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Summary

EDITORIAL

"Youth Is a Disease that Is Cured with Age"

"La juventud es una enfermedad que se cura con los años"

George Bernard Shaw

JORGE LERMAN[1, MTSAC]

Young people generally assume that they are healthy, do not undergo medical examinations often, and are unaware of their blood pressure levels. According to the 4th National Survey of Risk Factors, published in October 2019, the prevalence of hypertension was 14.8% among individuals aged 18–24, 20.7% among those aged 25–34, and 29% among those aged 35–49. (1) In the RENATA 2 study, conducted between August 2015 and March 2016 and published in 2017, 18.5% of men and 6.9% of women < 35 years had hypertension as well as 37.9% of men and 19.5% of women between 35 and 44 years of age. (2) A relevant fact is that in these age groups of young adults, the prevalence of hypertension is increasing more rapidly than in older people, especially in men and in middle- and low-income countries. (3,4) This could be attributed to factors such as increasing sedentary lifestyles, obesity, alcohol consumption, tobacco use, drug use, and poor diet. In young adults, adherence to adequate treatment and blood pressure control is significantly lower. (5) A recent Finnish publication analyzed a group of 1889 adolescents and young adults who were followed up for 38 years. At the conclusion of the study period, 745 (39.4%) of the subjects had developed atheromatous plaques in their carotid arteries. Multivariate analysis demonstrated a close correlation between systolic, diastolic, mean, and pulse pressure initially recorded and the development of these plaques. (6) These findings confirm the well-established association between the presence of a specific risk factor, its intensity, and the duration of endothelial exposure to that risk factor. Another relevant finding is the confirmation that hypertension is associated not only with arterial remodeling (increased intima-media thickness) but also with the deposition of atheromatous plaques.

In this issue of the journal, researchers from the Favaloro Foundation publish a cross-sectional observational study with prospective follow-up of individuals who underwent cardiovascular evaluation between January 2017 and December 2023. (7) A total of 6071 participants between 18 and 49 years were included in this analysis (age 35.3 ± 9.6 years, 45.3% female). Of these, 576 patients (9.5%) had systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or both (HTNg). The characteristics of the HTNg were compared with those of normotensive individuals (CTRLg). Patients were excluded if they had previous HTN, were taking antihypertensive treatment, or had secondary HTN. Subjects in the CTRLg were older and had higher values of body mass index and blood glucose, creatinine, total cholesterol, LDL, and triglycerides. These data reinforce the long-standing concept that cardiovascular risk factors are often associated and that identifying one of these factors typically prompts the investigation of the others to determine the overall cardiovascular risk score. On exercise stress test, this group exhibited lower performance and a greater exaggerated hypertensive response to exercise compared to the CTRLg. In addition, the echocardiograms demonstrated higher left ventricular mass index and larger left atrial diameter in the HTNg. Probably, an indeterminate proportion of these patients were unaware they had HTN, as we do not know the medical records of this population. In that case, this would be the first time they became aware of their condition. Furthermore, analysis of the results indicates that target organ damage to the kidney and heart had already occurred at an early age.

This study analyzes a highly selected population made up of individuals who voluntarily attended a prevention program at a cardiovascular center (motivational bias). This decision identifies them as people who are naturally more concerned about their health and, consequently, healthier than the average population. Given their attendance at a private institution, it is reasonable to assume that these individuals possess health coverage and thus belong to a more privileged socioeconomic class (socioeconomic bias). These

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facts contribute to consider it difficult to extrapolate these results to the broader community. The diagnosis of hypertension was made in the context of a single measurement taken as part of a general health check-up, without corroboration by additional methods such as home or ambulatory blood pressure monitoring, as recommended by recent guidelines. (8)

Despite these observations, I believe that this paper presents a novel and valuable incentive to warn the community (particularly the medical community) and underscore the importance of detecting, correctly treating, and adequately controlling hypertension over a lifetime.

Conflicts of interest

None declared

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

Ethical considerations

Not applicable.

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ORIGINAL ARTICLE

High Blood Pressure in Young Patients and its Association with Other Risk Factors. Importance of Searching for Hypertensiom at All Ages

Hallazgo de presión arterial elevada en pacientes jóvenes y su asociación con otros factores de riesgo. Importancia de la búsqueda de hipertensión arterial en todas las edades

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ABSTRACT

Background: Hypertension (HTN) is the risk factor with the greatest impact on cardiovascular (CV) disease. Several studies indicate that HTN can be present from an early age and that its adequate treatment is key to prevent organ damage and CV events. However, young adults are often unaware of their blood pressure (BP) levels.
Objective: The aim of this study was to evaluate the prevalence of HTN in young patients and its association with other cardiovascular risk factors (CVRF).
Methods: A cross-sectional observational study with prospective follow-up evaluated patients aged 18-49 years, participating in a CV prevention program between January 2017 and December 2023. Elevated BP was defined as ≥140 mmHg systolic blood pressure (SBP) or ≥90 mmHg diastolic blood pressure (DBP). Patients with pre-existing HTN, on antihypertensive treatment, or with secondary HTN were excluded. The study included echocardiograms to measure left ventricular mass index (LVMI) and left atrial (LA) size, and ergometric testing to assess the hypertensive response to stress (SBP ≥210 mmHg or DBP ≥90 mmHg). Multiple logistic regression analysis was performed to determine the association of HTN with other CVRF.
Results: Among a total of 6071 participants (mean age 35.3 ± 9.6 years, 45.3% women), 576 (9.5%) showed elevated BP at consultation. Patients with HTN were older and had higher values of body mass index (BMI), glycemia, creatinine and lipid parameters (total cholesterol, LDL-c, HDL-c and triglycerides). In the HTN group (HTNg), 73.8% had elevated SBP, 91.1% elevated DBP and 64.9% had both elevated values. The prevalence of HTN was higher with increasing age. In the ergometric test, patients with HTN presented lower performance: 12.2±2.8 METS vs. 13±2.8 METS in the control group (CTRLg) , p<0.001; and an exaggerated hypertensive response: 8.3% vs. 1%, p<0.001. The LVMI was also higher in the HTNg: 66±16 g/m^2 vs. 62.5±14.5 g/m^2 (p<0.001), as well as the LA diameter: 35.9±5 mm vs. 33.9±4.9 mm (p<0.001). Multiple logistic regression analysis showed that age (OR 1.049, 95% CI 1.034-1.065), HDL-c (OR 0.985, 95% CI 0.973-0.996), triglycerides (OR 1.002, 95% CI 1.000-1.003), LA diameter (OR 1.048, 95% CI 1.019-1.078) and hypertensive response on the stress test (OR 8,897, 95% CI 5,151-15,367) were independently associated with the presence of HTN.
Conclusion: A significant number of young patients with HTN was found in a control medical consultation. This finding was significantly associated with factors that increase cardiovascular risk (CVR), demonstrating that it is not an innocent finding. Early identification, categorization and treatment of this population is a priority to prevent the onset of cardiovascular events.

Key words: Hypertension - Atherosclerosis - Risk factors - Primary prevention

RESUMEN

Introducción: La hipertensión arterial (HTA) es el factor de riesgo con más impacto en la patología cardiovascular (CV). Diversos estudios indican que la HTA puede estar presente desde edades tempranas y que su tratamiento adecuado es clave para prevenir daño de órganos y eventos CV. Sin embargo, los adultos jóvenes (AJ) suelen desconocer sus niveles de presión arterial (PA).
Objetivo: Evaluar la prevalencia de HTA en pacientes jóvenes y su asociación con otros factores de riesgo cardiovascular (FRCV).
Material y métodos: En un estudio observacional transversal con seguimiento prospectivo, se evaluaron pacientes de 18 a 49 años que participaron en un programa de prevención CV entre enero de 2017 y diciembre de 2023. Se definió PA elevada un valor ≥140

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mmHg para la presión arterial sistólica (PAS) o ≥90 mmHg para la presión arterial diastólica (PAD). Los pacientes con HTA preexistente, en tratamiento antihipertensivo o con HTA secundaria fueron excluidos. El estudio incluyó ecocardiogramas para medir el índice de masa del ventrículo izquierdo (iMVI) y el tamaño de la aurícula izquierda (AI), y pruebas ergométricas para evaluar la respuesta hipertensiva al esfuerzo (PAS ≥210 mmHg o PAD ≥90 mmHg). Se realizó un análisis de regresión logística múltiple para determinar la asociación de la HTA con otros FRCV.

Resultados: De los 6071 participantes (edad promedio de 35,3 ± 9,6 años, 45,3% mujeres), 576 (9,5%) mostraron PA elevada en la consulta. Los pacientes con HTA eran mayores y tenían valores más altos de índice de masa corporal (IMC), glucemia, creatinina y parámetros lipídicos (colesterol total, C-LDL,C-HDL y triglicéridos). En el grupo con HTA (gHTA), el 73,8% tenía PAS elevada, el 91,1% PAD elevada y el 64,9% ambos valores elevados. La prevalencia de HTA fue mayor cuanto mayor la edad. En la prueba ergométrica, los pacientes con HTA presentaron menor rendimiento: 12,2 ± 2,8 METS vs. 13 ± 2,8 METS en el grupo control (gCTRL), p<0,001; y más frecuentemente respuesta hipertensiva exagerada: 8,3% vs. 1%, p<0,001. El iMVI también fue mayor en el gHTA: 66 ± 16 g/m² vs. 62,5 ± 14,5 g/m² en el gCTRL (p<0,001), así como el diámetro de la AI: 35,9 ± 5 mm vs. 33,9 ± 4,9 mm (p<0,001). En el análisis de regresión logística múltiple la edad (OR 1,049, IC 95% 1,034-1,065), el C-HDL (OR 0,985, IC 95% 0,973-0,996), los triglicéridos (OR 1,002, IC 95% 1,000-1,003), el diámetro de la AI (OR 1,048, IC 95% 1,019-1,078) y la respuesta hipertensiva en la prueba de esfuerzo (OR 8,897, IC 95% 5,151-15,367) se asociaron independientemente con la presencia de HTA. En el seguimiento luego de seis meses, el 62% de estos pacientes estaba bajo tratamiento antihipertensivo.

Conclusión: Se observó un número significativo de pacientes jóvenes con hallazgo de HTA en una consulta de control. Este hallazgo estuvo significativamente vinculado con factores que incrementan el RCV, demostrando que no se trata de un hallazgo inocente. La identificación, categorización y tratamiento temprano de esta población es prioritaria para evitar la aparición de enfermedad CV.

