, optimizing his/her quality of life, while maintaining an active treatment of the disease. As it progresses and the therapeutic options are exhausted, an adequate and fluid communication is essential to establish a plan of individualized care oriented to the patient and his/her environment preferences, which guarantees autonomy and tries to avoid futile actions that only prolong agony and suffering.

Conflicts of interest

None declared.

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

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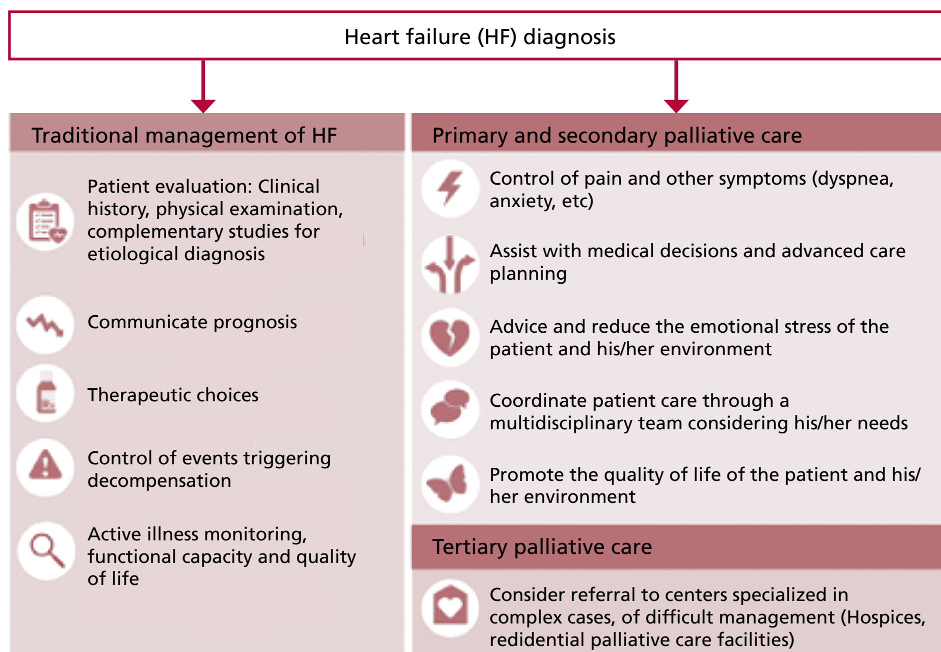

Fig. 2. Integrative care model with the palliative care, at different levels, in the active treatment of heart failure. From the early diagnosis of the disease, a continuum is established between the heart failure specialist with the comfort provided from palliative care specialist, while therapeutic goals are achieved and future planning is done.

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REVIEW ARTICLE

Accelerated Diagnostic Protocols Based on High-Sensitivity Troponin in the Diagnosis of Thoracic Pain: A Systematic Review

Protocolos de diagnóstico acelerado basados en troponina de alta sensibilidad en el diagnóstico del dolor torácico: una revisión sistemática

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ABSTRACT

Background: The progress of high-sensitivity troponin for accelerated diagnostic protocols to assess chest pain, allows the identification of patients admitted to the emergency room with low-risk chest pain for a major adverse cardiovascular event, that could be early and safely discharged, saving time and resources.
Objective: The aim of this study was to assess clinical trials using accelerated diagnostic protocols based on high-sensitivity troponin.
Methods: A search of randomized clinical trials evaluating accelerated diagnostic protocols based on high-sensitivity troponin in emergency services was carried out in MEDLINE/Ovid, Cochrane and EMBASE database, using the assessment criteria of the Cochrane manual and the PRISMA strategy.
Results: After screening 3509 studies, 5 clinical trials, including 1513 patients, were analyzed. Early discharges were identified in 409 (27%) of patients, in 91% of cases for ESC 0/3-h protocols, 72% for 0/1-h, 48% for EDACS, 40% for HEART, 19% and 32% for ADPT and 8% and 18% for standard care protocols. The negative predictive value was high, in the 99.1-100% range. Mean length of hospital stay was lower for the 0/1-h and ESC 0/3-h protocols, with 4.6 and 5.6 hours, respectively.
Conclusions: Accelerated diagnostic protocols in chest pain using high-sensitivity troponin allow a higher proportion of early discharges with a low rate of major cardiovascular events, with reduction in length of hospital stay and resources used.

Key words: Thoracic pain - Accelerated diagnostic protocols - High-sensitivity troponin - Acute coronary syndrome - Acute myocardial infarction - Coronary disease

RESUMEN

Introducción: Los protocolos de diagnóstico acelerado de dolor torácico, con el avance de la troponina de alta sensibilidad, permiten identificar a los pacientes que ingresan al servicio de urgencias con dolor torácico de bajo riesgo para un evento cardiovascular adverso mayor, que podrían ser dados de alta de forma temprana y segura, con ahorro de tiempo y recursos.
Objetivo: Evaluar ensayos clínicos que utilicen protocolos de diagnóstico acelerado basados en troponina de alta sensibilidad.
Material y métodos: se realizó una búsqueda de ensayos clínicos aleatorizados que evaluaran protocolos de diagnóstico acelerado basados en troponina de alta sensibilidad en los servicios de urgencias, en las bases de datos MEDLINE/Ovid, Cochrane y EMBASE utilizando los criterios de evaluación del manual Cochrane y la estrategia PRISMA
Resultados: Tras una tamización de 3509 estudios se incluyeron 5 ensayos clínicos que incluyeron 1513 pacientes; se identificaron 409 (27%) altas tempranas, el 91% para el protocolo 0/3 h ESC, 72% para el 0/1 h, 48% para el EDACS, 40% para el HEART, 19 y 32% para ADAPT y 8 y 18% para el cuidado usual. El valor predictivo negativo fue alto, en un rango de 99,1 al 100% La duración media de la estancia hospitalaria fue más baja para los protocolos 0/1 h y 0/3 h ESC, con 4,6 y 5,6 horas respectivamente.
Conclusiones: Los protocolos de diagnóstico acelerado en dolor torácico que implementan el uso de troponina de alta sensibilidad permiten lograr alta proporción de altas tempranas con baja tasa de eventos cardiovasculares mayores, con disminución del tiempo de estancia y recursos consumidos.

Palabras clave: Dolor torácico - Protocolos de diagnóstico acelerado - Troponina de alta sensibilidad - Síndrome coronario agudo - Infarto agudo del miocardio - Enfermedad coronaria

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INTRODUCTION

People consulting the emergency services for chest pain require a fast assessment to rule out conditions that may put their life at risk. (1) The standard procedure when myocardial ischemia is suspected is to determine its clinical probability according to risk stratification based on clinical history, physical examination, electrocardiographic findings and biochemical markers. (2,3) To optimize this process, accelerated diagnostic protocols (ADP), consisting of the periodic serial assessment of electrocardiograms and markers of myocardial injury to identify very low risk of coronary disease patients, have been established to adopt an early discharge conduct. (4)

The inclusion of high-sensitivity troponins has been an important landmark in the development of these protocols, as they allow the fast and safe detection of apparently healthy patients, (5) denoting a high negative predictive value (NPV) for the diagnosis of acute myocardial infarction, reducing the time of diagnosis and increasing by 4% the sensitivity compared with conventional troponins. This has improved the possibility of rapidly and safely defining patients' condition. (6) Normally, ADP classify patients for study in the following groups: those of very low probability (rule out), those of low or intermediate probability (rule-in) who are hospitalized for stratification, and those of high probability, considered non-ST-segment acute coronary syndromes (NSTE-ACS), who are managed accordingly. (7,8) Generally, the focus has been placed in achieving a greater proportion of cases safely classified as rule out, which implies the successful discharge that is met when the percentage of events in discharged patients is below 1% in the following 30 days. (9,10)

Three recent guidelines highlight the importance of using these protocols: the English National Institute for Health and Care Excellence guideline for the use of high sensitivity tests for the early discharge of NSTE-ACS, (11) several American Societies of Cardiology, Emergency and Imaging guidelines for chest pain assessment and diagnosis, (12) and the European guidelines for NSTE-ACS diagnosis and treatment. (13) In light of this situation, we carried out a systematic review of randomized clinical trials evaluating ADP using high-sensitivity troponins to assess chest pain in patients presenting at the emergency room with suspected NSTE-ACS.

METHODS

Inclusion and exclusion criteria

Randomized clinical trials (RCT) published in English, evaluating ADP to manage patients with chest pain and suspected NSTE-ACS in the emergency services, that used high-sensitivity troponins and reported clinical events as early discharge (within 4 to 6 hours after admission to the emergency room), major cardiovascular events (MACE), and length of hospital stay were included. Studies whose protocols did not have early discharge as endpoint, those considering the concomitant use of other biomarkers, and those evaluating troponin only once after admission were excluded. Also, studies published as poster or abstracts, as well as duplicate reports were excluded from the analysis. Titles and abstracts of studies identified were independently screened by two authors (JCB and JEH); the final decision of eligibility was given by consensus and disagreements were resolved by a third investigator (JJS).

Study search and selection

A search of the literature was carried out in three databases: MEDLINE, Cochrane and EMBASE. The terms used for the search were those grouping the following key words: chest pain, acute coronary syndrome, accelerated diagnostic protocols, 0/1-, 0/2- and 0/3-hour protocols, high-sensitivity troponin, emergency department, risk stratification, rule-out strategies and fast confirmation. Figure 1 shows the search strategy. The search was updated on February 20, 2023.

Data collection

Information was independently collected by two reviewers (GEH and JAG) using a format in which the information collected from the studies was recorded: authors, publication year, center or centers where the studies were performed, study design and methodology, number of randomized patients in each group, as well as effectiveness taking into account 30-day, 6-month or one-year MACE, early discharges, length of hospital stay and data for building a 2 × 2 table to calculate the operative characteristics for the detection of infarction or death at 30 days.

Risk of bias assessment

Two reviewers (GEH and JAG) independently performed risk of bias assessment of the studies using the checklist of the Cochrane collaboration. (14) The points assessed included random sequence generation, concealment, blinding, incomplete output data, selective output report and other biases. They were classified by judgement as low, intermediate or high risk of bias creating graphical descriptions and summaries. The decision was taken by consensus and disagreements were resolved by a third investigator (JPA).

Statistical analysis

Considering the study methodological heterogeneity assessed using the I2 test and the concept resulting from the individual evaluation of studies under a clinical orientation, it was seen that they were not comparable, and therefore, we decided against a statistical combination of results (meta-analysis).

The number of events and the total population of each study were recorded in 2 × 2 tables to calculate the operative characteristics for the presence of 30-day MACE outcomes for the different protocols in the cases in which this information was available in the articles.

The present systematic review is registered as PROSPERO CRD42021255495.

RESULTS

Initial screening identified 3509 studies, among which 5 met the inclusion criteria. Figure 1 shows the selection process and Table 1 summarizes the methodological characteristic of the studies included. (15-19). These studies used three types of high-sensitivity troponin: two Abbot TnI, (16,17) one Siemens TnI (18) and two Roche TnT (15,19). Three studies compared

ADP versus standard management (15,16,18) and the other two compared different protocols. (17,19) One work was a pilot study with a small number of patients; (15) and only one was a multicenter trial (RAPID-TnT), which included the highest number of patients and was proposed as a non-inferiority study.

Main effectiveness outcomes

The five studies described the outcomes of early discharges, 30-day MACE and length of hospital stay (Table 2). (15,19) In the three trials comparing a protocol versus standard care, the use of ADAPT, HEART and MACS protocols evidenced higher percentages of early discharges versus standard care. In the study comparing two protocols, the EDACS trial showed higher percentages of early discharge compared with the ADAPT trial (41.6% vs. 30.5%, respectively). (17) In the RAPID TnT trial, the 0/1-h and ESC 0/3-h protocols reported effective early discharge rates of 45% and 33%, respectively. (19) Among the studies comparing protocols (ADAPT and HEART) versus standard care and which reported length of hospital stay in hours, the protocols significantly reduced these times: 6 vs. 20 hours and 9.9 vs. 21 hours, respectively. The operative characteristics of the intervention regarding 30-day MACE for each study (Table 3) demonstrate a reduced rate of false negatives, high sensitivity and high negative predictive values in all the protocols evaluated.

Risk of bias assessment

Most studies presented an intermediate risk classification, mainly due to the difficulty of blinding the intervention. Only one study could appropriately blind the intervention (15) (Table 4).