Palabras clave: Hipertensión arterial – Aterosclerosis – Factores de riesgo – Prevención primaria

INTRODUCTION

Hypertension (HTN) is the most relevant modifiable cardiovascular risk factor (CVRF) due to its frequency and association with cardiovascular morbidity and mortality. One of the key terms associated with HTN is "HTN-mediated organ damage" (HMOD), which describes how the presence of HTN subclinical complications are indicators of a higher risk of serious clinical events in the future, such as heart failure or chronic kidney disease. (1,2) Hypertension is defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg at the medical consultation. For an accurate diagnosis, it is recommended to take at least two measurements at different visits, or to confirm the elevated values with complementary ambulatory studies, such as ambulatory blood pressure monitoring at home (ABPM) or 24-hour ambulatory monitoring. These measurements provide a more reliable description of the patient's hypertensive status outside the clinical setting, where blood pressure (BP) can vary due to external factors. (3)

In recent years, there has been a notable increase in the prevalence of HTN in young adults (YA), both men and women. This increase has been promoted by factors such as unhealthy lifestyles (poor diet, sedentarism, and alcohol and tobacco consumption), obesity, and unfavorable socioeconomic conditions. These factors contribute to a higher risk of developing HTN at younger ages, which in turn increases the long-term risk of cardiovascular disease. In fact, the impact of HTN in terms of mortality or years of life lost due to disability has increased especially in low- and middle-income countries, where resources for diagnosis and treatment may be limited. (4)

It is important to note that both systolic and diastolic HTN, and even isolated diastolic HTN, are associated with an increased risk of cardiovascular events (CVE) in YA, an age group that has traditionally been considered at lower risk. However, this risk is often underestimated, as awareness of HTN, its treatment, and control is considerably lower in YA compared with older age groups. This phenomenon contributes to underdiagnosis and insufficient treatment in this population, which increases the likelihood of mid- and long-term cardiovascular complications. (5,6)

METHODS

A cross-sectional observational design with prospective follow-up was carried out, evaluating patients who attended a cardiovascular health prevention program (HPP) at Fundación Favaloro University Hospital. The HPP is designed to assess general health, counsel and educate on healthy lifestyle habits, and detect patients at high cardiovascular risk (CVR). Patients between 18 and 49 years of age who attended for cardiovascular assessment between January 2017 and December 2023 were included. Anthropometric, clinical, and laboratory data were collected from medical records. Waist circumference (WC) was measured with a non-extensible tape measure at a midpoint between the lower edge of the ribs and the iliac crests with the patient standing in normal expiration and body mass index (BMI) was calculated: weight/height2: kg/m²). BMI allowed patients to be divided into normal weight (<25 kg/m²), overweight (≥25- 30 kg/m²) and obese (≥30 kg/m²).

Diabetes mellitus (DM) was defined as the presence of two fasting blood glucose (FBG) measurements ≥126 mg/dL or treatment with insulin or oral hypoglycemic agents ; (7) dyslipidemia in the following circumstances: low-density lipoprotein cholesterol (LDL-c) ≥190 mg/dL, high-density lipoprotein cholesterol (HDL-c) <40 mg/dL for men or <50mg/dL for women, total serum triglycerides (TG) ≥150 mg/dL, or being medicated with lipid-lowering drugs; current smoking defined as patients who had smoked at least one cigarette in the last 6 months and more than 100 cigarettes throughout their lives; and family history of atherosclerotic cardiovascular disease, as having first-degree relatives and manifestations before the age of 55 years in men and 65 years in women. (8) High blood pressure was considered for SBP ≥140 mmHg or ≥90 mmHg for DBP in the medical consultation . Metabolic syndrome (MS) was diagnosed according to the criteria of the National Cholesterol Education Program

– Adult Treatment Panel III (NCEP-ATP III). (9) The components of MS were defined as follows: 1) high BP (SBP ≥130 mmHg and/or DBP ≥85 mmHg or taking antihypertensive medication); 2) elevated WC (>102 cm for men and >88 cm for women); 3) hyperglycemia (FBG ≥100 mg/dL or hypoglycemic treatment); 4) hypertriglyceridemia (TG ≥150 mg/dL); and 5) low HDL-c (<40 mg/dL for men and <50 mg/dL for women). Metabolic syndrome was considered to be present with at least 3 of the components described.

A color Doppler echocardiogram was performed using an Affinity 50 ultrasound system (Philips HealthCare, USA) to evaluate the left atrial structure (LA) and calculate left ventricular mass index (LVMI). A graded exercise test was used to assess the hypertensive response to exercise (SBP ≥210 mmHg or DBP ≥90 mmHg).

The characteristics of the hypertensive group (HTNg) were compared with those of the normotensive group (control group, CTRLg). Patients with previous HTN, under treatment with antihypertensive drugs, or with secondary HTN were excluded.

Statistical analysis

Quantitative variables were expressed as mean±standard deviation (SD) or median and interquartile range (IQR), according to the normal distribution evaluated by the Kolmogorov-Smirnov test. Qualitative variables were expressed as number and percentage. Comparisons between groups were performed using Student's t-test or Mann Whitney test for continuous variables and the Chi2 test or Fisher's exact test for categorical variables. A multiple logistic regression analysis was performed to test the independent association between HTN and other CVRF. Variables with a known biological relationship or those with statistically significant differences in the univariate analysis (age, gender, BMI, FBG, HDL-c, TG, LA diameter, LVMI, and exaggerated hypertensive response in the ergometric test) were employed for the model. A two-tailed p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 16 (SPSS Inc, Chicago, Illinois, USA) and R version 4.3.1. This study was approved by the institutional bioethics committee.

RESULTS

Among a total of 6071 participants who met the inclusion criteria (age 35.3±9.6 years, and 45.3% female), 576 patients (9.5%) had elevated BP values during the medical consultation. The comparative data for this population, showing that patients in the HTNg had more unfavorable clinical characteristics compared with the CTRLg, are summarized in Table 1.

In the HTNg, patients had older age, greater BMI, higher FBG levels, and elevated creatinine concentrations. In addition, lipid parameters, including total serum cholesterol, LDL-c, HDL-c, and TG, also showed significant alterations in this group of patients, reinforcing the relationship between HTN and other CVRFs.

Regarding specific findings in the HTNg, 73.8% had elevated SBP, 91.1% had high DBP, and 64.9% had both elevated pressures. There was a strong relationship between increasing age and high BP, as can be seen in Figure 1.

On the other hand, the results of the ergometric test, an assessment of physical performance during exercise, indicated that the HTNg patients showed significantly lower performance, measured in METS (metabolic equivalents) compared with the CTRLg. On average, HTNg patients reached 12.2±2.8 METS, while normotensive patients reached 13±2.8 METS (p<0.001). In addition, the probability of an exaggerated hypertensive response during exercise was sta-

Table 1. Total population characteristics, with normal or high blood pressure at consultation. Quantitative variables are presented as mean ± standard deviation or median and interquartile range, according to their distribution

Variable	Total (n=6071)	Normal BP at Consultation (n=5495)	HTN at consultation (n=576)	p value
Age (years)	35.3 ± 9.6	34.9±9.7	38.9±8.5	<0.001
Female sex (%)	43.5	46.6	32.3	<0.001
Body mass index (kg/m^2)	26.8 ± 14	26.5±14.4	30.5±6.8	<0.001
Diabetes mellitus (%)	58 (0.9)	49 (0.9)	9 (1.6)	0.115
Active smoking (%)	1167 (19.2)	1058 (19.2)	109 (18.9)	0.911
Blood glucose (mg/dL)	92,2 ± 16,6	91,8 ± 15,4	96,2 ± 25,1	<0,001
Creatinine (mg/dL)	0.86 ± 0.16	0.86±0.16	0.89±0.17	<0.001
Total cholesterol (mg/dL)	189.7 ± 37.6	188.8±37.4	198.7±32.6	<0.001
HDL-c (mg/dL)	54.4 ± 13.5	54.8±13.6	50.7±11.9	<0.001
LDL-c (mg/dL)	113.1 ± 32.8	112.4±32.6	120.5±33.7	<0.001
Triglycerides (mg/dL)	92 (67-132)	90 (66-128)	115 (83-168)	<0.001

BMI: body mass index; BP: blood pressure; HDL-c: High density lipoprotein cholesterol; HTN: hypertension; LDL-C: Low density lipoprotein cholesterol

Qualitative variables are presented as percentages and quantitative variables as mean ± standard deviation or median and interquartile range, according to their distribution.

tistically much higher in the HTNg compared with normotensive individuals:8.3% vs. 1% (p<0.001).

Another relevant finding was the increase in LVMI in the HTNg (66±16g/m² vs. 62.5±14.5g/m², p<0.001) suggesting a greater hemodynamic load in hypertensive patients. Similarly, patients in the HTNg had a statistically significant larger anteroposterior LA diameter (35.9±5 mm vs. 33.9 ± 4.9mm in the CTRLg, p<0.001).

Multiple logistic regression analysis revealed that several factors were independently associated with the presence of HTN in the consultation. Age (OR 1.049, 95% CI 1.034-1.065), HDL-c (OR 0.985, 95% CI 0.973-0.996), triglycerides (OR 1.002, 95% CI 1.000-1.003), LA diameter (OR 1.048, 95% CI 1.019-1.078) and hypertensive response on the stress test (OR 8,897, 95% CI 5,151-15,367) were independently associated with the presence of HTN. (Table 2)

DISCUSSION

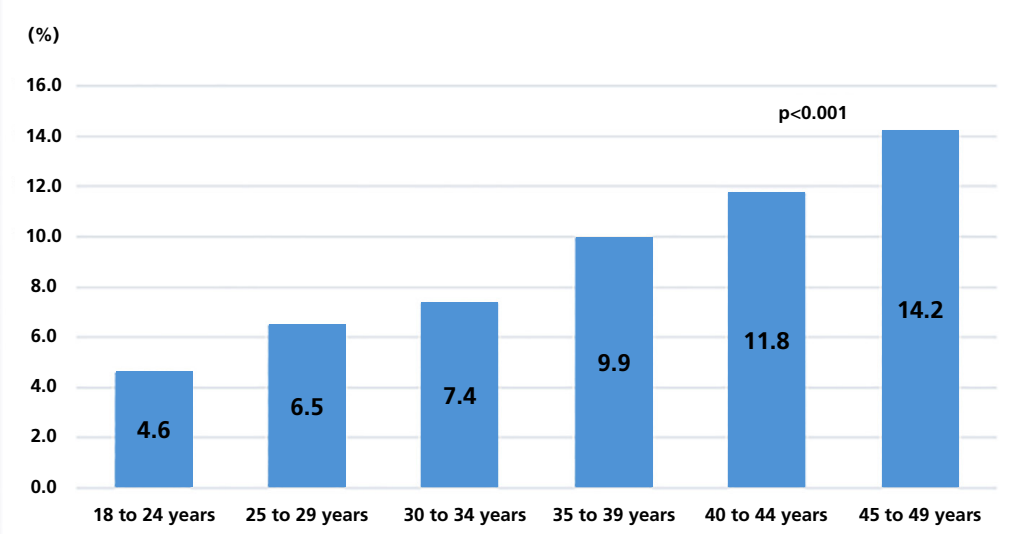
Hypertension is the most common modifiable CVRF with the greatest impact on CV health. In recent years, various factors, such as unhealthy lifestyles, greater obesity, and sedentarism, have contributed to the increase in the incidence of HTN in younger populations. (10,11) Our findings show an important number of young individuals with HTN, which is significantly associated with the presence of other CVRFs, such as dyslipidemia, obesity, and DM. What is worrying about these findings is that the diagnosis of HTN in young people, which is often underestimated or delayed, and the lack of adequate treatment, can have a

Table 2. Variables associated with the finding of arterial hypertension. Multiple logistic regression.

Variable	OR	95% CI	p
Age	1.049	1.034-1.065	<0.001
Male gender	0.793	0.592-1.064	0.122
BMI	1.004	1.000-1.008	0.069
FBG	1.001	0.995-1.007	0.789
HDL-c	0.985	0.973-0.996	0.009
TG	1.002	1.000-1.003	0.010
LA diameter	1.048	1.019-1.078	0.001
LVMI	0.999	0.990-1.007	0.745
Hypertensive response on the stress test	8.897	5.151-15.367	<0.001

BMI: body mass index; FBG: fasting blood glucose; HDL-c: high density lipoprotein cholesterol; LA: left atrium; LVMI: left ventricular mass index; OR: odds ratio; TG: triglycerides; 95% CI: 95% confidence interval

Fig. 1. Percentage of patients with elevated blood pressure values at the consultation according to the age group



severe impact on long-term CV health. Traditionally, youth has been considered to confer a certain degree of protection against CVE. However, our results suggest the opposite: age, in this context, does not always act as a protective factor, and subclinical damage can progress silently if early intervention is not provided.

The prevalence of HTN in people under 50 years of age has shown a steady increase in recent decades. New studies, such as the analysis of the National Health and Nutrition Examination Survey (NHANES) conducted between 2017 and 2020, reported a prevalence of 11.5% HTN in YA between 20 and 44 years of age. (12) Moreover, other publications have highlighted that the prevalence increases with age, and it has been observed that HTN affects approximately 14.5% of adults between 18 and 49 years of age. (13) These data reflect the growing burden of CVRF among YA, including obesity, sedentarism, and poor diet. In Argentina, the RENATA 2 study showed a prevalence of 18.5% HTN for men and 6.9% for women under 35 years of age, and between 37.9% and 19.5% among those aged 36 to 44 years old. (14) Espeche et al. also showed that this worrying situation could be magnified in vulnerable populations in Argentina. (15) In this context, our data coincide in revealing a high prevalence of elevated BP in the clinic.

In this population of YA, detection of HTN in the clinic was associated with an increase in LVMI which is a well-known significant marker of CVR in patients with HTN. (16,17) Schilacci et al. demonstrated that LVMI was continuously related to an increased risk of CVE. (18) It is interesting to remark that in this study, age, male sex, and a LVMI in the upper quintile were independent predictors of cardiovascular morbidity and mortality. Our interpretation is that this link is showing early signs of incipient target organ damage, which should be taken into account in the management of these patients. Another important finding is the presence of enlarged LA diameter. This echocardiographic finding is generally associated with increased left ventricular end-diastolic pressure, representing an atrial adaptation to pressure overload. The presence of LA enlargement has been associated with the incidence of CVE in YA. (19) Particularly in young patients with HTN, the presence of an enlarged LA increases the risk of stroke. (20) This relationship could be explained by increased blood stasis and the consequent formation of clots, although it is also suspected that atrial enlargement may be promoting the onset of atrial fibrillation. (21,22) Regardless of whether an exact cause can be established, the presence of increased LA diameter as an independent predictor in the multivariate analysis, is an alarming finding in this population of young patients.

The exaggerated response to the stress test was also a distinctive pattern associated with elevated BP during the consultation. This phenomenon has also been widely described previously. In a study by Yzaguirre et al., it was observed that the exaggerated response of SBP or DBP to moderate load (100W) is an independent predictor of future development of essential HTN. (23) In our population, the probability of presenting an exaggerated BP response was 8 times higher in participants with HTN at the medical consultation, which was also associated with reduced exercise test performance. We consider this to be another characteristic of these patients that should be noted for close follow-up and eventual early treatment.

We must consider some limitations of this study. First, it was conducted in a single center population, which may have influenced our results. In addition, the participants have health coverage and may represent a socioeconomic bias, which we recognize as very relevant when addressing the issue of HTN and CVRF. Even with these limitations, we think our population reflects the reality that many physicians face in their regular office care when they find high BP.

CONCLUSION

In conclusion, our findings are consistent with other reports of an increase in the prevalence of HTN in YA. The association with other CVRF and the presence of HMOD are an additional concern and a warning for the care of this population. Improving detection, prevention, and early treatment strategies are priorities for preventing early CVE. Future studies with long-term follow-up and measurement of CVE may define the benefit of early detection of CVRF, together with an appropriate preventive and therapeutic approach to avoid future complications and reduce the burden of CV disease in the general population.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Weight, Height and Body Mass Index: Effectiveness of the "Clinical Insight" in the Correct Interpretation of Anthropometric Parameters

Peso, altura, índice de masa corporal: efectividad del "ojo clínico" en la correcta interpretación de parámetros antropométricos

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ABSTRACT

Background: Excess weight, defined as body mass index (BMI) ≥25 kg/m², is associated with increased cardiovascular risk. While BMI is easy to obtain, medical professionals often rely on their own clinical perception.
Objectives: The aim of the present study was to 1) evaluate the concordance between subjective estimates and actual measurements, 2) analyze if there is agreement between BMI categories as determined by objective measurements and as perceived by physicians, and 3) assess if there is inter-observer variability in subjective perceptions of weight, height and BMI category.
Methods: We conducted a prospective and observational study. Cohen's kappa index was used to analyze the degree of agreement between observers. A value greater than 0.6 was considered "good correlation." The Bland-Altman test was used to evaluate the differences between actual and estimated measurements. A difference greater than 5 kg in weight and greater than 5 cm in height between the actual and estimated measurements was considered clinically significant.
Results: A total of 87 patients were evaluated; 54% were men. More than 58% of the subjective perceptions of weight and 44% of height were significantly different from the objective measurements. The concordance between objective measurements of BMI and subjective impressions was not good.
Conclusion: In more than half of the cases, subjective perceptions of physicians when calculating weight, height, and BMI are inappropriate. There is significant variability in clinical perceptions. It is essential to measure objectively in order to properly categorize patients.

Keywords: Obesity - Excess weight - Anthropometric indices - Correlation

RESUMEN

Introducción: El exceso de peso, definido como un índice de masa corporal (IMC) ≥25 kg/m2 implica un aumento del riesgo cardiovascular. Si bien es una medida sencilla de obtener, los médicos utilizamos muchas veces nuestra propia impresión clínica.
Objetivos: 1) Evaluar si existe correlación entre el peso y la altura obtenidos por estimación subjetiva y las medidas reales; 2) analizar si hay concordancia entre las categorizaciones del IMC por medidas objetivas y por impresiones subjetivas; 3) analizar si hay variabilidad inter observador en las impresiones subjetivas de peso, altura y categorías del IMC.
Material y métodos: estudio prospectivo, observacional. Se utilizó la prueba Kappa de Cohen para analizar el grado de concordancia entre los observadores, estableciendo como "buena correlación" un valor mayor a 0,6, y el test de Bland Altman para evaluar las diferencias entre las medidas reales y las estimadas. Se consideró clínicamente significativas una diferencia de peso mayor de 5 Kg y de altura mayor de 5 cm entre las medidas reales y las estimadas.
Resultados: Fueron evaluados 87 pacientes, 54% varones. Más del 58% de las impresiones subjetivas de peso y del 44% de las de altura fueron significativamente distintas a las objetivas. No hubo buena correlación entre las categorías objetivas y subjetivas del IMC.
Conclusión: Las impresiones subjetivas de los médicos en el cálculo del peso, altura e IMC son inapropiadas en más de la mitad de los casos y hay gran variabilidad entre las impresiones clínicas. Es imprescindible medir objetivamente para catalogar adecuadamente a los pacientes.

Palabras Clave: Obesidad - Exceso de peso - Índices antropométricos - Correlación

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INTRODUCTION

Excess weight, defined as a body mass index (BMI) ≥ 25, affects more than 50% of the Western population and 62.5% of the population of the World Health Organization Region of the Americas. (1) This issue has emerged as a major public health concern in the 21st century, underscoring its global health priority due to its increasing prevalence and its association with various complications such as type 2 diabetes, hypertension, heart failure, dyslipidemia, osteoarthritis, obstructive sleep apnea, depression and several types of cancer. (2) Since 1975, obesity rates have almost tripled, affecting people of all ages and social groups worldwide and have increased by almost five times in children and adolescents. (3) In Argentina, there has been a clear upward trend in the prevalence of overweight and obesity across all age and social groups over the years, particularly among the most socially vulnerable groups (4) and has increased from the third edition of the National Survey of Risk Factors (ENFR), where it was 57.9%, to the fourth edition, where it reached 61.6%. Clearly, the trend continues to rise compared to the previous three editions. (5)

While other anthropometric measures are also currently used to better stratify the risk of excess body fat and fat distribution is also considered, BMI is the most validated and widely used tool worldwide. (6) Although BMI can be easily calculated, it requires the availability of a scale and an altimeter which may not be present in all medical offices. Additionally, the measurement process can be time-consuming. Therefore, the trend is to rely on weight and height self-reported by the patient or a family member. Alternatively, a BMI category is assigned according to the subjective perception of the physician. The aim of the present study was to 1) evaluate the concordance between subjective estimates of weight and height and the actual measurements, 2) analyze if there is agreement between BMI categories as determined by objective measurements and as perceived by physicians, and 3) assess if there is inter-observer variability in subjective perceptions of weight, height and BMI category.

METHODS

We conducted an observational and cross-sectional study. Hospitalized patients in the Cardiology Service who were able to ambulate and could be weighed and measured were included in the study. Pregnant patients and those with cachexia, edema, ascites or heart failure were excluded.

Each patient was evaluated by three different physicians. One physician performed the objective measurement of weight and height and calculated the BMI according to the formula. (7) The remaining two physicians examined the patient at different times on the same day, each documenting their subjective assessment of the patient's weight and height and BMI category on the record sheet.

The categories were established according to objective criteria in underweight (UW) if BMI was < 18 kg/m², normal weight (NW) if BMI was between 18.1 and 24.9 kg/m², overweight (OW) if BMI was between 25 and 29.9 kg/m², and obesity (O) if BMI was > 30 kg/m². All overweight or obese patients were grouped together as "excess weight."