DISCUSSION

This systematic review identified a small number of RCT in which the safety of ADP application was demonstrated with a clear decrease in the length of hospital stay. The results distinctly demonstrate that the different protocols are more effective in identifying patients who are candidates for early discharge compared with standard care, as well as for the reduction of hospital stay. The discussion that we will carry out below will focus on the analysis of each of the protocols used in the various studies.

0/1 hour protocols: The results seen in the RAPID-TnT study showed that 72% expected early discharges and 45% effective discharges were achieved with a

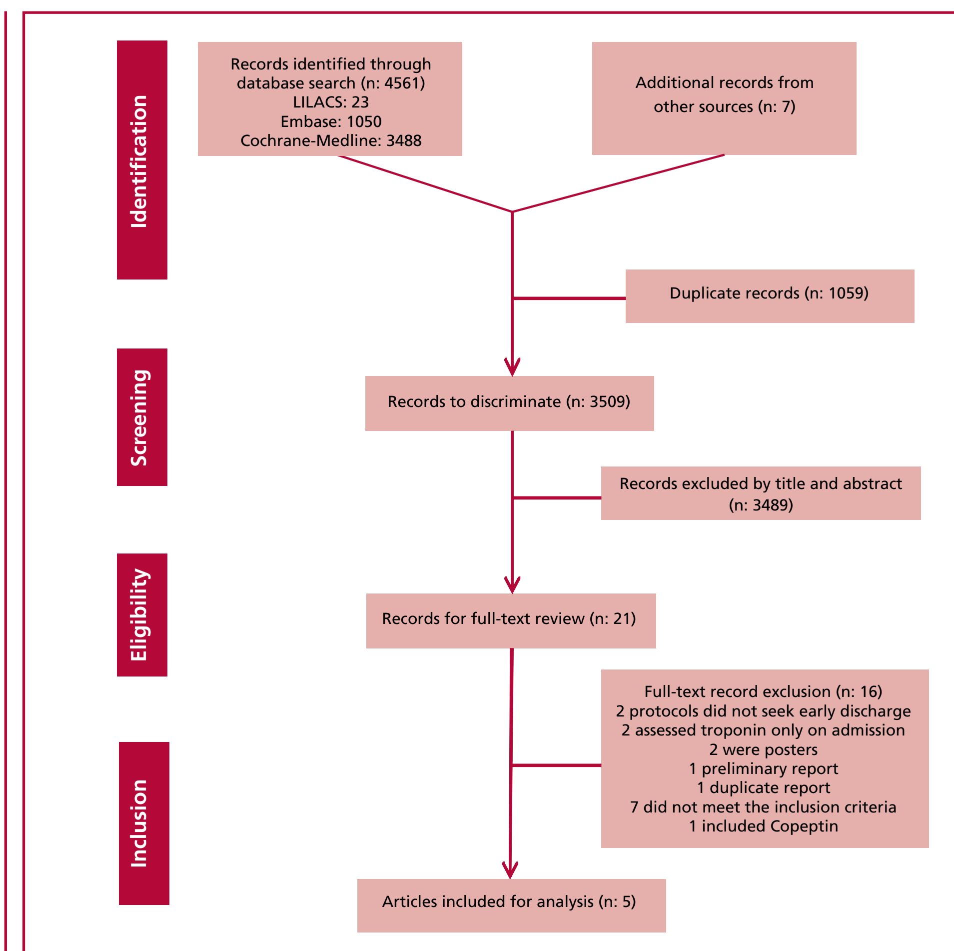

Fig. 1. PRISMA flow diagram of articles included in the study

Table 1. Summary of methodological characteristics of studies included in the systematic review

Study	Protocol	Type of study	Number of patients	Type of troponin	Primary outcome	Other outcomes
Than, 2014 (16)	ADAPT Standard care	Single center	544	Abbott Architect high-sensitivity troponin I (hs-cTnI)	Successful early discharge (6 hours)	MACE on admission and at 30 days
Mahler, 2015 (18)	HEART Standard care	Single center	282	ADVIA Centaur platform TnI-Ultra™ assay (Siemens)	Rate of objective cardiac tests within 30 days of presentation	(1) Successful early discharges (2) length of hospital stay (3) recurrent emergency visits and non-indexed hospitalization at 30 days.
Than, 2016 (17)	EDACS ADAPT	Pragmatic single center	560	Abbott Architect high-sensitivity troponin I (hs-cTnI)	Successful early discharge (6 hours)	Proportion of low-risk patients and 6-month MACE
Body, 2017 (15)	MACS Standard care	Single center	60	hs-cTnT; Roche Diagnostics Elecsys and heart type fatty acid binding protein	Successful early discharge (4 hours)	30-day, 3- and 6-month MACE and length of hospital stay
Chew, 2019 (19)	0/1 hour protocol ESC 0/3 protocol	Non-inferiority multicenter	3288	hs-cTnT; Roche Diagnostics Elecsys 5th generation	30-day MACE	Length of hospital stay; percentage of early discharges.

ADAPT: Accelerated Diagnostic protocol to Assess Chest Pain using Troponins
EDACS: Emergency Department Acute Coronary Syndrome
HEART: History, ECG, Age, Risk factors, Troponin
MACE: Major Adverse Cardiovascular Events
MACS: Manchester Acute Coronary Syndrome

Table 2. Effectiveness results of the different protocols used in the studies

Study	Protocol	Early discharge	30-day MACE	6-month MACE	Average length of hospital stay
Than, 2014 (16)	ADAPT	52 (19.3%)	1	N/R	6 hours
	Standard care	30 (11.0%)	0	N/R	20 hours
Mahler, 2015 (18)	HEART	56 (39.7%)	0	N/R	9.9 hours
	Standard care	26 (18.4%)	0	N/R	21.9 hours
Than, 2016 (17)	EDACS	133 (41.6%)	0	N/R	6 hours
	ADAPT	90 (30.5%)	0	N/R	6 hours
Body, 2017 (15)	MACS	17 (26%)	3	6	1 day
	Standard care	5 (8%)	3	5	1 day
Chew, 2019 (19)	0/1-hour protocol	Effective: 748 (45%) Expected: 1187 (72%)	17 (1%)	N/R	4.6 (3.4–6.4) hours
	ESC 0/3-hour protocol	Effective: 545 (33%) Expected: 1493 (91%)	16 (1%)	N/R	5.6 (4.0–7.1) hours

ADAPT: Accelerated Diagnostic protocol to Assess Chest Pain using Troponins
EDACS: Emergency Department Acute Coronary Syndrome
HEART: History, ECG, Age, Risk factors, Troponin
MACE: Major Adverse Cardiovascular Events
MACS: Manchester Acute Coronary Syndrome
N/R: not reported

NPV of 99.6%. This result is consistent with a systematic review that included 11 014 patients from 10 cohorts, documenting an early discharge rate of 55% with Roche's high-sensitivity troponin, and greater than 50% for those of Abbott and Siemens with a NPV of 99. 9% for 30-day MACE. (20) In the TRAPID-AMI study, 63% early discharges were obtained among 1282 patients, with a NPV of 99.1%, (21) while in the HIGH-US Study of 2113 patients, 50.4% were discharged with a NPV of 99.7%. (22) Another meta-analysis that included 14 cohorts and 13 899 patients reported an aggregate result of early discharge of 54% and a NPV of 99.8%. (23) The application of this protocol has certain practical limitations since it is necessary to have fifth-generation high-sensitivity troponins that have been validated and whose cut-off values vary depending on each test. (24) According to the English NICE guidelines, 9 high-sensitivity troponin tests are currently validated for application in 0/1-hour protocols. (11)

ESC 0/3-hour protocol: The same RAPID-TnT study documented an expected early discharge rate of 92% with a NPV of 99.4% for the 0/3-hour protocol, the highest documented outcome for any protocol. It exceeds the aggregate result of early discharge of 66% and NPV of 98.7% reported by the previously mentioned meta-analysis on 9 works that included 10 237 patients, (23) and the highest report obtained for an individual cohort, 78.9% (961 of 1,218 patients) with a NPV of 97.9%. (25) However, if the results of effective early discharges of the RAPID-TnT trial are considered, the interpretation is different, taking into account the 33% obtained, lower than for the 0/1-hour protocol. This is also consistent with the results of the cohort presented by the Badertscher group, which compared the 0/1- and ESC 0/3-hour protocols among 2547 patients, with early discharges of 60% for 0/1-hour and 44% for 0/3-hour protocols. ($p<0.001$) with a NPV of 99.8% and 99.7%, respectively. (26) A third study on 1920 patients found that early discharges for the 0/3-hour protocol could reach 65%, although their NPV was lower than that of the 0/1-hour protocol

Table 3. Operative characteristic results for the diagnosis of the different protocols used in the clinical trials

Study	Protocol	Sensitivity	Specificity	Precision	PPV	NPV	LR+	LR-
Than, 2014	ADAPT	97.9	22.9	35.9	21.1	98.1	1.270	0.090
(16)	Standard care	100.0	12.6	23.9	14.4	100.0	1.145	0.000
Mahler, 2015	HEART	100.0	49.3	51.8	9.3	100.0	1.971	0.000
(18)	Standard care	100.0	23.5	28.4	8.2	100.0	1.307	0.000
Than, 2016	EDACS	97.3	47.5	54.1	22.1	99.1	1.854	0.057
(17)	ADAPT	100.0	34.0	40.9	14.9	100.0	1.515	0.000
Body, 2017	MACS	100.0	27.0	30.3	6.1	100.0	1.370	0.000
(15)	Standard care	100.0	8.1	12.3	5.0	100.0	1.088	0.000
Chew, 2019	0/1-hour protocol	88.1*	94.7*	N/A	38.2*	99.6&	16.5*	N/A
(19)	ESC 0/3-protocol	N/A	N/A	N/A	N/A	99.4&	N/A	N/A

* for rule in
& for rule out
PPV: Positive predictive value, NPV: negative predictive value, LR: Likelihood ratio, N/A: not applicable
ADAPT: Accelerated Diagnostic protocol to Assess Chest Pain using Troponins
EDACS: Emergency Department Acute Coronary Syndrome
HEART: History, ECG, Age, Risk factors, Troponin
MACE: Major Adverse Cardiovascular Events
MACS: Manchester Acute Coronary Syndrome

Table 4. Risk of bias assessment

	Than, 2014	Mahler, 2015	Than, 2016	Body, 2017	Chew, 2019
Random sequences	•	•	•	•	•
Allocation concealment	•	•	•	•	•
Intervention blinding	•	•	•	•	•
Blinding of outcome	•	•	•	•	•
Incomplete outcome data	•	•	•	•	•
Selective reporting	•	•	•	•	•
Other biases	•	•	•	•	•

Black mark: Low risk of bias
Grey mark: Intermediate risk of bias

(98% vs 99%). (27)

Undoubtedly, the issue is under discussion and the definitions of expected and effective early discharges influence the interpretation of results.

EDACS protocol: It reported 42% early discharges, with 99.1% NPV, (17) a slightly lower result than that seen in the cohort study of the same research group, which reported 51% early discharges and 99.6% NPV (28). Other validation cohort studies documented possible early discharges of 66.7% (29), 41.6% (30), 35.2% (31), and 58.1% (32), all with NPV higher than 99%. These findings confirm good performance for this protocol along with a high degree of safety.

HEART protocol: the RCT in which it was evaluated obtained 39.7% early discharges with a NPV of 100%; (18) it also had a one-year follow-up in which MACE was documented in 9.9% in the HEART arm vs. 11.3% in the standard care group (p=0.85). (33) A validation cohort found early discharge rates of 38.4% with a NPV of 99.6 %. (32) Another publication questions the safety of this protocol by documenting a NPV of 98.1% with a possible early discharge rate of 33.2% (264/794). (34)

ADAPT protocol: it was evaluated in two clinical trials with an early discharge rate of 19.3% and 30.5% and a NPV of 98.1% and 100%. One of the validations for this protocol by the Than group (2012), prior to the use of high-sensitivity troponins, found a possible early discharge rate of 20% with a NPV of 99.7%. (35) A subsequent validation , with high-sensitivity troponin, reached a possible early discharge rate of 19.6%, with a NPV of 99.7%.(36) These results are consistent with what is documented in this systematic review and questions its clinical usefulness, especially taking into account that in one of these studies better results were obtained with the comparator protocol, EDACS.