Statistical analysis

Qualitative variables are presented as percentages and were compared with the chi-square test or Fisher's test. Quantitative variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR). Cohen's Kappa index was used to assess the agreement between the diagnoses of the different BMI categories, considering the following cut-off points < 0: poor, 0 - 0.20: slight, 0.21 - 0.40: fair, 0.41 - 0.60: moderate, 0.61 - 0.80: substantial and 0.81 - 1.0: excellent. The Bland-Altman plot method was used to estimate the differences in the measurements of the variables. This analysis permitted the evaluation of both systematic bias and the dispersion between the two methods evaluated. A p value < 0.05 was considered statistically significant.

A difference greater than 5 kg in weight and greater than 5 cm in height between the actual and estimated measurements, as well as between those estimated by different operators was considered clinically significant. All the statistical calculations were performed using Stata 22 software package.

Ethical considerations

Informed consent was not required since the information was anonymized and obtained noninvasively.

RESULTS

A total of 87 patients were included; median age was 59 years (IQR 37-72) and 54% were men.

Table 1 shows the percentage of measurements with significant variations (> 5 or 10 kg) in weight or > 5 cm in height.

The Bland Altman plots (Figure 1) illustrate the distribution of the subjective measurements compared with the actual one and the distribution between subjective perception 1 and 2.

In the objective calculation of BMI, 8 patients (9%) were UW, 26 (30%) had normal weight NW, 35 (40%) OW and 18 (21%) were obese. Table 2 shows the categories according to objective measurements of the patients and how many of them are assigned to other categories according to the subjective perception of the operators. The coincidence between the objective determination and the subjective estimation is remarked green. The underestimation of OW stands out, in one third of the patients for observer 1 and almost 50% for observer 2. When the objective determinations of NW and OW were compared with the subjective determinations of observer 1, the subjective determinations of observer 2 and the two subjective determinations with each other, Cohen's kappa indices ranged from 0.3 to 0.5, so the agreement was low. Agreement was somewhat better in the extreme categories: underweight and obesity (Table 3).

DISCUSSION

Excess weight is an epidemic in the Western world associated with increased risk of diabetes and cardiovascular disease. A BMI ≥ 25 kg/m² is the most common tool used to define excess weight. While it is a simple

Table 1. Percentage of significant differences between subjective perceptions of operators 1 and 2 versus actual measurements and those of operator 1 versus operator 2

Measurements	DIF > 5 KG (%)	DIF > 10 KG (%)	DIF > 5 cm (%)
Subjective 1 vs. objective	60.92	29.1	44.8
Subjective 2 vs. objective	58.62	28.8	44.8
Subjective 1 vs. subjective 2	63.22	43.7	59.7

DIF: difference

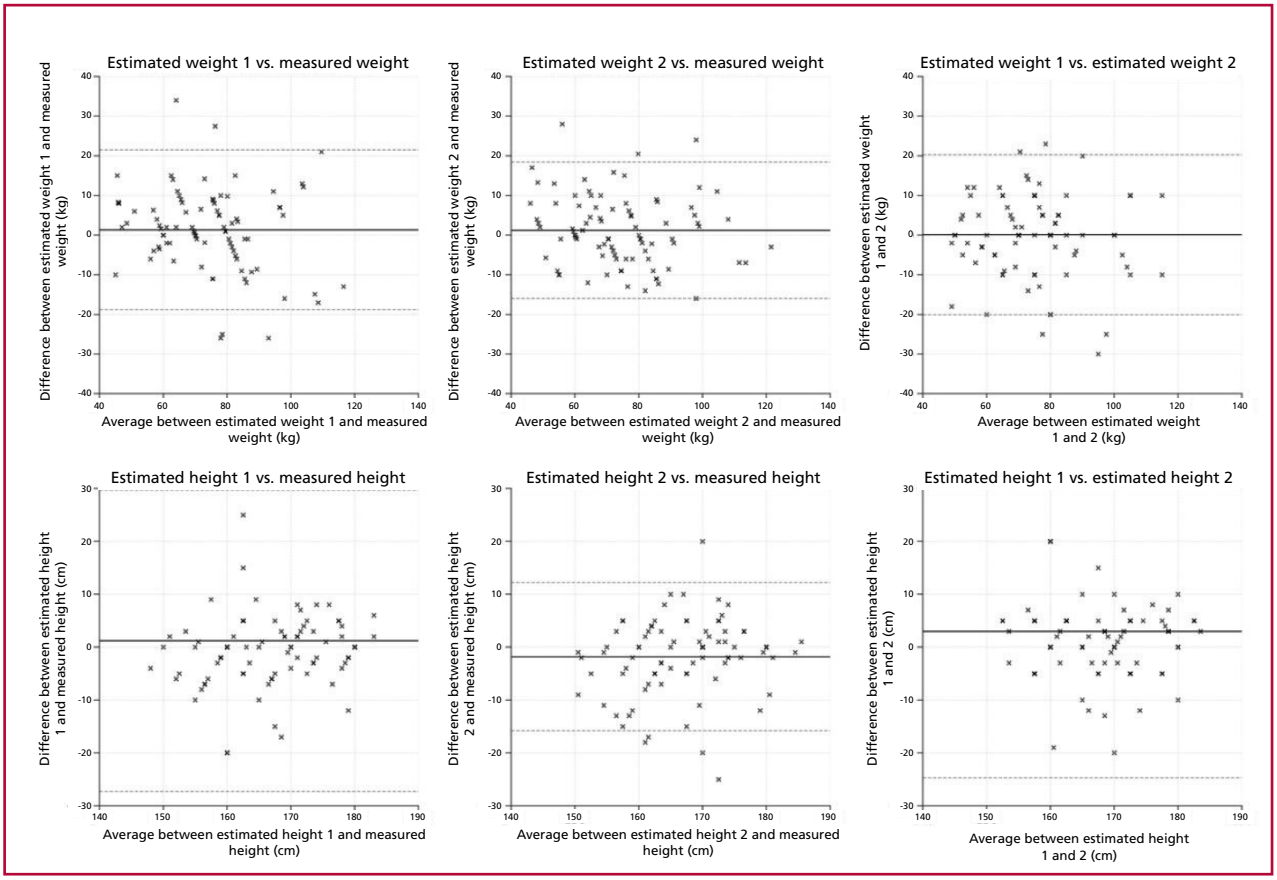

Fig. 1. Bland Altman plots for the analysis of differences in weight (top, in kg) and height (bottom, in cm) between the values estimated by the different operators and measured values.

Table 2. Assignment to different BMI categories according to the subjective perceptions of operators 1 and 2

	N:87	Subjective measurement 1				Subjective measurement 2			
Objective measurement	n	UW	NW	OW	O	UW	NW	OW	O
n		6 (6.89)	37 (42.53)	25 (28.74)	19 (21.84)	6 (6.8)	42 (48.2)	21 (24.1)	17 (19.5)
UW	8 (9)	5	2	1	0	4	4	0	0
NW	26 (30)	1	22	2	1	2	20	2	2
OW	35 (40)	0	12	18	5	0	17	11	7
O	18 (21)	0	1	4	13	0	1	8	9

BMI: body mass index; NW: normal weight; O: obesity; OW: overweight; UW: underweight

Table 3. Cohen's kappa indices for the different comparisons. An index >0.6 implies good concordance

	Low weight	Normal weight	Overweight	Obesity
Subjective 1 vs. objective	0.69	0.53	0.39	0.62
Subjective 2 vs. objective	0.53	0.37	0.13	0.39
Subjective 1 vs. subjective 2	0.64	0.53	0.17	0.44

measure to obtain, it is not typically collected during physical examination because physicians generally categorize patients based on the patient's self-reported information or on their own clinical assessment. While some reports indicate that self-reported weight is generally consistent with measured weight, (8,9) discrepancies have been observed in studies ranging from 20 to 84%. (10-14) These inconsistencies have been observed in self-reported BMI and in reports from family members. This lack of association is influenced (among other factors) by sex, age and socioeconomic level. (15-17) Women tend to underestimate their weight while men tend to overestimate their height. It has also been demonstrated that, irrespective of other sociodemographic factors, there are differences in the self-reported incidence of overweight and obesity among the ethnic groups analyzed. (18)

As medical professionals, we recognize the importance of knowing our patients' weight to ensure proper dosing of medications and their weight and height to calculate BMI. We are trained to see many patients and probably have the perception that our "clinical insight" allows us to accurately "calculate" instead of measuring. In addition, there is often a lack of time and equipment for the correct measurement at the time of consultation. As a result, most physicians who are not specialized in nutrition or diabetes calculate BMI instead of measuring it.

Our study revealed significant and clinically relevant differences in both weight and height measurements, with these subjective measurements being erroneous in more than half of the patients. Additionally, there is significant variability in the subjective perception of physicians. Strikingly, the estimated differences in weight and height between physicians' impressions and the actual ones are significantly greater than those observed in self-reported weight and height. (19-21)

The assignment to a given BMI category based on self-reported data compared to objective measurement is also subject to bias and may lead to errors in categorization (22,23). In this sense, physicians tend to overestimate normal weight and underestimate overweight. There is a higher probability of a correlation between subjective perception and objective measurement, as well as interoperator agreement, in the extreme categories of underweight and obesity.

There are no similar studies in the literature, so we cannot compare our results. However, due to the high margin of error in subjective clinical assessments, the low cost of necessary equipment, and the ease of obtaining objective measurements, we believe it is crucial to share our findings. This will help us correctly classify our patients and perform the necessary interventions without avoidable biases.

CONCLUSIONS

In more than half of the cases, subjective perceptions of physicians when calculating weight, height, and BMI are inappropriate. There is significant variability in clinical impressions between physicians, except for obesity assessments, where there is greater agreement between subjective and objective measurements. However, the lack of correlation between normal weight and overweight ranges underscores the importance of objective measurements for accurate patient categorization.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Right Ventricular Function and Prognosis in Patients with Transthyretin Amyloid Cardiomyopathy

Función ventricular derecha y pronóstico en pacientes con cardiopatía amiloidótica por transtiretina

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ABSTRACT

Background: Transthyretin amyloid cardiomyopathy (ATTR-CM) is an infiltrative disease that impairs the diastolic and systolic function of the heart, affecting both left and right chambers.
Objective: To evaluate the frequency of right ventricle (RV) function involvement and its prognostic impact.
Methods: A retrospective analysis of a cohort of 154 patients with ATTR-CM in a specialized cardiology center. Clinical, laboratory and echocardiographic data, risk factors and cardiovascular events were collected. The relationship of RV function with prognosis was assessed using the Cox proportional hazards model.
Results: Median age was 81 years (interquartile range, IQR, 75-85), and 95% of patients were men. Forty-seven percent of cases had tricuspid annular plane systolic excursion (TAPSE) <17 mm and 52% had RV S-wave <9.5 cm/s. Mean pulmonary pressure was 40 mmHg (IQR 33-50), and 21.7% showed moderate-severe tricuspid regurgitation. During a median follow-up of 528 days (IQR 159-1004), total mortality was 19.3%, cardiovascular mortality 11.8%, hospitalization for heart failure (HHF) 30.5%, and incidence of atrial fibrillation (AF) 30.4%. TAPSE was an independent predictor of total mortality (HR 0.847, 95% CI 0.730-0.983, p=0.028), cardiovascular mortality (HR 0.725, 95% CI 0.600-0.875, p=0.001), HHF (HR 0.859, 95% CI 0.755-0.977, p=0.001), and AF (HR 0.841, 95% CI 0.727-0.972, p=0.019).
Conclusion: Right ventricular dysfunction is frequent in ATTR-CM. TAPSE, as a simple parameter, independently predicts mortality, cardiovascular events and AF in the mid-term.