The decision to exclude two recently published randomized clinical trials should be especially mentioned. Both trials evaluated the rule out strategy based on undetectable levels in patients presenting within the first 6 hours of symptoms. The reason for exclusion was that it was not considered it could be applied to all emergency patients, and it is therefore a study of troponin rather than an ADP, although its results are worth presenting as they are part of the initial strategy of the 0/1-hour protocols: the first was a study that included eight centers in England and Wales, which obtained a 4-hour early discharge rate of 141/309 (46%) patients compared with 114/311 (37%) for standard care. (37) The second was the HiSTORIC (High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction) study, which included 31 492 patients from 7 hospitals, reduced the length of hospital stay by 3.3 hours and hospital admissions by 59%; non-inferiority was not demonstrated, but the observed differences in myocardial infarction or cardiac death at 30 days and 1 year favored the early rule-out pathway over standard care. (38)

The proliferation of ADP makes us carry out a careful exercise to select the one that adapts to the daily environment of work in the emergency room. Although guideline recommendations seem to favor protocols that focus on fixed high-sensitivity troponin values and their variations at 1, 2, or 3 hours of admission, and do not include clinical prediction rules, we must make the caveat that it is necessary to have a troponin that has been evaluated for the selection of cut-off values and the training of staff so that they become familiar with its implementation. We should note that the 2020 European NSTE-ACS guidelines (13) removed the ESC 0/3-h protocol from their recommendations based on the results of three previously discussed large cohorts (25-27) under the assumption of lower efficacy and safety. What is stated in this review shows that the results are still contradictory and that it is necessary to continue exploring the safety of the ESC 0/3-h protocol.

The high complexity of the problem in question becomes a limitation of this work. Although we guided the discussion towards the safe discharge of patients, the issue of cost-effectiveness, which is tangentially addressed in the studies presented, is beyond discussion. We must note that the approach to chest pain does not end at this point and the evaluation of intermediate probability cases that must be hospitalized implies a series of additional steps not covered by this study.

CONCLUSIONS

The use of ADP in chest pain provides consistent evidence on the possibility of achieving early discharge with a very low rate of major cardiovascular events, as well as a benefit in significantly reducing the length of hospital stay, which decreases overcrowding emergency services, and allows more efficient use of health resources. The results seem to favor the 0/1-h and ESC 0/3 h protocols in accordance with current recommendations.

Conflicts of interest

None declared.

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

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OPINION ARTICLE

Contributions to the Understanding of the Current Problems of the Doctor-Patient-Technology Trilogy

Aportes a la comprensión de la problemática actual de la trilogía médico-paciente-tecnología

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INTRODUCTION

The current need of reassessing the clinical act becomes essential in the context of the humanistic crisis concerning the evolution of knowledge, which should not only be considered an anthropological situation but also an epistemological one, as medicine is isolated from the cognitive condition of the rest of the sciences. This reality makes the current doctor a disoriented being; even in the face of such an essential fact, as is the clinical act. (1)

The progress that medicine has experienced in the last half century can be summarized in two points of reference: 1) the technological advance at the service of diagnosis and therapeutics; 2) the collectivization of medical care. However, this remarkable development was carried out in violation of the pillar of medical art, the doctor-patient relationship. (2)

Obviously, the current clinical act must be articulated in a trilogy made up by the doctor, the patient and technology. The latter, a fundamental tool in diagnosis, must be understood as complementary to the doctor-patient relationship, as a support and not with exclusive profiles of the other two actors.

APPROACH TO THE TOPIC

There is nothing as moving as the sight of a sick person. The moral damage caused by the disease is equal to or greater than the physical one. Anguish stirs in his bowels. This man hides his illness as the last bastion against the inexorable. He disguises his disease. Given this situation, how can the doctor-patient relationship be downplayed with the surge of technology and algorithms in medicine?

The relationship between consciousness and matter implies a friction between the doctor and the organic-psychic-social-ecological system that constitutes a sick being. In this aspect, a humanistic science such as medicine can profit from complementary sciences, and it even needs to incorporate consciousness as an essential variable in its study and art. Here, in clinical medicine, lies a gap that includes its holistic understanding, the language before the patient, and the methodology. (3,4)

Obviously, the scientific observation of the phenomenology of consciousness does not have a defined connotation on the organic, but constitutes a process that is fundamentally ignored due to the difficulty of being assessable from a quantitative point of view. This concept recreates the doctor-patient relationship. The prevailing positivist medicine clearly interferes in the relationship between the doctor's consciousness (observing subject) and the body-mind-spirit integrity (5) that constitutes a patient (observed subject).(6-8) With an algorithmic clinical methodology, the phenomenology that implies the doctor-consciousness before the patient-consciousness is not taken into account.(9) At this point, the development of technology implies an essential approach for the most accurate and rapid diagnosis, as long as it does not constitute a divorce between the doctor and his patient by conferring it superlative properties.

There is a gap at this point that can only be solved in contact with the patient's integrity, in which it is possible to build the clinical concept that is perceived, but always referring to one's own mind. Its uniqueness cannot be excluded. This brings a closer vision of the clinical act to the diagnostic problem to be solved.

This communication between patient and doctor is promoted by a knowledge that is not absolutely conscious, but also has perceptive bases. Each being has its individuality to respond to the disease. The doctor possesses the knowledge to understand the patient's problems. And this instrument needs time and dedication. It is complemented by algorithms

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that are currently trying to unravel the pathology, as well as placing the technology as a determining action. This strategy can be a starting point, but never a final goal. In medicine, the sum of knowledge does not replace medical criteria. We need strategies that place us before the uniqueness of the patient with the necessary tools and enough time to act in accordance with human and medical ethics.

DISCUSSION

Reason and the logic of progress led to technical development. (10) Now, in the clinical act, has the patient´s knowledge and reality been maintained in the context of advances in instrumental technique? There is a mismatch in this evolution and the goal must be changed, since in the clinical act we are facing the alteration of a person's life and not only facing an organic disorder. Herein lies the conflict of postmodern medicine, which, albeit bringing together excellent faculties such as instrumental technification and collective assistance, has developed conveying difficulties:

1) The technification that distanced the patient from the doctor.
2) Super-specialized work, which, despite its benefits, bypasses the integral psycho-organic unity that should be formed with the patient.
3) An organization in which the doctor no longer has a direct contract with his patient, but rather a company that determines times, fees and possibilities, both for the doctor and for his patient. With this modality, the doctor has lost the freedom of his relationship with the patient´s history. (11)

In medical sciences we need to incorporate to the quantitative tools of probability, the responses to the disease by the patient´s consciousness. Therefore, the study of the physical structure of corporeity must be interrelated with the exploration of consciousness in the subject-patient during the medical act.

The observer must work with induction, intuition, observation and experience to incorporate clinical and biological physical-corporal measurements to less sensitive quantitative observations as are the answers of the conscience. Consequently, the experience gives a higher margin of approach to the singularity of the patient, a situation that is not feasible with only the physical and technological examination. (12)

At this point, the doctor needs more than technical knowledge to assess his patient. This position includes conditions that help the therapeutic process of the disease, as well as attributes in the patient's response to defend himself against the morbid (Table 1). From this it can be deduced that in this act of consciousness, between doctor and patient there must be: a) intentionality when referring to the patient and b) correspondence that must be achieved between the doctor and the patient. With intentionality, the object-patient (actually subject-patient) who also perceives, judges and decides, is constituted. For this perception it is necessary to observe from different perspectives. This intentionality is intrinsic to consciousness. (13, 14)

When we include the concept of *epoché* within medical conditions, we are provisionally canceling not only the certainties and theories that are naturally offered. An attempt is made to evade the dominant dogma in favor of the singularity of the patient. *Epoché* is the suspension of *a priori* judgment. This attitude must be complemented with *phenomenological reduction*, which allows us to put consciousness and its experiences before us. In the positivism of medical science there is a dogmatic and realistic assumption of a pro-theoretical nature. This makes it difficult to search for a different consideration of that reality with the concepts of *epoché and phenomenological reduction*. The latter tries to reach the hidden subjectivity of the patient, where he "*is*" independent of his correlation fabricated by the surrounding world. The phenomenology produced is a knowledge of the essence. Here, there is an intuition. Suddenly, this intuition passes from sensibility to understanding, as Husserl said: "*... every intuition that originally gives itself is a legitimate source of knowledge, everything that is originally presented to us in intuition must simply be accepted as it is, but also only within the limits in which it is given.”* (14)

CONCLUSIONS

This articulation deficit in the doctor-technology-patient trilogy is due to a series of causes that range from the phenomenology of consciousness between patient and doctor, through the interpretative deficit of these advances within a clinical context, to economic, social and political situations in medical practice. Obviously, this situation causes fractures in the doctor-patient association on a daily basis, to which is added the factor of technology, which should be interpreted as an aid to that relationship and not as an exclusive resource.(15) And this is of vital importance, since this relationship belongs to the consciousness between two people and to the "human factor" that we can define as the analysis of the emotional factors that impress the senses, those that are cause or contributors in the understanding of the processes that lead to the disease as well as its healing flow in man.

There is seduction by laboratory and imaging studies as if they alone could make the diagnosis be-

Table 1. Doctor-patient intersubjectivity. Capabilities

Doctor	Patient
Observation	Responsability
Perception	Behaviour
Epoché	Temperament
Phenomenological reduction	Corporeity
Dialectic	Dialectic

cause they are infallible. The fact that these tools are operator-dependent, that obey machine algorithms and that are an instant of the patient's health-disease complementarity is not taken into account. This situation has reached such an extreme that it has erased the practice of the clinical act with its postulates of observation, anamnesis and semiology, without considering the "human factor" or the possible level of randomness of all knowledge.

This leads to a polarity: clinic or technology? which causes a greater divorce between the patient´s psycho-physical-social integrity and the doctor´s act of caring. In this scenario, the uniqueness of each being disappears by becoming copies of a pathophysiological mechanism with the exclusion of individuality, forgetting the Hippocratic aphorism "there are diseases, but only in patients".

Actually, there should be no dilemma. The help provided by technological tools is beneficial to the clinical act. At this point, it is necessary for the physician to know how to investigate auxiliary procedures to achieve the diagnostic complementarities offered by semiology. Technology is not an isolated entity in the interpretation of elements that are added to the clinical act; in fact, it cannot decide by itself. Also, this does not lead to proper medical training. There should be no technological abuse in pursuit of a diagnosis. This does not improve or replace the clinical act, because unless properly interpreted, these studies can be misleading. An excessive value given to auxiliary procedures can lead to clinical error and neglect the "human factor", a pillar in medical practice.

The non-observance of the need for the clinical act and the inadequate interpretation in the auxiliary mechanisms implies that the error begins with the doctor. The analysis and synthesis of the clinical act are not always valued as fundamental, not only due to a lack of training, criteria or patience, but also due to the scarce time currently given by medical collectivization to the care of each patient. The clinical act in its semiological approach is not closed to the intelligence of the doctor, since this does not need any essential attribute nor does it demand exceptional virtues. Sometimes error happens, beyond doing the right thing to avoid it, surely because the information provided by the clinical act has been scarce or difficult to interpret.

The risk is to opt for the simpler path of technology, with less effort and perhaps avoiding the doctor´s "diagnostic anguish" when faced with the need to reach it. Clinical practice is strenuous, surprising, a path of study and interpretation of what is seen, heard and explored in the patient, before the eventuality that an image or numerical figures from the laboratory perform the magic that can do everything. Technology must be accessory in the clinical act, before it the doctor must take into account fundamental questions: and the human factor? the mind and the spirit? Clinical practice needs experience. Sometimes it is elusive, it is necessary to "reinterrogate the signs", over and over again. When we leave the clinical act aside, we only interpret the “reality of the machine”, not that of the patient.

Where is it proposed that anamnesis, observation and semiological maneuvers became trivial before the machines? From a lack of technical and anthropological medical training, from easiness in the face of effort, need for a number of patients in a limited time?

This position supported in the previous paragraphs is far from ignoring the importance of technological means in patients; it only seeks to incorporate them within the framework of the relationship and clinical judgment essential in a humanistic science. In this way we will be harmonizing technological progress with medical science in a deeply human act as a doctor does before a sick person. It is up to the doctor, almost an archaeological piece called "general practitioner", to interpret the studies in relation to his patient and not be bewitched by the numbers that technology offers him. This has perfected these interpretations, but its mistakes can be fatal in the absence of the clinical act.

Ultimately, anthropological medicine deals with not including the patient within an algorithm, but building an algorithm in each patient.

Conflicts of interest
None declared.
(See authors’ conflict of interests forms on the web).