Keywords: Cardiac amyloidosis - Right ventricle - Heart failure

RESUMEN

Introducción: La cardiopatía amiloidótica por transtiretina (CA-TTR) es una enfermedad infiltrativa que compromete la función diastólica y sistólica del corazón, y afecta tanto las cavidades izquierdas como las derechas.
Objetivo: Evaluar la frecuencia de afectación de la función del ventrículo derecho (VD) y su impacto pronóstico.
Material y métodos: Análisis retrospectivo de una cohorte de 154 pacientes con CA-TTR en un centro especializado en cardiología. Se recopilaron datos clínicos, de laboratorio y ecocardiográficos, factores de riesgo y eventos cardiovasculares. La relación de la función del VD con el pronóstico se evaluó mediante el modelo de riesgos proporcionales de Cox.
Resultados: La edad mediana fue 81 años (rango intercuartílico, RIC, 75-85), con 95% de hombres. El 47% presentó excursión sistólica del plano del anillo tricuspídeo (TAPSE) <17 mm y el 52% onda S del VD <9,5 cm/s. La presión pulmonar media fue 40 mmHg (RIC 33-50), y el 21,7% mostró insuficiencia tricuspídea moderada-grave. Durante una mediana de seguimiento de 528 días (RIC 159-1004), la mortalidad total fue 19,3%, la mortalidad cardiovascular 11,8%, la hospitalización por insuficiencia cardíaca (HIC) 30,5%, y la incidencia de fibrilación auricular (FA) 30,4%. El TAPSE fue predictor independiente de mortalidad total (HR 0,847, IC95% 0,730-0,983, p=0,028), mortalidad cardiovascular (HR 0,725, IC95% 0,600-0,875, p=0,001), HIC (HR 0,859, IC95% 0,755-0,977, p=0,001) y FA (HR 0,841, IC95% 0,727-0,972, p=0,019).
Conclusión: La disfunción del VD es frecuente en la CA-TTR. El TAPSE, como parámetro simple, predice independientemente mortalidad, eventos cardiovasculares y FA a mediano plazo.

Palabras clave: Amiloidosis cardíaca - Ventrículo derecho - Insuficiencia cardíaca

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INTRODUCTION

Amyloid cardiomyopathy (ACM) is characterized by the deposition of misfolded proteins in cardiac tissue, leading to progressive dysfunction of the heart. In its transthyretin-associated form (ATTR-CM), these proteins adopt abnormal folding and form fibrillar aggregates that accumulate mainly in the myocardium. This process initially affects diastolic function, and in advanced stages leads to heart failure (HF) with a significant impact on patients' quality of life. (1-3)

Historically, attention in ACM has been focused on left ventricular (LV) function, characterized by the development of cardiomyopathy with restrictive physiology. (4,5) The importance of the right ventricle (RV)has been underestimated, despite its growing recognition as a key determinant of prognosis in this disease. (6,7) Right ventricular dysfunction not only aggravates systemic venous congestion, but, together with tricuspid regurgitation and elevated pulmonary pressures, contributes to the functional and clinical deterioration of patients. (8,9)

In this context, the aim of our study was to evaluate the frequency of RV systolic dysfunction in patients with ATTR-CM and its prognostic impact. A deeper understanding of this alteration could improve risk stratification and favor the implementation of more effective therapeutic strategies aimed at optimizing the prognosis and quality of life of patients.

METHODS

Study design

A retrospective observational study was performed using data prospectively obtained from the electronic medical records of patients at Instituto Cardiovascular de Buenos Aires. Patients with ATTR-CM diagnosis under ambulatory follow-up performed by physicians from the cardiomyopathy clinic of the institution, were included between January 2011 and March 2024, according to the usual diagnostic criteria in force during that period. (10) Baseline demographic, clinical, laboratory, and echocardiographic data were collected, as well as risk factors and cardiovascular events before and after the diagnosis of amyloidosis.

Confirmation of cardiac amyloidosis by transthyretin.

Transthyretin amyloid cardiomyopathy was defined as the combination of typical echocardiographic imaging features (e.g., wall thickness ≥12 mm) with grade 2 or 3 cardiac uptake on ^{99}mTc-HMDP (hydroxymethylene diphosphonate) scintigraphy, plus exclusion of clonal dyscrasia by serum free light chain assay (Freelite, Binding Site) and immunofixation in blood and urine to detect a monoclonal component. (11,12) Scintigraphy was performed in all patients with 20 mCi of ^{99}mTc-HMDP administered intravenously, taking planar images 2 hours after dose administration. The degree of cardiac uptake in relation to bone tissue was assessed using two methods: 1) Semi-quantitative procedure, following the Perugini visual scale, where cardiac uptake was compared with the sternum: grade 0 =no cardiac uptake, 1=cardiac uptake less than the sternum, 2=cardiac uptake equal to the sternum, 3 = cardiac uptake greater than the sternum; and 2) Quantitative procedure: heart-lung ratio.

The final diagnosis of ATTR-CM was based on the results of clinical evaluation, electrocardiograms, echocardiograms and scintigraphy, after exclusion of plasma cell disease (free light chains, serum and urine immunofixation). (6,7) Magnetic resonance imaging with gadolinium was performed in selected patients. In inconclusive cases, a tissue biopsy was performed.

Objective

To evaluate the frequency of RV systolic function involvement in our population with ATTR-CM and its prognostic impact.

Definition of right ventricular function impairment by echocardiography (Figure 1)

- Tricuspid annular plane systolic excursion (TAPSE) <17 mm
- Right ventricular S-wave by tissue Doppler imaging (TDI) <9.5 cm/s. (13)

Events analyzed in the follow-up

- Hospitalization or urgent emergency department visit for HF
- Development of atrial fibrillation (AF)
- Cardiovascular death
- All-cause mortality

Statistical analysis

Discrete variables were expressed as percentages and continuous variables were described using mean and standard deviation (SD) or median and interquartile range (IQR), according to normal or non-normal distribution, respectively. Normality of distribution was assessed using the Kolmogorov-Smirnov method. Categorical variables were analyzed using the Chi-square test or Fisher's exact test, and quantitative variables were analyzed with Student's t-test or the Mann-Whitney U test, depending on the distribution.

Univariate analysis was performed with Cox regression, including all variables biologically relevant to the event. After confirming statistical significance, multiple Cox regression was performed using a backward selection strategy, based on the Z value associated with each variable (Wald test), estimated from the ratio of each coefficient over its standard error. In this multivariate analysis, variables with a level of statistical significance in the univariate analysis with $p < 0.10$ were included.

Event-free survival during follow-up was analyzed using the Log-Rank test and plotted on Kaplan-Meier curves. Statistical significance was considered with $p < 0.05$ (two-tailed test). All data analyses were performed using IBM SPSS version 29.0 software.

Ethical considerations

This study was evaluated and approved by the institutional Ethics Committee. The study was registered in the PRIISA. BA platform of the Ministry of Health of the Autonomous City of Buenos Aires and was conducted in accordance with national and international regulations for the protection of research subjects, such as the latest version of the Declaration of Helsinki, (14) Resolution 1480/2011 of the National Ministry of Health, Law 3301 of the City of Buenos Aires, and ANMAT Resolution 6677/10 and its amendments 4008 and 4009.

RESULTS

A total of 154 patients were included in the study, 95% male (n=147), and with median age of 81 years (IQR 75-85). Most patients had comorbidities: 77% hyper-

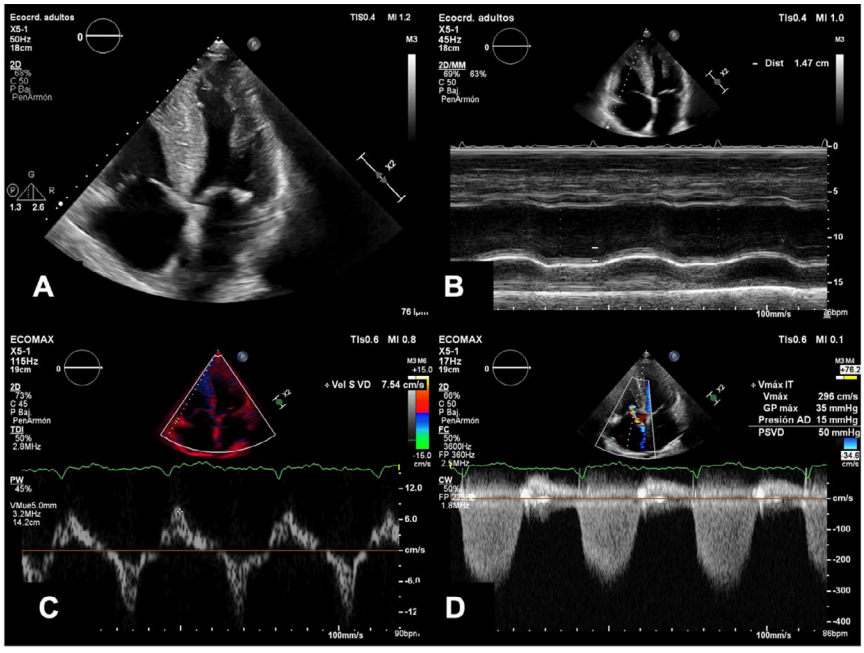

Fig. 1. Evaluation of the right ventricle. **A:** 4-chamber view of a patient with amyloid cardiomyopathy. **B:** Tricuspid annular plane systolic excursion (TAPSE). **C:** Right ventricular S-wave. **D:** Estimation of pulmonary artery systolic pressure.

tension, 17% diabetes, 58% dyslipidemia and 41% had a history of smoking or were ex-smokers. Regarding other relevant conditions, 25% had coronary artery disease and 8% previous coronary artery bypass grafting (CABG). Twenty-seven percent of patients had a permanent pacemaker (PPM) and only one patient had an implantable cardioverter-defibrillator (ICD). Atrial fibrillation was present in 53% of cases before diagnosis. Among the red flags associated with ATTR-CM, 6% had neuropathy, 29% carpal tunnel syndrome and 6.5% narrow spinal canal.

Laboratory parameters showed a median N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 3800 ng/L (IQR 1200-7600) and high-sensitivity troponin T of 62 ng/L (IQR 42-91), along with an estimated glomerular filtration rate of 54 ml/min/1.73 m^2 (IQR 40-68).

Echocardiogram showed a median left ventricular ejection fraction (LVEF) of 50% (IQR 42-60), interventricular septum (IVS) of 16 mm (IQR 14-19) and posterior wall of 13 mm (IQR 12-15).

Median TAPSE was 17 mm (IQR 14-19), and RV S-wave 9 cm/s (IQR 8-10). Median left atrial (LA) area was 29 cm^2 (IQR 26-32). Tricuspid regurgitation (TR) was mild in 47% of patients (n=67), moderate in 17% (n=25) and severe in 4.2% (n=6). In 6.2% of cases (n=9), patients had mild aortic stenosis, 10.3% (n=15) moderate and 5.5% (n=8) severe. Sixty per cent of patients (n=85) had mild mitral regurgitation, 17.5% (n=25) moderate, and there were no cases of severe mitral regurgitation (Tables 1 and 2).

With respect to the study objective, 47% presented TAPSE value <17 mm and 52% RV S-wave <9.5 cm/s.

Median follow-up was 528 days (IQR 159-1004), during which total mortality was 19.3% and cardiovascular mortality 11.8%. In addition, 30.5% of patients were hospitalized for HF and 30.4% of those free of AF at baseline developed this arrhythmia during follow-up.

Univariate analysis identified TAPSE as an independent predictor of adverse clinical events. Even after adjusting for multiple echocardiographic (LVEF, IVS, LV lateral and medial S-wave, filling pattern, pulmonary systolic pressure, RV S-wave and E/e´ ratio), demographic (age and sex) and clinical (previous HF, diabetes, PPM, previous coronary artery disease, and previous AF) variables, TAPSE remained as an independent predictor of total mortality (HR 0.847; 95% CI 0.730-0.983, p=0.028), cardiovascular mortality (HR 0.725; 95% CI 0.600-0.875, p=0.001), hospitalization for HF (HR 0.859; 95% CI 0.755-0.977, p=0.001) and development of AF (HR 0.84; 95% CI 0.727-0.972, p=0.019). (Figure 2)

DISCUSSION

This study evaluated a cohort of patients diagnosed with ATTR-CM followed up by physicians from the cardiomyopathy service of a single center in Argenti-

Tabla 1. Population characteristics

Variable	Value
Male sex	147 (95.2%)
Age, years	81 (75-85)
Hypertension	126 (77.3%)
DM	29 (17.8%)
Dyslipidemia	95 (58.3%)
Smoking	66 (41.3%)
Stroke / TIA	20 (12.4%)
PCI	34 (21.1%)
CABG	14 (8.7%)
Coronary artery disease	41 (25.5%)
PPM	44 (27%,3)
VRS	10 (6.3%)
ICD	1 (0.6%)
CRT	2 (1.3%)
Previous AF	82 (50.9%)
Neuropathy	9 (6.2%)
Carpal tunnel	46 (29.3%)
Narrow medullary canal	10 (6.5%)

AF: atrial fibrillation; CTA: coronary transluminal angioplasty; CABG: coronary artery bypass grafting; CRT: cardiac resynchronization therapy, DM: diabetes mellitus; ICD: implantable cardioverter-defibrillator; PCI: percutaneous coronary intervention; PPM: permanent pacemaker; TIA: transient ischemic attack; VRS: valve replacement surgery.
Qualitative variables are presented as frequency and percentage, and quantitative as median and interquartile range.

Tabla 2. Baseline laboratory and echocardiogram characteristics

Variable	Value
Laboratory	
NT-proBNP, ng/L	3800 (1200-7600)
Glomerular filtration rate, mL/min/1.73 m^2	54 (40-68)
Ultra-sensitive troponin T, ng/L	62 (42-91)
Echocardiographic characteristics	
LVEF, %	50 (42-60)
IVS, mm	16 (14-19)
PW, mm	13 (12-15)
LVDD, mm	44 (40-49)
LVSD, mm	30 (25-25)
Lateral S-wave, cm/s	5.8 (5- 6.8)
Medial S-wave, cm/s	4.65 (3.9- 5.4)
LA, cm^2	29 (26-32)
Filling pattern	
Prolonged relaxation	8 (5.6%)
Pseudonormal	41 (29%)
Restrictive	34 (24%)
Monophasic	57 (40%)
TAPSE , mm	17 (14-19)
PASP, mmHg	40 (33-50)
RV S-wave, cm/s	9 (8-10)
E/e' ratio	16 (12-19)
Septal E, cm/s	5 (4-5.3)
Lateral E, cm/s	6.7 (5.3-8)
Tricuspid regurgitation	
M	67 (47%)
Mod	25 (17%)
S	6 (4.2%)
Aortic stenosis	
M	9 (6.2%)
Mod	15 (10.3%)
S	8 (5.5%)
Mitral regurgitation	
M	85 (60%)
Mod	25 (17.5%)
S	0 (0%)

LA: left atrium; IVS: interventricular septum; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVEF: left ventricular ejection fraction; M: mild; Mod: moderate; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PW: posterior wall; PASP: pulmonary artery systolic pressure; RV: right ventricular. S: severe; TAPSE: tricuspid annular plane systolic excursion.
Qualitative variables are presented as frequency and percentage and quantitative variables as median and interquartile range.

na. The frequency of RV systolic dysfunction was analyzed in this population and its prognostic impact was investigated. We consider it is important to highlight three aspects of our work.

Firstly, it is relevant to know the prevalence of RV impairment in our population. In the echocardiogram, we found TAPSE <17 mm in 47% of patients and RV S-wave < 9.5 cm/s in 52%, as an expression of right ventricular dysfunction. In the study by Diane Bodez et al. non-survivors showed worse RV systolic function on echocardiography assessed by TAPSE and RV free wall deformation. Significantly, RV free wall deformation was independently associated with all-cause mortality in several multivariate Cox regression models, with incremental prognostic value over conventional parameters of RV function. (15) Right ventricular involvement is common in patients with cardiac amyloidosis. (16) It is proposed that this dysfunction may be mediated by amyloid infiltration of the RV wall itself, by increased afterload in cases of pulmonary hypertension, and by ventricular interdependence.

Secondly, it is crucial to understand the role of the right ventricle in the prognosis of patients with cardiac amyloidosis. Right ventricular dysfunction, often underestimated in clinical practice, plays a crucial role in the progression of HF and in the development of AF, probably due to pressure overload and fibrosis induced by amyloid infiltration. TAPSE, a simple and widely available echocardiographic parameter, emerged in our study as an independent predictor of adverse clinical events even after adjusting for other demographic and echocardiographic variables. Our

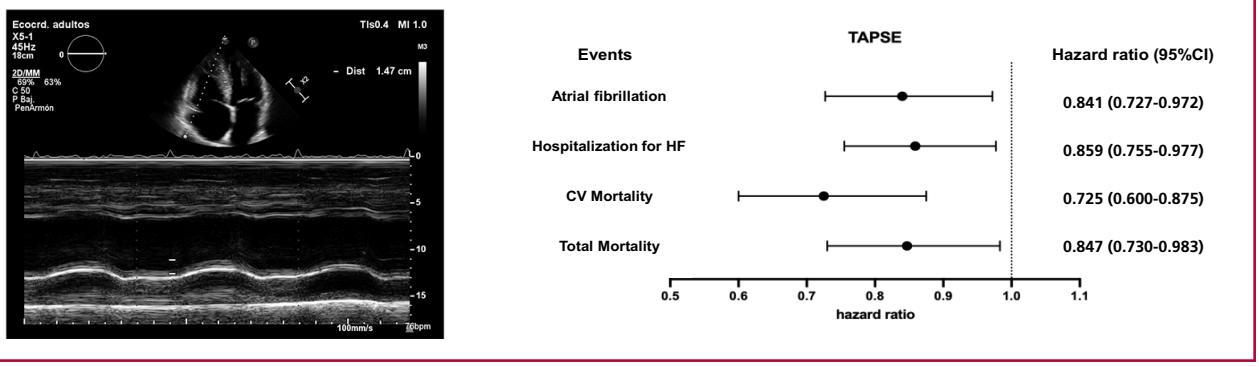

Fig. 2. Prognostic value of TAPSE (tricuspid annular plane systolic excursion) for major events.

results are in the same direction of published data in patients with light chain (AL) amyloidosis. (17-19) In 2007, Ghio et al. reported the association of TAPSE <17 mm with BNP elevation and mortality in patients with AL amyloidosis. (17)

Finally, the findings of our study, which show an inverse association between TAPSE and heart failure, mortality, and atrial fibrillation events in patients with ATTR-CM, reinforce its potential value as a prognostic tool in this disease. It is essential to have a widely available and simple to obtain parameter, to stratify risk in this population. Although our observational design does not allow us to establish causality, the detection of RV dysfunction could motivate closer clinical surveillance, favoring the early detection of events such as AF, in which case timely intervention -such as the initiation of anticoagulation- could have a relevant clinical impact. (20,21)

Limitations

The retrospective and single-center nature of the study limits the generalization of results, highlighting the need to reproduce them in other cohorts. Furthermore, it was not possible to evaluate myocardial deformation parameters in all patients, which prevented the inclusion of this variable, despite its recognized diagnostic and prognostic value, as well as right ventricular ejection fraction by a 3-dimensional method. Nevertheless, the fact that simple and accessible parameters, such as TAPSE, demonstrate prognostic value reinforces its clinical relevance.