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Thrombi in Both Atria Detected by Cardiovascular Tomography in a Patient with Atrial Fibrillation

Trombos en ambas aurículas en paciente con fibrilación auricular detectados por tomografía cardiovascular

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An 84-year-old female patient with a history of hypertension, diabetes, stroke and atrial fibrillation under anticoagulant treatment with acenocoumarol presented with severe aortic stenosis (peak gradient 74 mmHg, mean gradient 44 mmHg, area 0.6 cm^2) and mildly depressed global left ventricular function. A cardiovascular tomography was performed to schedule a transcatheter aortic valve implantation (TAVI).

The study showed filling defects in early and late phases contrast-enhanced images in the roof of the right atrium near the atrial appendage and in the left atrial appendage, consistent with thrombi (Figures 1 and 2).

Thrombosis of the left atrial appendage is frequent in atrial fibrillation, and its prevalence (up to 8% with anticoagulant therapy and 5-27% without) depends largely on the studied population. However, thrombosis of the right atrial appendage is rare (estimated at 0.6-0.75%), and its incidence is lower due to its anatomy (more open and with less potential for blood stasis –"remora phenomenon"– than the left one) and to a search performed less systematically as well as difficulties in evaluating its structure.(1) However, autopsy studies suggest that the prevalence of thrombosis in both atria is similar.(2)

Cardiovascular tomography is an excellent tool to evaluate atrial thrombosis, which is observed as a defined structure with clear borders generating filling defects both in early and late phases after the contrast agent is administered (it distinguishes from the remora phenomenon in which defects in early phases are corrected in late phases). It has very high sensitivity and specificity for the detection of thrombi in the left atrium.(3) However, in some cases, it is difficult to achieve an adequate contrast in the right chambers, mainly the right atrial appendage, by using imaging to evaluate "left structures" (coronary arteries, pulmonary veins, valves); thus, right atrial thrombosis may be undetected. The low signal in Hounsfield units on non-contrast-enhanced tomography or the Hounsfield units ratio between thrombus and the aorta using dual-source equipment (4) may be helpful in identifying atrial thrombosis by cardiovascular tomography.

Conflicts of interest

None declared (See authors' conflicts of interest forms on the website).

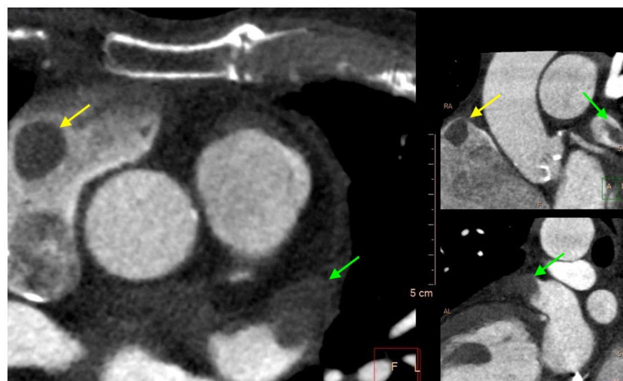

Fig. 1. Early phase contrast-enhanced images. Filling defects consistent with mass in the roof of the right atrium (yellow arrow) and distal body of left atrial appendage (green arrow).

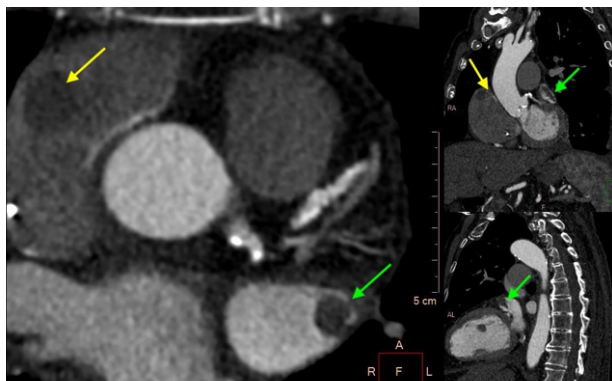

Fig. 2. Late phase contrast-enhanced images. Defect persistence in both atria

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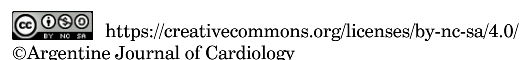

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Hybrid Strategy. A Novel Method for the Management of Complex Congenital Heart Diseases

Bicuspid aortic valve is a congenital cardiac defect, involving a wide range of presentations, from aortic valve stenosis with severe cardiac failure in the newborn, to aortic dissection in the adult, or remaining unnoticed throughout life without requiring any treatment.

We present the case of a preterm patient with prenatal diagnosis of bicuspid aortic valve with severe stenosis. On admission, physical examination shows tachypnea and retraction, pale-cyanotic coloring, heart rate of 187 beats per minute, single S1 and S2, 2/6 systolic aortic murmur, symmetric brachial and femoral pulses, prolonged capillary filling >3 seconds, blood pressure 65/49 mm Hg and SpO_2 78%. Chest X-ray presents cardiomegaly and pulmonary edema. Mechanical respiratory assistance is initiated and prostaglandins are administered. Color Doppler echocardiography shows critical aortic stenosis with severe left ventricular dysfunction (Figure 1A).

At 18 hours of life, combined cardiac catheterization and aortic valvuloplasty with 6.0 × 20 mm Tylshak Mini hybrid balloon is performed through right carotid access (dissection) (Figure 1B). On the fourth day the echocardiogram evidences 16 mm Hg peak transaortic gradient with mild aortic regurgitation, and wide interatrial communication and patent ductus.

Hemodynamic instability with multiple organ failure (kidney failure, intraventricular hemorrhage and supraventricular tachycardia) persists from the fifth to the thirteenth day of life. Without clinical improvement, bilateral cerclage with polytetrafluoroethylene (PTFE) band is performed (Figure 1C) and the hybrid procedure is completed 48 hours later (reopening of the sternotomy and 1.7 mm Type E Krichenko stent implantation in the ductus).

At 5 days of treatment, the echocardiogram reveals decreased cardiac diameters, biventricular hypertrophy with improved function in both ventricles, and increased gradient through the cerclages and at the left ventricular outflow tract level due to improved function.

Three months after the hybrid procedure, percutaneous cerclage removal (Figure 2A and 2B) and ductal stent occlusion (Figure 2C) are carried out.

Neonatal critical aortic stenosis, in which the immature myocardium faces an abrupt increase in afterload, generates greater wall stress with left ventricular dilation, instead of the compensatory hypertrophy encountered in older children. The increased end-diastolic volume and pressure alter coronary flow producing diastolic dysfunction. (1,2) There are problems in the immature neonatal myo-

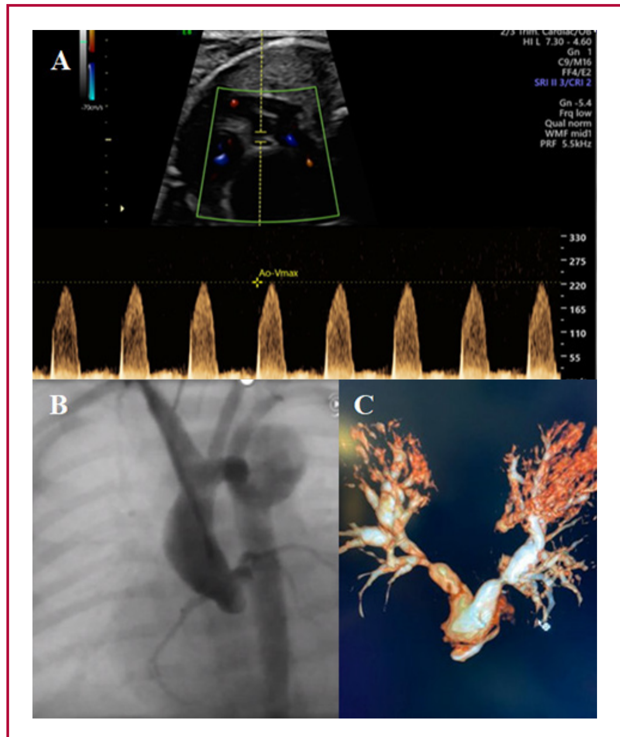

Fig. 1. Doppler echocardiography showing critical aortic stenosis (A). Angiography through carotid access post aortic valvuloplasty (B). Angiographic reconstruction of surgical cerclage in both pulmonary branches (C).

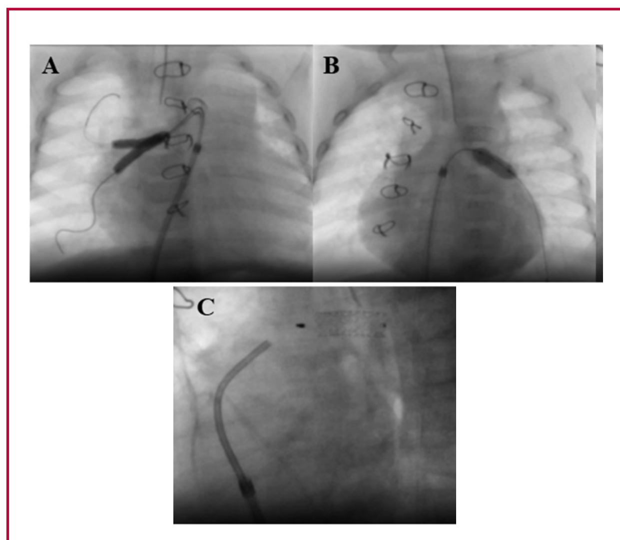

Fig. 2. Angiography. Dilation of both pulmonary branch cerclages (A and B). Percutaneous ductal stent occlusion (C).

cardium, a) structural: myocyte precursors replicate and increase in number (hyperplasia), but not in size (hypertrophy), myofibrils are disorganized, there is scant presence of the T tubule system and mitochondrial sarcoplasmic reticulum, high DNA concentra-

tion and predominance of non-contractile elements; b) biological, such as lower sarcoplasmic reticulum calcium uptake and lower density of alpha and beta receptors; and c) metabolic, as the preferred use of glucose as energy source. (2)

The hybrid approach in refractory heart failures of different etiology is a therapeutic alternative, consisting of bilateral cerclage in pulmonary branches, generation of a non-restrictive interatrial communication and ductal stent implantation. (3,4) Pulmonary cerclage increases contractility on the right ventricle (RV) (Anrep effect), producing hypertrophy and the capacity of myocyte regeneration in an immature heart, and improved right ventricular diastolic filling. (3,4) Biological and genetic changes at the level of the fibers shared by both ventricles (co-hypertrophy) may restore electromechanical synchrony between the two ventricles and ventriculoarterial coupling. (5)

The hemodynamic evolution post valvuloplasty can sometimes be unfavorable due to abnormal ventricular remodeling, with unexpected clinical consequences. The hybrid approach is a very useful novel technique for different pediatric heart failure scenarios which cannot be managed from a clinical point of view, or as bridge to transplantation. This approach activates various physiological mechanisms, producing a relevant balance between pressures, flows and resistances, corroborated by computational studies of flow dynamics. (6)

Conflicts of interest

None declared.

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Ethical considerations

Not applicable.

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From Cardiopulmonary Arrest to Extracorporeal Membrane Oxygenation in Pulmonary Thromboembolism: An Inter-Hospital Work

The pulmonary thromboembolism (PTE) is a prevalent entity that involves patients with a wide range of ages and comorbidities. It can affect young patients without relevant comorbidities, and cause a great impact in terms of morbidity and mortality. High-risk PTE implies the highest mortality, especially in those who present with cardiopulmonary arrest (CPA). In addition, a significant percentage of patients show severe symptoms or hemodynamic decompensation on admission or during their progress. The indicated strategy in these patients is the immediate reperfusion. Nowadays, the most widely supported strategy is the systemic thrombolysis, leaving surgical treatment –either surgical embolectomy or venoarterial extracorporeal membrane oxygenation (VA-ECMO)– as a second option when medical treatment fails or is contraindicated. However, data from experienced centers suggest that surgical techniques are safe and effective. The following is a case report of a patient with massive PTE and CPA, in which two centers worked together in pursuit of ventricular support as a rescue therapy.