CONCLUSION

Echocardiographic RV impairment is common in patients with ATTR, and TAPSE stands out as a simple and accessible echocardiographic parameter, due to its predictive capacity in the clinical course of these patients. A reduced TAPSE is associated with a higher risk of total and cardiovascular mortality, hospitalizations for HF and development of AF in the mid-term, highlighting the importance of its evaluation in clinical practice for better risk stratification and disease management.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Cardiovascular Evidence Gaps in Adults Over 80 Years of Age

Brechas en la evidencia cardiovascular en adultos mayores de 80 años

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ABSTRACT

Background: Current clinical practice guidelines show limitations regarding patients over 80 years of age due to their underrepresentation in clinical trials and the complex interaction between frailty, multimorbidity, polypharmacy and cardiovascular events.
Objectives: The aim of this study was to discuss existing management gaps and to establish recommendations for this population, through discussion with referring physicians in cardiology and geriatrics.
Methods: A meeting was held using structured consensus methodology in roundtables assembling 34 cardiologists and 6 geriatricians to analyze different clinical scenarios: frailty, polypharmacy, cardiovascular prevention, heart failure, atrial fibrillation and acute coronary syndromes. Management strategies were evaluated according to three categories (robust, mild frailty and moderate frailty) by structured discussion and anonymous voting. In this publication we present the results obtained in the first four scenarios.
Results: An inverse association was observed between therapeutic intensity and degree of frailty. Most physicians considered it relevant to assess frailty and extracardiologic medication, and to evaluate deprescribing during follow-up. In cardiovascular prevention, acceptance of lipid-lowering treatment initiation decreased significantly with increasing frailty (82.1% in robust vs. 23.1% in moderate frailty), whereas deprescription of statins increased (23.1% in robust vs. 41% in moderate frailty). In heart failure with preserved ejection fraction, gliflozins showed high acceptance in patients without volume overload (94.6% in robust vs. 54.1% in moderate frailty). For patients with reduced ejection fraction, initiation of quadruple therapy decreased significantly with frailty (45.9% in robust vs. 2.7% in moderate frailty), whereas maintenance of treatment in recovered ejection fraction decreased as frailty increased (91.9% in robust vs. 59.5% in moderate frailty).
Conclusions: The degree of frailty significantly influenced therapeutic decision-making in octogenarian patients, with a trend towards more conservative approaches as the degree of frailty increases. These findings suggest the need for treatment algorithms stratified by frailty and highlight the importance of incorporating comprehensive patient assessment into cardiovascular care protocols.

Keywords: Frailty - Comprehensive cardiology assessment - Evidence gaps - Cardiovascular disease - Older adults

RESUMEN

Introducción: Las guías de práctica clínica actuales muestran limitaciones respecto de los pacientes mayores de 80 años debido a su baja representación en ensayos clínicos y la compleja interacción entre fragilidad, multimorbilidad, polifarmacia y eventos cardiovasculares.
Objetivos: Discutir brechas en el manejo y establecer recomendaciones para esta población, mediante discusión con médicos referentes en cardiología y geriatría.
Material y métodos: Se realizó una reunión mediante metodología de consenso estructurado a través de mesas redondas (roundtables) para la cual se convocó a 34 cardiólogos y 6 geriatras y se analizaron diferentes escenarios clínicos: fragilidad, polifarmacia, prevención cardiovascular, insuficiencia cardíaca, fibrilación auricular y síndromes coronarios agudos. Las estrategias de manejo se evaluaron según tres categorías (robusto, fragilidad leve, fragilidad moderada) mediante discusión estructurada y votación anónima. En esta publicación presentamos los resultados obtenidos en los primeros cuatro escenarios.

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Resultados: Se observó asociación inversa entre la intensidad terapéutica y el grado de fragilidad. La mayoría consideró relevante evaluar fragilidad, la medicación extracardiológica y pensar en deprescripción durante el seguimiento. En prevención cardiovascular, la aceptación del inicio de tratamiento hipolipemiante mostró un descenso significativo con el incremento de la fragilidad (82,1% en robusto vs 23%,1% en fragilidad moderada), mientras que aumentó la deprescripción de estatinas (23,1% en robusto vs 41% en fragilidad moderada). En insuficiencia cardíaca con fracción de eyección preservada, las gliflozinas mostraron alta aceptación en pacientes sin sobrecarga (94,6% en robusto vs 54,1% en fragilidad moderada). Para pacientes con fracción de eyección reducida, el inicio de la cuádruple terapia disminuyó significativamente con la fragilidad (45,9% en robusto vs 2,7% en fragilidad moderada), mientras que el mantenimiento del tratamiento en fracción de eyección recuperada disminuyó a medida que aumentaba la fragilidad (91,9% en robusto vs 59,5% en fragilidad moderada).
Conclusiones: El grado de fragilidad influyó significativamente en la toma de decisiones terapéuticas en pacientes octogenarios, con una tendencia hacia abordajes más conservadores a medida que aumenta el grado de fragilidad. Estos hallazgos sugieren la necesidad de algoritmos de tratamiento estratificados por fragilidad y destacan la importancia de incorporar la valorización integral del paciente en los protocolos de atención cardiovascular.

Palabras clave: Fragilidad - Valoración integral en cardiología - Brechas en la evidencia - Enfermedad cardiovascular - Adultos mayores

INTRODUCTION

In people over 80 years of age, multiple factors limit the application of the different cardiovascular practice guidelines. This population faces higher mortality, a frequently compromised quality of life and, in addition, is underrepresented in the different clinical trials, generating gaps in the evidence.

The main challenges include the discrepancy between chronological and biological age, multimorbidity, atypical presentation of cardiovascular diseases often influenced by geriatric syndromes, and variable therapeutic response.

Another characteristic in this population group is the heterogeneity within the functional continuum, which includes robustness, frailty, disability, and terminality. In a context of growing life expectancy and increasing prevalence of cardiovascular diseases, it is a priority to identify these gaps in order to improve outpatient clinical management and outcomes. (1-6)

Roundtables are an effective tool for discussing controversial scenarios and promoting consensuses applicable to clinical practice.

OBJECTIVES

To address this problem, the Cardiogeriatrics Council of the Argentine Society of Cardiology proposed and organized the first national roundtable that brought together referring physicians. The following scenarios were selected for this first meeting: frailty, polypharmacy, cardiovascular prevention, heart failure, atrial fibrillation and acute coronary syndromes. The objectives of the meeting were to discuss gaps in management and establish recommendations for this population, to promote a critical analysis of existing guidelines, and to explore strategies adapted to local needs. In the present publication we present the results obtained in the first four scenarios

METHODS

The roundtable was held in person in June 2024 in the city of Buenos Aires, Argentina, and was attended by 40 referring physicians, 34 cardiologists and 6 geriatricians, with recognized clinical and academic careers.

The methodological process was structured in three stages to systematically address the knowledge gaps.

-Gap identification: In this initial phase, the organizing team of the Cardiogeriatrics Board of Directors conducted an exhaustive review of recent literature and clinical practice guidelines. This analysis allowed the identification of areas with insufficient evidence in the management of cardiovascular diseases in older adults and to draw up a preliminary list of gaps in knowledge.

-Scenario design: In this stage, the usefulness of various frailty tools and diagnostic and therapeutic strategies in patients over 80 years of age were discussed and analyzed. In scenarios with comorbidities, the condition was postulated to be stable, without terminal pathology. It was decided to divide this population into robust, mild frailty and moderate frailty, because they are different conditions in terms of prognosis and treatment. Based on the proposed clinical scenarios, the different rounds were designed. Selected literature was sent to the participating physicians and voting forms were designed for records that would be used during the discussion.

-Table of discussion and consensus: Finally, the meeting was conducted through a structured methodology that combined open discussion and then anonymous voting.

All these stages sought to ensure a comprehensive and systematic approach, aimed at generating practical recommendations to optimize cardiovascular management in elderly people.

In each case, the degree of recommendation is presented on a scale ranging from recommended to not recommended (Figure 1).

Discussion scenarios:

Round 1: Frailty

The bidirectionality between frailty and cardiovascular disease is influenced by pathophysiological mechanisms and common risk factors. In turn, treatment of cardiovascular disease impacts on frailty and vice versa. (7-10)

Frailty has been incorporated into cardiology guidelines as a variable that conditions the evolution and treatment in different scenarios, including prevention. The guidelines include it from a multidomain approach with a person-centered perspective and adapted to different clinical scenarios, although despite this, both in practice and in studies, the use of the functional frailty model continues to be prioritized. Lack of a universal definition, multiple assessment tools, the proposal of a functional phenotype and another based on the

accumulation of deficits, has conditioned its use to date in clinical practice. (11)

Results: The relevance of detecting frailty in patients with cardiovascular disease was discussed, and 100% of participants agreed on its importance. Functional assessment was considered more relevant by 32.5% of participants and 50% reported using some screening method to assess frailty. More than half (55%) considered the use of frailty tools oriented to specific diseases to be more appropriate, 22.5% did not consider this option and 22.5% were in doubt. If a multi-domain assessment tool had to be chosen, 35% would opt for the Clinical Frailty Scale (CFS), (12) 20% for the Comprehensive Geriatric Assessment-Frailty Index (CGA IF), (13) 15% for the Edmonton Frailty Scale, (14) 12.5% for the Frail-VIG index (15) and 17.5% would prefer a simple screening of each domain (Annex 1).

Opinion: Although all the participants considered the importance of detecting frailty in cardiology, only 50% used some type of frailty screening (it should be noted that 6 of the participants were geriatricians). It is relevant to note that only 32.5% believe it is more important to evaluate frailty from a functional approach.

The Cardiogeriatrics Council promotes multidomain assessment, which includes the functional component, with a person-centered approach. Although no agreement was reached at the meeting on which tool to use, we understand frailty as a global condition of the patient and prefer comprehensive assessment tools rather than those specific to each pathology. Not having reached agreement on this point opens the way for future research (Figure 2).

Round 2: Polypharmacy

Multimorbidity and polypharmacy are highly prevalent in this population group. (16)

Their association with frailty exponentially increases the likelihood of major adverse cardiovascular events and poor adherence to treatment. (17,18) The criteria for appropriate prescribing and potentially inappropriate drugs described for the elderly are not frequently used in cardiology practice.

Results: The evaluation of extracardiac medication was relevant for all participating physicians and 97.5% think of deprescribing drugs during follow-up.

In 75% of cases, participants would use STOPP/START (19,20) and BEERS (21) criteria and 87.5% found it interesting to generate our own criteria on inappropriate prescription (Annex 1).

Opinion: From the Council, we emphasize the importance of evaluating the patient's total medication, assessing appropriate prescription, encouraging deprescribing of potentially inappropriate drugs, and the search for criteria that facilitate their application in daily practice at the local level. This motivated us to work on a project on appropriate medication in cardiovascular therapeutics (MATE, in progress). (Figure 3).

Round 3: Primary cardiovascular prevention

The 2023 SAC guideline on cardiovascular prevention questions the use of cardiovascular risk (CVR) scores as they are not validated in the Argentine population. (22) However, the use of scores in primary prevention in validated populations is useful and necessary and is a IC recommendation in the guidelines. Within the IC recommendations, frailty and other morbidities are included as risk modulators. (23) A 10-year CV risk estimation using the SCORE2-OP for patients over 70 years of age, strongly recommends the evaluation of the treatment risk/benefit, the presence of frailty and other risk modifiers, polypharmacy and patient preferences.(24) The use of validated scores in this patient population has an impact on therapeutic decisions.

The European guidelines recommend the use of statins in patients over 70 years of age at high or very high risk (IIb recommendation) based mainly on the analysis of age subgroups of the JUPITER and HOPE-3 studies. (25) On the other hand, the American guidelines recommend their use in patients over 75 years of age at high risk (IIb recommendation), incorporating the use of calcium scoring by means of coronary angiography as a risk modifier. (26)

Results: The usefulness of CVR scores was considered to be inversely proportional to the degree of frailty: 66.7% in robust patients, 46.2% in mild frailty and 25.6% in moderate frailty.