We present the case of a 39-year-old male patient, with no risk factors or cardiovascular history, who reported an Achilles tendon surgery 45 days prior to his consultation. He came to the Emergency Department after having experienced an episode of sudden dyspnea associated with syncope without prodromes and traumatic brain injury (TBI) at home. During his stay in the Emergency Department, he presented a new syncopal episode. A Doppler transthoracic echocardiography (TTE) was performed (Figure 1) which showed dilatation of the right chambers; this, together with the recent history of trauma surgery, led to the suspicion of PTE. He immediately experienced a CPA, so advanced cardiopulmonary resuscitation maneuvers were performed and, based on his history of TBI, it was decided to start a percutaneous treatment by thromboaspiration and local thrombolysis. The patient progressed to hemodynamic instability so, after ruling out intracranial hemorrhage by computed tomography, systemic

thrombolytics were administered. However, the patient remained in refractory shock despite the administration of vasoactive drugs at maximum doses. Contact was established with a High Complexity Center and the mobile ECMO team was activated. Once the coagulopathy was stabilized, the patient received venoarterial ECMO at the first center and was subsequently transferred to the High Complexity Center. On admission, the patient was hemodynamically unstable, received ventricular and respiratory support and required maximum doses of noradrenaline, vasopressin and milrinone; laboratory tests showed acute kidney and hepatic injury, metabolic acidosis with hyperlactacidemia and marked coagulopathy. The values of high-sensitivity troponin T and NT-proBNP were 6700 ng/L and 480 pg/mL, respectively. The electrocardiogram (Figure 2) showed sinus tachycardia and the chest X-ray showed cardiomegaly and overt signs of bilateral flow redistribution. During the first 24 hours the patient remained in a mixed type of shock (both cardiogenic and vasoplegic) requiring vasoactive drugs, with multiorgan failure and marked coagulopathy; then, post cardiac arrest care, hemodynamic support, and internal correction with ventricular support were implemented. After the critical fibrinogen values were stabilized, an anticoagulant treatment with sodium heparin administered by continuous IV infusion was initiated and adjusted to anti-factor Xa values. His progress was favorable, the vasoactive drugs were reduced, and right ventricular function improved according to the TTE, so at 72 hours the ECMO weaning test was performed, and it was decided to withdraw circulatory support with no complications. The patient remained under orotracheal intubation, with intact neurological response and good urinary volume with response to intravenous diuretics (despite elevated serum creatinine levels with a peak of 10 mg/dL, but without requiring hemodialysis); therefore, 7 days after admission, the patient was successfully extubated. Subsequent exhaustive kinetic motor and respiratory rehabilitation was performed; antiphospholipid syndrome and other thrombophilias were ruled out; negative fluid balance with forced diuresis at the expense of furosemide was performed with good response, so the patient was transferred to his center of origin to continue with the rehabilitation in the general ward, with an ECG evidencing increased voltages (Figure 2) and a TTE showing completely normalized biventricular function.

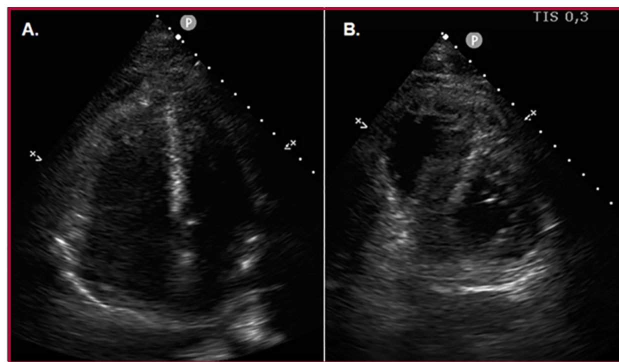

Fig. 1. Transthoracic echocardiogram on admission. A. End-systolic apical four-chamber view. Marked dilatation of right chambers. B. Parasternal short axis. Right ventricular enlargement with flattening of the interventricular septum.

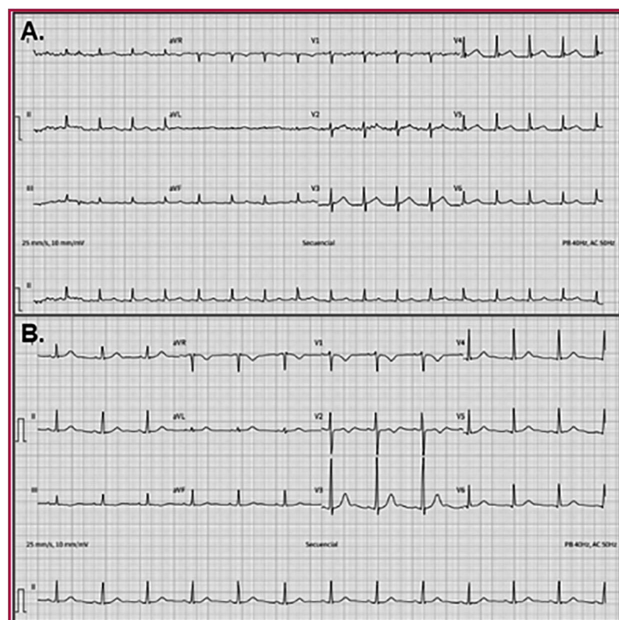

Fig. 2. A. Electrocardiogram on admission showing sinus tachycardia. B. Electrocardiogram at discharge showing sinus rhythm, normal heart rate with increased voltages in general and a more marked difference in right precordial leads.

The PTE is a life-threatening condition, so it is a cardiovascular emergency, with an annual incidence of 70 cases per 100 000 inhabitants. (1) It is the third leading cause of cardiovascular death, following myocardial infarction and stroke. (2,3) Mortality from massive pulmonary embolism is around 30%, while in those who experience cardiopulmonary arrest it can be near 95%. (4) Current clinical practice guidelines recommend immediate reperfusion therapy in patients with high-risk PTE: in patients with hemodynamic decompensation, systemic thrombolysis is recommended, leaving invasive methods (surgical or percutaneous embolectomy or ventricular support) in a second place whenever the former is contraindicated or fails. (5) However, in High Complexity Centers with wide experience in surgical methods (embolectomy and VA-ECMO), by implementing such methods mortality has been drastically reduced in patients with massive PTE, including those who have experienced cardiorespiratory arrest, to whom ECMO is indicated with a mortality rate near 25%. (2,3) Therefore, in a setting like ours, it is essential to create multidisciplinary and multicentre teams

to allow, firstly, early detection of high-risk PTE patients and, secondly, the implementation of action strategies according to each patient, such as referral to high complexity and experienced centers, and, in case of being a candidate, to perform ventricular support or surgical embolectomy when indicated. Thus, by establishing interhospital networks which quickly identify and respond to these needs, the morbidity and mortality associated with this high-risk subgroup could be reduced. Furthermore, a paradigm shift in the management of these patients could be considered, since surgical techniques could be implemented as the initial therapy in the centers where they have been developed, instead of using the rescue therapy, as they do at present, thus achieving a favorable impact on these patients' progress. These could become worldwide guidelines in the future, which in our setting are not yet reproducible. However, with the potential existence of reference centers that centralize referrals of patients requiring surgical salvage therapy from surrounding centers, in the future it could be implemented as the initial therapy according to the experience.

Conflicts of interest

None declared.

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

Ethical considerations

Not applicable.

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Dysphagia – an Uncommon Presentation of a Rare Pacemaker Implant Complication

We present a case of a 63-year-old patient admitted to the emergency room (ER) for complaints of dysphagia. He reported a left-sided neck distension which later affected his capacity to eat appropriately. These symptoms appeared after a pacemaker implantation for second-degree atrioventricular block, two weeks prior. There were no symptoms of heart failure, syncope, pre-syncope, palpitations, dizziness, constitutional symptoms, or fever. The physical examination showed a cervical asymmetry, with a distended left side, associated with local warmth, and discrete asymmetry between the right and left arms. The rest of the physical examination was unremarkable. The patient has a history of schizophrenia, depression, and dyslipidemia. Following an invasive procedure, the authors suspected an infection related to the procedure as the point of origin.

The patient underwent a computed tomography (CT) scan that reported thrombosis of the left internal jugular vein, with occlusion of the left brachiocephalic and subclavian veins (shown in Fig. 1). There was no evidence of collections/abscesses. A brief transthoracic echocardiography was performed in the ER, which rose the suspicion of thrombus/endocarditis. The subsequent transesophageal echocardiogram documented a thrombus adherent to the pacemaker leads. There was an equivocal image of vegetation. Blood cultures, blood panel with C-reactive protein (CRP) and procalcitonin (PCT) were collected. The patient was also scheduled for a repeat CT for evaluation of pulmonary embolism.

Anticoagulation was immediately started with low molecular weight heparin (LMWH). Blood cultures and PCT were normal. There was no evidence of pulmonary embolism on the new CT scan.

After treatment with LMWH for a week, there

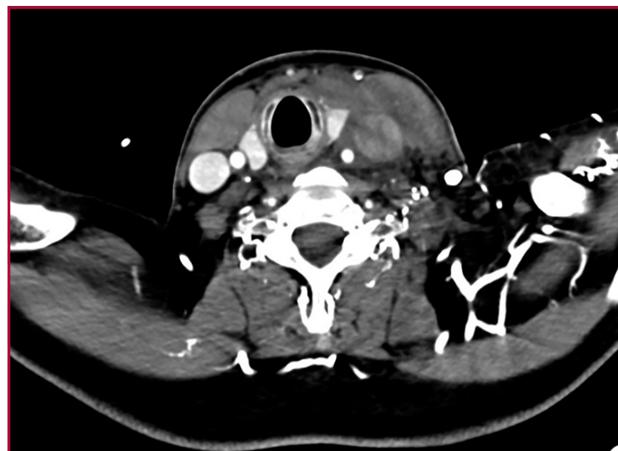

Fig. 1. **CT scan – axial plane**. Carinal shift due to jugular vein thrombosis and ipsilateral edema.

was a complete resolution of the thrombus (shown in Fig. 2). The patient was also seen in the immunohemotherapy clinic, and thrombophilia was discarded. After a 12-month follow-up, the patient remains asymptomatic and generally well.

Reported permanent pacemaker complications are mostly related to the risk of infection and thrombosis and embolic events. Other rarer complications also described are beyond the scope of this scientific letter. (1) Serious thrombotic events related to pacemaker implantation have been described, with an incidence from 0.6% to 3.5%. These serious events include heart failure presentation and pulmonary thromboembolism. (2) Nevertheless, clinically asymptomatic thrombus appears to be much more frequent, with an incidence of up to 35-45% in the same cohorts. (3) The symptomatic cases can be present in the acute, subacute or delayed setting, varying from days to years after lead implantation. (2,4) In the acute setting, there seems to be a hypercoagulable state and endothelial trauma that favors thrombosis. (5) There is no consensus on a therapeutic strategy and follow-up of the patient with symptomatic lead-induced thrombosis. There are some cases when oral versus intravenous medical therapy is discussed, as well as mechanical thrombectomy and thrombolysis, mostly in acute cases. (2)

We report on a case of an atypical presentation of thrombosis with the most prominent symptom being dysphagia. Early echocardiographic evaluation and therapy can be essential to prevent, avoid and improve clinical outcomes in these patients with no need for interventive action. We aim to bring to the reader's attention that acute pacemaker thrombosis is an entity that requires medical community awareness to an early diagnosis and prevent worse outcomes. Atypical presentations should not be disregarded and time from an intervention should raise our suspicion of its connection. Not everything attached to a lead or related to a recent intervention is a vegetation.

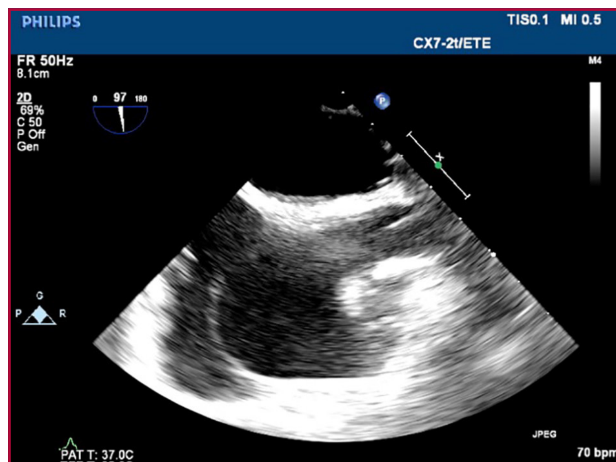

Fig. 2. Transesophageal echocardiography bicaval plane. Post anticoagulation image of the pacemaker leads, without evidence of thrombus

Conflicts of interest

None declared.

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

Ethical considerations

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Semaglutide in the treatment of patients with heart failure with preserved ejection fraction and obesity. STEP-HFpEF study

Kosiborod MN, Abildstrom SZ, Borlaug BA, Butler J, Rasmussen S, Davies M et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. **N Engl J Med 2023. https://doi.org/10.1056/NEJMoa2306963.**

One of the many adverse consequences of obesity is heart failure (HF). In the Framingham study it was seen that each unit increase in body mass index (BMI) translated into an excess risk of 5% in men and 7% in women for the development of HF. And this was confirmed in several prospective cohort studies, including the Physicians' Health Study, in which, compared to thin people, those who were overweight had an excess risk of HF of 49%, and those who were obese had an excess risk of HF of 180%. This increased risk is independent of the presence of confounding factors such as hypertension, diabetes, dyslipidemia, or coronary heart disease. However, once HF is installed, different observational studies agree on the existence of the so-called obesity paradox: the prognosis of patients with HF, who are overweight or obese, is better than that of their counterpart with normal or low weight. Among other factors, this phenomenon is attributed to tolerance to higher doses of beta-blockers or inhibitors/antagonists of the renin-angiotensin system due to higher blood pressure, to the greater metabolic reserve in a catabolic state such as HF, to the anti-inflammatory action of adipokines. produced by adipose tissue, to having lower levels of adiponectin, which increases energy expenditure, etc. A striking fact is the lower values of natriuretic peptides (NP) in obese patients compared to non-obese patients, attributed among other factors to the decrease in wall stress (a fundamental determinant of the generation of NP) due to pericardial restriction, and the increase in its clearance in adipose tissue due to its excess.

In recent years, strong emphasis has been placed on the relationship between obesity and HF with preserved ejection fraction (HFpEF). In the Northern Hemisphere, fundamentally a very high proportion of patients with HFpEF are overweight/obese. In fact, obesity is recognized as one of the predominant phenotypes presented by patients with HFpEF, linked to greater volume overload and elevation of left ventricular filling pressures at rest and exertion, more biventricular concentric remodeling and dilation of the right cavities, greater elevation of pulmonary pressures with a lower capacity for pulmonary vasodilation. Added to this, the pericardial restriction linked to the increase in ventricular volume coinciding with excess epicardial fat. So, obese HFpEF patients have lower effort capacity and poorer quality of life.

In the HF treatment, the effect of weight loss in obese patients has been evaluated very little, in low-n studies, often observational. In recent years, GLP-1 receptor agonists have gained a predominant place in the pharmacological treatment of obesity. Among them, semaglutide has been and continues to be extensively evaluated in the STEP program. Depending on the presence or absence of diabetes, an average weight loss between 10% and 15% is recognized. It is in this context that we now know the results of the STEP-HFpEF study.

This trial included patients with HF, left ventricular EF (LVEF) ≥ 45%, FC II to IV, with a BMI ≥ 30 kg/m², and a distance walked in the 6-minute walk test (6MWT) of at least 100 meters. They also had to have a Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) < 90. The KCCQ is a standardized 23-item self-administered instrument that quantifies heart failure in different domains: related symptoms (frequency, severity, and recent changes), physical function, quality of life and social function. Scores are expressed on a scale from 0 to 100; higher scores express better status. The KCCQ-CSS specifically expresses the symptoms and physical function domains. And, at least, one of the following had to be added: invasive demonstration of elevation of LV filling pressures, elevation of NP according to BMI coincident with echocardiographic alterations, or history of hospitalization for HF in the last year, with current diuretic treatment or echocardiographic abnormalities. Those who had changed their weight by more than 5 kg in the last 3 months or had an HbA1c value ≥ 6.5% or a known history of diabetes were excluded.

Patients were randomly assigned, stratified by BMI (< 35 vs. ≥ 35 kg/m²) and in a 1:1 ratio, to receive semaglutide or placebo. Semaglutide was administered as a weekly subcutaneous injection, starting with 0.25 mg for the first 4 weeks and increasing the dose until reaching the goal of 2.4 mg weekly at week 16. There were 2 primary end points: the change in the KCCQ-CSS and percent change in body weight assessed at week 52. There were also confirmatory secondary endpoints. One of them was the change in 6MWT distance from baseline to week 52. Another, a hierarchical composite end point that included death from any cause, number and timing of HF events (hospitalization or ur-

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gent emergency room visit with intravenous therapy) in both cases from baseline to week 57; differences of at least 15, at least 10, and at least 5 points in change on the KCCQ-CSS through week 52; and a difference of at least 30 m in the change in 6MWT at week 52. This hierarchical end point was evaluated with the win ratio method, in which for each component the number of wins and losses was compared between the semaglutide and placebo groups. Finally, the change in C-reactive protein (CRP) was evaluated. It was estimated that with 516 participants there would be a 90% power to detect a difference between groups of 4.1 points in the change in the KCCQ-CSS, and 99% to detect a difference of 9.9% in weight loss. with p values of 0.04 and 0.01 respectively. To assess the difference in the end points, an intention-to-treat analysis and a per-protocol analysis were used, considering all randomized patients who had received at least one dose of the instituted treatment.

Between March 2021 and March 2022, 529 patients were randomly assigned, 263 to semaglutide; 16% of patients in both groups discontinued treatment prematurely. Of those who did not do so, at week 52, 83.7% were receiving the planned dose of semaglutide, and 97.8% were receiving the placebo. More than 70% of patients were included based on elevated NT-proBNP values, almost 15% due to demonstration of elevated filling pressures, and the remainder due to a history of hospitalization for HF. Fifty-six percent were women; the median age was 69 years. The median body weight and BMI were 105.1 kg and 37 kg/m^2 respectively; 66% had a BMI ≥ 35. The median KCCQ-CSS was 58.9 points and the median of the 6MWT was 320 m. The median LVEF was 57% and the median NT-proBNP was 450.8 pg./mL. Near 82% were hypertensive; 52% had a history of atrial fibrillation (AF) and 15.3% had been hospitalized for HF in the previous year. Two thirds of the patients were in FC II, the rest in CF III-IV. Eighty percent received diuretics, the same number renin-angiotensin system inhibitors/antagonists or sacubitril valsartan, and 79% betablockers; 35% mineralocorticoid receptor antagonists and less than 4% gliflozins.

In the intention-to-treat analysis, at week 52 the mean change in the KCCQ-CSS score was 16.6 points with semaglutide and 8.7 points with placebo, with an estimated difference of 7.8 points, 95% CI 4.8-10.9; p<0.001. In the per-protocol analysis, the corresponding changes were 19.1 and 10.3 points (estimated difference, 8.8 points; 95% CI, 5.9 to 11.7). The weight change in the intention-to-treat analysis was -13.3% for semaglutide and −2.6% for placebo, with an estimated difference of −10.7%, 95% CI −11.9 to −9 ,4 %; p<0.001. In the per-protocol analysis, the corresponding changes were −15.1% and −2.4% (estimated difference, −12.7%, 95% CI, −13.9 to −11.5%). The change in 6MWT at week 53 was 21.5 m in the semaglutide group and 1.2 m in the placebo group (estimated difference, 20.3 m; 95% CI, 8.6 to 32.1; p<0.001); the results were similar in the per protocol analysis. There was a greater decrease in CRP with semaglutide: 43.5% vs 7.3% decrease in the geometric means, and a greater decrease in NT-proBNP: approximately 20% vs 5%.

In the hierarchical end point analysis, semaglutide treatment resulted in more wins than placebo, with a win ratio of 1.72 (95% CI, 1.37 to 2.15; p < 0.001) in the intention-to-treat analysis and 2.1 (95% CI 1.67 to 2.63) in the pe- protocol analysis. Although there were more victories for semaglutide in all hierarchical point components, the bulk of the effect was a change of ≥ 15 points on the KCCQ-CSS. There was no difference in the incidence of death (1.1% vs 1.5%) but there were fewer cardiac events with semaglutide (arrhythmias, hospitalization for HF, etc.: 2.7% vs 11.3%). The incidence of serious adverse events was half with semaglutide: 13.3% vs 26.7%.

STEP-HFpEF is the first randomized study that evaluates the action of an agent that generates weight loss in hundreds of obese patients with HF. Due to the strong association with preserved LVEF, a population with HFpEF was chosen. Now, being a study in HF, we would have preferred that the study objectives and therefore the primary end points were clearly related to the pathology. It seems obvious that a drug that results in a drop in body weight will generate a greater decrease in body weight than a placebo. And likewise, it is not unexpected that if patients with marked obesity (average BMI of 37 kg/m^2) lose weight as expected (approximately 10%), their quality of life will improve. That is why we insist: these are not results that surprise us. We believe the study offers more, paradoxically, with secondary and confirmatory endpoints effectively linked to HF. As we already saw, at the same amount of IC, the most obese patients have lower NT-proBNP values. And it is often said that as these patients lose weight, their peptide levels increase, as the adipose tissue (where their clearance occurs) decreases. In this study, however, weight loss was associated with a decrease in natriuretic peptides. This implies that HF clearly improved, and that the NT-proBNP corroborated this. Similarly, the improvement in walking (not exciting, it must be recognized), coinciding with a decrease in NP, can be thought of as an expression of less HF. Finally, although not sized to demonstrate a significant reduction in cardiac events, the difference in favor of semaglutide in their incidence suggests a beneficial effect that will have to be corroborated in future studies. This prognostic improvement coinciding with weight loss seems to argue against the obesity paradox. Perhaps, voluntarily losing weight when there is marked obesity (in this study there were 66% of patients with at least grade II obesity and more than 25% with grade III obesity) is beneficial, and on the other hand, unintentional loss due to malabsorption, inflammation and activation of catabolic phenomena is what is truly associated with worse outcomes. It remains to corroborate the effect of GLP-1 agonists in overweight, and even normal weight, HF patients. Given the postulated effects of vascular protection, nephroprotection and anti-inflammatory, we can ask ourselves this question.

Switching to resynchronization therapy in patients with a pacemaker or defibrillator and ventricular dysfunction. BUDAPEST- CRT Study

Merkely B, Hatala R, Wranicz JK, Duray G, Foldesi C, Som Z et al. Upgrade of right ventricular pacing to cardiac resynchronization therapy in heart failure: a randomized trial. **Eur Heart J 2023. https://doi.org/10.1093/eurheartj/ehad591.**

As we know, dyssynchrony induced by left bundle branch block (LBBB) generates ventricular dilation, drop in left ventricular ejection fraction (LVEF), mitral regurgitation, and onset and progression of heart failure (HF); finally, mortality increases. In patients with HF, sinus rhythm, LVEF < 35%, LBBB and QRS width > 150 msec, resynchronization therapy (CRT) with biventricular pacing is a class I A indication. In patients with pacemaker stimulation of the right ventricle generates a conduction pattern similar to a LBBB. In 30% of cases, this is associated with left ventricular dysfunction. The BLOCK-HF study, in patients with LVEF ≤ 50% and indication for definitive pacing in whom a predominant pacing rhythm was assumed, biventricular pacing was associated with a better outcome than exclusive pacing of the right ventricle. Until now, there was no demonstration that in patients with low LVEF, who have a pacemaker or cardiodefibrillator (ICD), upgrading to CRT would improve the prognosis. The BUDAPEST-CRT study set out this objective.

Patients with a pacemaker or ICD placed more than the last 6 months, with HF in CF II-IV, LVEF ≤ 35%, paced QRS width ≥ 150 msec and stimulation of the pacemaker or ICD in at least 20% of beats were included. Patients with intrinsic LBBB, marked dilation of the right ventricle, and those with pathologies that, such as renal failure, shortened life expectancy to less than 1 year, were excluded. Patients were randomly assigned in a 3:2 ratio to receive upgrade to CRT-D (resynchronization with ICD), or ICD alone. If the patient already had an ICD, and was assigned to ICD at randomization, there were 2 options: do nothing, or upgrade to CRT-D, keeping the resynchronization function inactive. The primary end point was a composite of all-cause death, hospitalization for HF, or a <15% reduction in LV end-systolic volume at one-year follow-up. It was considered that 360 patients would be sufficient to demonstrate a significant difference in the primary end point, with 80% power and 2-tailed p value < 0.05, with an incidence of 80% in the ICD arm and 68% in the CRT-D arm, and a monthly loss of 1%.

Between November 2014 and August 2021, 360 patients were included, 215 of them in the CRT-D arm and 145 in the ICD arm, in 17 sites in 7 countries, most of them in Hungary. The mean age was 72.8 years, 89% were men; 47% were in FC II, the average LVEF was 25%; 58% had ischemic etiology, 35% had diabetes, 56% had atrial fibrillation (AF), 49% had been hospitalized for HF in the last year. Ninety-two percent of the patients were treated with renin-angiotensin system inhibitors/antagonists and an additional 6% with sacubitril valsartan; 91% with beta blockers and 62% with mineralocorticoid receptor antagonists. Sixty-eight percent had a pacemaker placed, and 32% had an ICD. The average pacing amount was 85% in the CRT-D arm and 88% in the ICD arm. Median follow-up was 12.4 months. During it, 32.4% in the CRT-D arm and 78.9% in the ICD arm reached the primary endpoint (OR adjusted for age, sex, FC, etiology, diabetes, AF and indication for ICD for secondary prevention secondary 0.11; 95% CI 0.06-0.19, p < 0.001). The composite of death from all causes and hospitalization for HF occurred in 12.3% vs 36%, HR 0.27, 95% CI 0.16-0.47. The difference resided specifically in the lower incidence of hospitalization, with no significant difference in mortality. CRT-D compared to isolated ICD generated a difference in the drop in LV end-diastole volume of 39 ml, and in an increase in LVEF of almost 10% in absolute terms. The incidence of ventricular arrhythmia was lower, 0.5% vs 14.5%; and the incidence of complications linked to the procedure 12.3% vs 7.8%.

This randomized study demonstrates the value of upgrading to CRT in patients with pacemakers or ICD and ventricular dysfunction. Although it may be argued that in the presence of ventricular pacing, ventricular dysfunction is not always due to it (consider, for example, the presence of valvular or coronary disease, or high-response AF), the fact that it was stipulated that the QRS should have a width > 150 msec, and that in the study the proportion of paced beats was at least 85% allows us to assume causality, or at least contribution, in the relationship between pacemaker therapy and ventricular dysfunction. The upgrade to CRT generated a notable reverse remodeling effect, but the most important thing is that there was a net clinical benefit, with a significant reduction in hospitalization for HF. There was no decrease in mortality, but the follow-up was short (about 1 year) to be able to demonstrate it. The reduction in ventricular volumes and the increase in LVEF, the decrease in ventricular arrhythmia and the aforementioned reduction in the hospitalization rate, allow us to assume that in a longer period we would have seen a reduction in mortality. The benefit achieved becomes more important if we consider that more than half of the patients had AF, a condition that restricts the favorable effect of CRT. As limitations we can mention that they were the long inclusion time necessary to reach the expected number of patients, which implies around 3 patients per site per year, and casts some doubt on the external validity. We can also ask ourselves if the notable effects that were verified would occur if the pacing rate were lower. Although not significant, there was a difference in the incidence of complications with a greater number of them in the upgrade arm. Would taking the risk be justified in patients with a much lower stimulation rate?

Ideal timing of complete revascularization in ST-segment elevation AMI and multivessel disease. MULTSTARS AMI Study

Stahli BE, Varbella F, Linke A, Schwarz B, Felix SB, Seiffert M et al. Timing of Complete Revascularization with Multivessel PCI for Myocardial Infarction. **N Engl J Med 2023. https://doi.org/10.1056/NEJMoa2307823**

An old dilemma that arose when considering the best course of action for acute ST-segment elevation myocardial infarction (STEMI) was whether to proceed with exclusive revascularization of the culprit vessel versus also intervening in the rest of the vessels with significant lesions. Until 2019, there were 5 randomized trials (n=2487) that compared both strategies, with percutaneous coronary intervention (PCI) of non-culprit vessels carried out during the index procedure, or deferred, but during the same hospitalization. The need for repeated revascularization and, in some of them, the incidence of non-fatal AMI decreased. In none of these studies was a reduction in cardiovascular or all-cause mortality demonstrated. The COMPLETE study, published at the end of 2019, compared both strategies in similar patients. Randomization was carried out within 72 hours of primary angioplasty, and was done in a stratified manner, considering the decision to perform revascularization of non-culprit arteries during hospitalization or after discharge (no later than 45 days), regardless of the presence of symptoms or ischemia in an evocative test. PCI was decided if the lesion was >70%, and according to the result of fractional flow reserve (FFR) measurement if it was 50%-69%. The complete revascularization strategy demonstrated a greater than 30% reduction in a composite of cardiovascular death and AMI, basically due to a reduction in AMI, with no effect on mortality. There was also a significant reduction in the need for repeat revascularization and heart failure up to 3 years of follow-up, with no difference between performing revascularization of non-culprit arteries before or shortly after hospital discharge. No reduction in cardiovascular or all-cause mortality was demonstrated in COMPLETE. A meta-analysis involving the 6 aforementioned studies (n=6528, mean age 63 years) with a median follow-up of 2 years demonstrated that complete revascularization reduced cardiovascular mortality by almost 40% (HR 0.62, 95% CI). 0.39-0.97). There was also a significant reduction in the incidence of reinfarction (HR 0.65, 95% CI 0.53-0.80) and repeat revascularization (HR 0.29, 95% CI 0.22-0.38). The number needed to treat was 45 to prevent a reinfarction and only 8 to prevent a new episode of revascularization. No reduction in all-cause mortality could be demonstrated.

One point not completely resolved was the moment at which PCI of the non-culprit arteries should be performed. At the initial moment, in the same act in which the artery responsible for the AMI was treated, or in a delayed manner? The MULTISTARS AMI study, multicenter, randomized, and open, aimed to answer this question, based on the hypothesis of non-inferiority of the strategy of intervening on non-culprit arteries at the time of primary PCI versus deferred PCI of these arteries, between 19 and 45 days from the index procedure. Patients with STEMI within 24 hours of symptom onset, who had multivessel disease (defined as the presence of ≥70% stenosis in at least one non-culprit artery, with a diameter between 2.25 and 5.75 mm), and who had successfully undergone PCI of the infarct related artery, were included. Patients had to be hemodynamically stable and were randomly assigned 1:1 to undergo immediate PCI of non-culprit lesions vs. staged PCI (between 19 and 45 days later). Everolimus-eluting stents were used. Whether PCI was guided by FFR or intravascular imaging (including the use of intravascular ultrasonography or optical coherence tomography) was left to the discretion of the operator. The primary end point was a composite of death from any cause, nonfatal MI, stroke, unplanned revascularization driven by the presence of ischemia, or hospitalization for heart failure at 1 year. Unplanned revascularization was defined as revascularization carried out in the presence of angina, ECG changes, or evidence of ischemia in an evocative test.

To calculate the sample size, a primary end point composed of death from any cause, non-fatal MI, or unplanned revascularization was initially considered. To demonstrate non-inferiority, 1200 patients would be necessary. In July 2019, after the inclusion of 217 patients and due to slow enrollment, the primary end point was modified, and stroke and hospitalization for heart failure were added. Based on an estimated annual incidence of 18% for this expanded primary end point, a noninferiority margin of 1.46 and a one-sided significance level of 0.05 were assumed. A sample size of 800 patients was thus defined, necessary to reject the null hypothesis. Considering a dropout rate of 5%, it was decided to recruit 840 patients. An intention-to-treat analysis was performed, and the results were corroborated in a per-protocol analysis. It was established that, if the non-inferiority of immediate PCI compared to delayed PCI was demonstrated, an analysis would then be carried out to demonstrate the superiority of this strategy.

Between October 2016 and June 2022, 2907 patients in 37 centers in Europe were considered for inclusion; 840 patients were included, 418 randomly assigned to immediate PCI and 422 to deferred PCI of non-culprit arteries. The patients had a mean age of 65 years, 79% were men. 52% had hypertension, 15% diabetes and 27% dyslipidemia. Almost 6% had previous AMI. The location of the AMI was anterior in just over 40%, lateral in 42%, inferior in 12% and posterior in 21% (the sum exceeds 100% due to AMI with more than one strict ECG location). The culprit lesion was located in the in the left anterior descending artery in 40%, in the circumflex artery in 17%, and in the right coronary artery in 43%. In 82% of cases, only one artery had a lesion considered not culprit, and in 18% its presence was defined in 2 arteries. The location of the non-culprit le-

sions was in the left anterior descending artery in just over 50%, in the circumflex in 45% and in the right coronary artery in 34%. The median time from the initial to the deferred procedure in the corresponding arm was 37 days. There was a 2.9% crossover from the immediate to the deferred branch. The use of FFR or image guidance for the procedure decision in non-culprit arteries was low, but more frequent when the PCI was performed on a delayed basis, 13.2% vs. 6.3% in immediate PCI; in both cases FFR was mainly used. In the immediate revascularization branch, a total of 3 stents were used in total; in the delayed revascularization arm, a median of 1 stent in the initial procedure, and a total of 3 when also considering the distant procedure. The median volume of contrast medium was 250 ml in the immediate CTA arm, compared to 170 ml in the initial procedure and 333 ml in total in the delayed CTA arm. The duration of the index procedure was logically longer in the immediate arm, with medians of 73 versus 52 min, but when considering the distant procedure, the final duration was longer in the delayed arm, 105 min. The median total length of hospital stay was 4 days in the immediate arm and 5 in the deferred arm.

At 1 year, the incidence of the 5-component primary endpoint was significantly lower in the immediate non-culprit arteries revascularization arm: 8.55 vs 16.3%, with RR 0.52; 95% CI 0.38-0.72; $p < 0.001$ for non-inferiority and $p < 0.001$ for superiority. The difference was mainly due to the lower incidence of non-fatal AMI (2% vs 5.3%) and unplanned revascularization (4.1% vs 9.3%), both with a significant difference. In contrast, there was no difference in the incidence of all-cause mortality (2.9% vs 2.6%), stroke (1.2% vs 1.7%), or hospitalization for heart failure. The large difference between both groups occurred in the first 45 days after randomization, with incidence of the primary end point of 3.6% in the immediate arm vs. 10.7% in the staged PCI arm, with HR 0.33; 95% CI 0.18-0.59. There was no significant difference between 45 days and one year.

In the context of STEMI, complete revascularization is a class I indication. Practice guidelines, the most recent the European Society of Cardiology (ESC) 2023 guideline for acute coronary syndromes, establish that the revascularization procedure of non-culprit arteries in a STEMI can be performed up to day 45. The MULTISTARS AMI study confirms the usefulness of proceeding with initial complete revascularization in the treatment of STEMI. It is regrettable, once its results are known, that the study was not designed as one of superiority. If so, and in view of the significant advantage that initial complete revascularization gained over staged revascularization (reduction by half of the primary composite end point, with a significant reduction in non-fatal AMI, although without a difference in total mortality), perhaps a definitive answer could be proposed to the issue of the ideal moment to carry out this revascularization. Evidence based on strict methodological criteria allows us to speak only of non-inferiority. A point to note is that the advantage of initial complete revascularization was established within the first 45 days. It is the early events that are prevented. Seeing the facts in this way, it is legitimate to ask if the comparison we are witnessing is the only valid one: immediacy vs. a procedure carried out at a median of 37 days. It has been argued that, since initial complete revascularization is only non-inferior to delayed revascularization, postponing revascularization of non-culprit lesions allows it to be carried out in conditions far from the index infarction, with the patient being more stable, better medicated, etc. But if MULTISTARS AMI demonstrates a notable initial gain (risk reduced by one third), can it not be considered for practical purposes that, in descending order, we could initially prefer initial complete revascularization, and then, finally, deferred complete revascularization? Beyond that, of course, individual criteria must always prevail in the decision: hemodynamic stability, renal function, frailty, comorbidities, time of day and physical condition of the treating team, among others.

Complete revascularization in elderly patients with AMI. FIRE Study

Biscaglia S, Guiducci V, Escaned J, Moreno R, Lanzilotti V, Santarelli A et al. Complete or Culprit-Only PCI in Older Patients with Myocardial Infarction. **N Engl J Med 2023; 389:889-98. https://doi.org/10.1056/NEJMoa2300468**

Although complete revascularization appears clearly indicated in patients with AMI and multivessel disease, doubt persists about its indication in elderly patients. We know that in them the coronary artery disease is more extensive, the presence of comorbidities is greater, and this includes kidney dysfunction and anemia; that the propensity to bleed is greater, and that, in short, these are more fragile patients and are therefore exposed not only to a worse evolution of their AMI, but also to more complications linked to the different therapeutic procedures. In this sense, is a complete revascularization strategy justified in them or should only the infarct related artery be treated at the moment, and treatment of the rest of the lesions deferred? The FIRE study was dedicated to answering this question.

FIRE was a multicenter randomized study that, in patients at least 75 years old, with STEMI or NSTEMI and multivessel disease, compared a strategy of revascularization of only the artery responsible for the AMI with another of revascularization of all arteries with significant lesions. Patients had to have undergone a successful PCI of the infarct related artery, and also have at least one lesion in an additional artery, with a minimum diameter of 2.5 mm and a stenosis of between 50 and 99%. Patients in whom it was not possible to clearly define a culprit lesion, those with a non-culprit lesion in the left main coronary artery, those with previous or planned surgical revascularization, and those with a life expectancy of less than one year were excluded. After PCI of the culprit lesion, patients were randomly assigned either immediately or within 48 hours to undergo

this PCI alone (in which case no further study was performed), or to, based on physiology (invasive, hyperemic or non-hyperemic demonstration, or by angiographic images, of decreased fractional flow reserve with cut-off values of 0.80, 0.89 and 0.80 respectively) to define the presence of non-culprit lesions with indication of PCI in other arteries. In case of values equal to or less than those mentioned, PCI of those lesions was performed. The primary end point was a composite of death, AMI, stroke, or revascularization directed by demonstration of ischemia within 1 year of randomization. The secondary endpoint was a composite of cardiovascular death or AMI. The primary safety end point was a composite of contrast-induced acute kidney injury, stroke, and BARC 3, 4, or 5 bleeding. It was assumed that with an annual incidence of the primary end point of 15% in the culprit artery-only revascularization arm, a 30% reduction with complete revascularization, 80% power, a 2-tailed p value <0.05, and a loss of 2%, 1385 patients would be required. The analysis was done by intention to treat.

Between 2019 and 2021, 1445 patients were included, 725 in the single revascularization arm of the culprit artery. The median age was 80 years, 36% were women, 32% had diabetes, 46% had estimated glomerular filtration rate <60/ml/min; 35% of the cases corresponded to STEMI. The average left ventricular ejection fraction (LVEF) was 49%. The assigned strategy was fulfilled by between 96% and 97% of patients in both arms. The artery responsible for the AMI was the left anterior descending, the right coronary, and the circumflex artery in just over 45%, 28% and 18% respectively. Just over 5% corresponded to the left main coronary artery. The number of non-culprit vessels per patient was 1 in 70% of cases and ≥ 2 in the remaining 30%. The determination of fractional flow reserve in the complete revascularization branch was invasive in 65% and non-invasive in 35% of cases. At least 1 functionally significant lesion in a non-culprit vessel was found in almost 50% of cases, and PCI was performed in a similar proportion. The median hospital stay was slightly longer in the complete revascularization arm: 6 vs. 5 days. The use of dual antiplatelet therapy was the rule, and there was more than 95% indication of statins and more than 75% indication of neurohormonal antagonists at discharge.

At one-year follow-up, the incidence of the primary end point was 15.7% in the complete revascularization arm versus 21% in the exclusive infarct related artery revascularization arm (HR 0.73, 95% CI 0 .57-0.93, p= 0.01). The incidence of the secondary end point was lower: 8.9% vs 13.5% (HR 0.64, 95% CI 0.47-0.88), and also the incidence of all-cause mortality: 9.2% vs 12.8% (HR 0.70, 95% CI 0.51-0.96). There was no difference in the primary safety end point. There were no differences according to age, diabetes, or type of AMI (STEMI vs NSTEMI)

The FIRE study extends the benefit of early complete revascularization in two directions: towards older patients, and towards NSTEMI. Regarding age, patients aged 75 years or older are traditionally underrepresented in randomized studies, unless the study design emphasizes their inclusion. And in daily practice, complete revascularization is usually left aside for the reasons we mentioned at the beginning: more extensive coronary artery disease, more calcified lesions, more comorbidities, fear of complications, assumption of therapeutic futility. In this sense, the FIRE results are a resounding denial of these preconceptions. This does not imply, however, that the results can be extrapolated to any elderly patient in these circumstances. More than half, for example, had preserved kidney function; the incidence of stroke in the control arm in the complete revascularization arm (1.7%) was lower than in previous studies. All of this speaks of a population that is not so fragile, less prone to complications from the procedure. Individual choice is still the rule, but we now know that a complete procedure is possible.

Regarding the evidence in NSTEMI, let us remember that complete revascularization appears in the recent European guideline on acute coronary syndromes as an indication 2a, but with level of evidence C. The BIOVASC study had already demonstrated the non-inferiority of an initial complete revascularization compared to of the delayed one in patients with STEMI and NSTEMI. We have 936 patients with NSTEMI in this study, and the evidence of superiority of complete revascularization is resounding. It remains for discussion whether determining the lesion severity guided by physiology is imperative. In the FAME study, 20% of angiographic lesions 71-90% were non-significant with FFR. And in FIRE, half of the patients with presumably significant lesions did not require PCI after functional determination (values above the cut-off value). This certainly may have avoided unnecessary procedures. For the aforementioned guideline, physiology-guided determination in the context of NSTEMI is II b with level of evidence B. Will the indication change in the future following the FIRE results?

The value of atrial fibrillation ablation in patients with end-stage heart failure. CASTLE-HTx study

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Atrial fibrillation (AF) and heart failure (HF) are conditions that frequently coexist. Both increase their incidence and prevalence with age, and have common precursors: high blood pressure, obesity, and valvular disease. Each of them creates conditions that favor the appearance of the other. The loss of the atrial kick, a rapid and irregular ventricular response, dyssynchrony, ultrastructural alterations, the development of mitral regurgitation and the sympathetic activation present in AF favor the appearance of HF. Structural changes, with hypertrophy and dilation of the left cavities, hemodynamic

phenomena, electrical remodeling, neurohormonal and inflammatory activation typical of HF create the appropriate substrate for the appearance of AF. In the context of heart failure, the prevalence of AF is greater as the functional class progresses. In numerous observational and randomized studies in HF, patients with AF have a worse prognosis. A series of randomized studies conducted before 2010 compared a rhythm control strategy with a rate control strategy in patients with both conditions. No significant differences could be demonstrated in mortality or incidence of embolic events between both strategies, and in fact there was a higher hospitalization rate in the rhythm control arm. The explanation lies in the use of antiarrhythmic drugs in the rhythm control arm, with the inherent difficulty in achieving persistent maintenance of sinus rhythm, in addition to the adverse effects from the use of the medication, which increase in patients with impaired ventricular function. In the last decade, catheter ablation therapy for AF, especially pulmonary vein isolation, has grown markedly. Studies have been published that suggest improvement in ventricular function. The CASTLE AF study reported improved prognosis in patients with HF and depressed left ventricular ejection fraction (LVEF). However, the fact that it was a highly selected population (only one patient out of every 10 evaluated was included) diminished the impact of its conclusions. Different meta-analyses confirm the favorable effect of AF ablation in the context of HF, especially in improving LVEF and functional capacity. There is, however, consensus that patients with more advanced HF, worse ventricular function and functional class, greater atrial dilation, and fibrosis, have a lower chance of successful ablation.

We now know about the CASTLE-HTx study, which included patients with end-stage HF and symptomatic AF, referred for evaluation for ventricular assistance or heart transplantation. To be included, they had to have LVEF ≤ 35%, deterioration in functional capacity and be clinically stable. All of them had an implantable device with the ability to detect arrhythmia. Patients were randomly assigned 1:1 to catheter ablation of their AF and optimal medical therapy (OMT) or to receive OMT alone. The ablation procedure was isolation of the pulmonary veins. Electrical cardioversion was attempted after transseptal puncture and before ablation. If cardioversion was unsuccessful, ablation was performed and attempted again later. Antiarrhythmic medication was suspended after ablation and was only resumed in case of AF recurrence. The primary endpoint was a composite of death from any cause, left ventricular assist device implantation, or emergency heart transplantation. Secondary endpoints were each of the primary components, cardiovascular death, change in LVEF, and AF burden, defined as the percentage of time in AF in the 3 months prior to the 6- and 12-month visit. Under the assumption of an year event rate of 20% in the OMT arm, and a decrease by half in the ablation arm, it was understood that 194 patients would be necessary to demonstrate this effect with 80% power and two-tailed alpha error of 0.05

Between November 2020 and May 2022, 194 patients were included, 97 in each arm. In May 2023, the study was suspended when a notable reduction in events was demonstrated in the ablation arm, with a p value <0.001. The average age of the patients was just over 63 years, 80% were men, 31% were in FC II, 55% in FC III and the rest in FC IV. The mean LVEF was 27%; AF was paroxysmal in 31% and persistent in the rest, including almost 14% with persistent AF for more than a year. AF had an average duration of between 3 and 4 years. In 61% the etiology of HF was non-ischemic. The implantable device was ICD in 56.5% and CRT-D in 37.5%; in the rest, a pacemaker, or a device to monitor the rhythm. Only 25% of patients could perform a walking test. Ninety-five percent were treated with beta blockers, 46% with amiodarone, 37% with renin angiotensin system inhibitors/antagonists, 63% with sacubitril valsartan and 50% with mineralocorticoid receptor antagonists; 25% received gliflozins.

Of the 97 patients assigned to the ablation arm, the procedure was performed in 81 (84%), only pulmonary vein isolation in 51, and some additional procedure in 30. Of the 97 assigned to OMT alone, 16 underwent an ablation procedure. The median follow-up was 18 months. During it, the primary end point occurred in 8% of the ablation arm and 30% of the OMT arm (HR 0.24, 95% CI 0.11-0.52, p < 0.001). There was a significant reduction in death from any cause (6 vs 20%) and urgent implantation of a left ventricular assist device (1 vs 10%). There was a tendency to reduce the indication for urgent heart transplantation (1 vs 6%). At 6 and 12 months there was an increase in LVEF of just over 1% in the OMT arm, and more notable in the ablation arm, with an average difference between both arms of 5.5% at 6 months and 6.4% at 12 months. The AF burden was reduced by 31% at 6 and 12 months in the ablation arm, compared to 8% in the BMT arm.

The CASTLE-HTx study confirms the beneficial effect of AF ablation in patients with HF and impaired ventricular function. Some objections may be raised about the terminal IC character; almost a third of the patients were in CF II, and 18-month mortality was 20% in the OMT arm; Both data allow us to assume a not so serious condition in all participants. But, on the other hand, we should consider the high rate of use of neurohormonal antagonists, with more than 90% having an ICD or CRT-D; and, finally, that the most serious patients were deliberately excluded: those who were on the urgent transplant list, those who were on circulatory assistance and those who had a life expectancy <12 months. The reduction in AF burden appears to be the phenomenon responsible for the prognostic improvement. The limitations are that it is a single-center study, the short follow-up, and the small number of patients, although that was anticipated in the initial sample size calculation. It seems increasingly difficult to do more similar randomized studies; perhaps observational studies will clarify the remaining doubts.

At Full Tilt

A plena máquina

We have been very busy lately, with the main upcoming event for our Society: the annual Congress. The constant work performed by the Scientific Committee intends to update and present all subject matters and situations of interest for the practice of cardiology in general, as well as for its different subspecialities.

The current social and economic scenario in Argentina continues to be difficult, especially for us, healthcare professionals, who want to achieve our purposes in the field. However, from October 19 to 21, the SAC will become an optimistic compass that, thanks to the participation of many members and international guests, will guide us along different scientific and practical paths to be followed for the sake of our patients and ongoing medical training.

At the international level, we were able to sign beneficial agreements for our Society, such as the agreement with the WHF (World Health Federation), which has included free access to Wikicardio in different languages in their website using a smart online translator and acknowledged the SAC's copyright.

Together with the AHA (American Heart Association), we made progress regarding bilateral participation in various events in the US and Argentina. Argentine registries on regional endemic diseases and the healthcare situation in the region have sparked the interest of the President of the AHA, Dr. Joseph Wu, as well as other authorities. Dr. Wu offered to provide support for these registries, including financial support.

Thanks to the ACC (American College of Cardiology) Argentine Chapter, the grant for residents in New York will continue and might be increased from one to two a year. SAC members' involvement in the ACC societal activities is also being promoted. They are particularly interested in receiving our members' applications to become part of The Global Graduate Educators Workgroup (GGEWG), and younger members' applications for the grant provided by Dr. William Zoghbi (former ACC President) in order to fund research in low- and middle-income countries.

Furthermore, we continue to work closely with the members of the European Society of Cardiology, who have invited us to take part in a pilot project selecting only five Societies to create a network of affiliated associations for the young, and foster exchange and involvement in different educational activities.

As we are aware of the importance of progress in scientific research and the financial restraints affecting it, we have decided to offer six grants aimed at promoting the activity in our field.

We continue to work with the aim to achieve the purpose of this Society to the full extent, shown by the exchange of information and experiences grounded in shared professional interests, as well as medical education standards.

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President of the Argentine Society of Cardiology

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