A hundred percent of participating physicians considered frailty as a CVR modifier. The relevance of these modifiers in clinical decision making reached 84.6% in both robust and

Fig. 1. Grade of recommendation

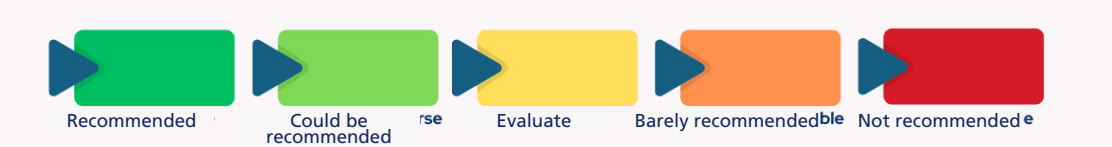


Fig. 2. Frailty

Fig. 3. Polypharmacy

mild frailty patients, dropping to 64.1% in moderate frailty (with 33.3% doubt/indecision in this scenario).

Regarding the initiation of lipid-lowering treatment, acceptance showed a descending gradient according to frailty: 82.1% in robust patients, 69.2% in mild frailty and 23.1% in moderate frailty, with significant uncertainty (51.3%) in the latter group.

Screening for subclinical atherosclerosis was accepted by 64.1% of participants in robust patients, 56.4% in mild frailty (30.8% of doubt) and 20.5% in moderate frailty (43.6% of doubt).

In the case of statin prescription in primary prevention with documented subclinical atherosclerosis, acceptance was 76.9% in robust patients (12.8% of doubt), 64.1% in mild frailty (15.4% of doubt) and 38.5% in moderate frailty (28.2% of doubt).

Statin deprescribing with documented subclinical atherosclerosis was considered in 23.1% of robust patients, 20.5% with mild frailty and 41% with moderate frailty. (Annex 1).

Opinion: As we can see, the lack of evidence in older patients limits decisions, whether from risk stratification with scores or their use in primary prevention.

Although the guidelines postulate frailty as a modifier of CVR, and taking into account that frailty increases the risk of major events, the indication for statins decreased as the degree of frailty increased, even in the presence of subclinical atheromatosis. (27,28) The board recommends the use of statins in these groups of patients while the evidence progresses (Figure 4).

Round 4: Heart failure

Heart failure (HF) represents a major epidemiological challenge with a high number of hospitalizations, deterioration in quality of life and high morbidity and mortality. Multimorbidity, polypharmacy and frailty are highly prevalent in both aging and HF, to which we must add the heterogeneity of this population and their longer life expectancy, turning decision-making difficult.

Frailty may affect up to 45% of HF patients and, in turn, increases the risk of HF. (29)

Symptoms are often assumed to be part of aging, which generates difficulty and delay in their diagnosis. Moreover, in this group of patients the cut-off values of natriuretic peptides for diagnosis are higher and are strongly influenced by renal function and other comorbidities, which often reduces their degree of certainty. (30)

Heart failure with preserved left ventricular ejection fraction (HF-pEF) is a complex clinical syndrome affected by comorbidities, and it is also multicausal, since it can be a manifestation of cardiovascular dysfunction or a combination with other morbidities. At the time of the Round Table discussion, the specific therapy was reduced to gliflozins. (31) The publication of the FINEARTS-HF study with finerenone was later. (32)

In HF with reduced left ventricular ejection fraction (HF-rEF), quadruple therapy is the cornerstone of treatment with class IA indication (33-35).

a. HF-pEF

Results: The indication of gliflozins in patients without volume overload was accepted by 94.6% of participants in robust patients, 86.5% in mildly frail patients and 54.1% in moderately frail patients (40.5% of doubt). In the scenario of creatinine clearance between 20 and 30 ml/min, 78.4% would indicate them in robust patients (16.2% of doubt), 45.9% in mildly frail patients (43.2% of doubt) and 24.3% in moderately frail patients (51.4% of doubt).

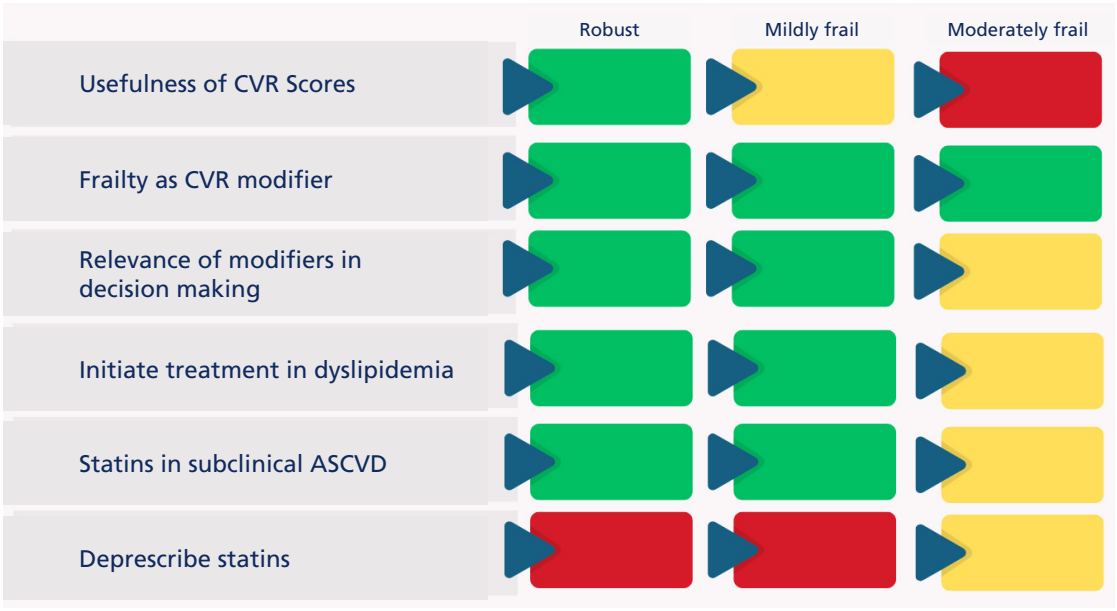
In patients with atrial fibrillation (AF) and obesity, the use of glucagon-like peptide 1 receptor agonists (GLP-1 RA) had an acceptance rate of 40.5% in robust, 16.2% in mildly frail and 5.4% in moderately frail patients. Uncertainty was 29.7%, 45.9% and 32%, respectively.

The usefulness of the N-terminal pro B-type natriuretic peptide (NT-proBNP) as a diagnostic tool was accepted by 59.5% of participants for robust, 48.6% for mildly frail and 40.5% for moderately frail patients, with 21.6% were in doubt about its usefulness in robust, and 29.7% in mild and moderate frailty (Annex 1).

b. HF-rEF

Results: Simultaneous initiation of the four therapeutic pillars in the absence of clinical signs of HF showed an acceptance rate of 45.9% in robust, 27% in mildly frail, and 2.7% in moderately frail patients (24.3%, 29.7%, and 35.1%, respectively). In the pharmacological prioritization, in the 3 scenarios, gliflozins emerged as the first option, followed by sacubitril valsartan and mineralocorticoid receptor antagonists.

Fig. 4. Primary cardiovascular prevention



ASCVD: atherosclerotic cardiovascular disease; CVR: cardiovascular risk.

In the presence of a clearance <30 ml/min, in all three scenarios, gliflozins were the drugs of choice with 81.1% acceptance for robust and mildly frail patients and 70.3% acceptance in cases of moderate frailty.

In patients with recovered left ventricular ejection fraction, 91.9% of participating physicians would maintain treatment in robust, 73% in mildly frail and 59.5% in moderately frail patients, with a doubt rate of 8.1%, 24.3% and 21.6% for the respective scenarios.

The implementation of palliative care from the diagnosis of HF was supported by 32.4% for robust patients, 43.2% for mild frailty (with an equal percentage of doubt) and 89.2% for moderate frailty. The use of tools such as the NECPAL (36) appeared to be useful in 43.2% for robust, 51.4% for mildly frail and 64.9% for moderately frail patients.

Prioritizing intensive care management in the emergency room over hospitalization had an acceptance rate of around 64.9% in both robust and moderately frail patients (Annex 1).

Opinion: In HF-pEF, the use of NT-proBNP as a tool was not considered of great relevance, losing even more value as the degree of frailty increases. We consider that in the case of HF presentation and multimorbidity in this group, the diagnosis remains a major challenge. Regarding the prescription of specific treatment with gliflozins, it had high acceptance for robust and mildly frail patients and decreased by half in moderate frailty, with a high percentage of doubts, and the indication was somewhat lower in renal patients as frailty increases.

Treatment of multimorbidity in HF-pEF is a priority, together with potential decompensating causes. Following appropriate prescribing criteria, we recommend considering the use of gliflozins.

Concerning HFrEF, the upper range for inclusion in clinical trials has typically been 75 ± 5 years; for this reason, we have very few data on randomly assigned interventions in patients over 80 years of age. This could be one of the reasons why simultaneous treatment with quadruple therapy has been considered by less than half in robust patients, decreasing significantly to almost zero in moderate frailty, with a relevant percentage of doubt as frailty increases. In both HF-pEF and HF-rEF it has a generally consistent efficacy in older individuals, where target doses could be attempted with slow titration and close monitoring, considering that the greater the frailty, the greater the risk of HF and its complications and vice versa. There is also no evidence to suggest that therapies should be discontinued or doses modified in the context of frailty (Figures 5 and 6).

This shows how the degree of frailty conditions therapeutic decisions. As frailty increases, the indication for treatment decreases, with greater uncertainty about the balance between risks and benefits.

The observed results underscore the need to create clear guidelines, design specific strategies, identify and individualize clinical and hemodynamic profiles, in order to provide adequate guidance for this population group.

Limitations

The main limitations derive from the methodology used, based on expert consensus, which implies that the recommendations reflect the experience and clinical judgment of the participants. Although the group consisted of experts in cardiology and geriatrics, most of them are not exclusively dedicated to cardiogeriatrics. Therefore, it is necessary to validate these recommendations in future studies to confirm and adjust these findings in clinical practice. The approach of multiple scenarios also limited the discussion time.

CONCLUSION

The number of elderly patients has increased significantly, reaching 20% of the total population, and demographic trends show that this population will increase even more in the coming decades. The evidence

and guideline recommendations for the management of older patients are often not as robust and rigorous as for younger patients (atypical presentations, presence of frailty, evidence gaps, etc.).

Aging is a complex and heterogeneous biological process, where we can observe that chronological age alone is not sufficient to define conducts. The results show how frailty significantly conditions therapeutic decisions in most scenarios, with a tendency towards more conservative approaches as the degree of frailty increases.

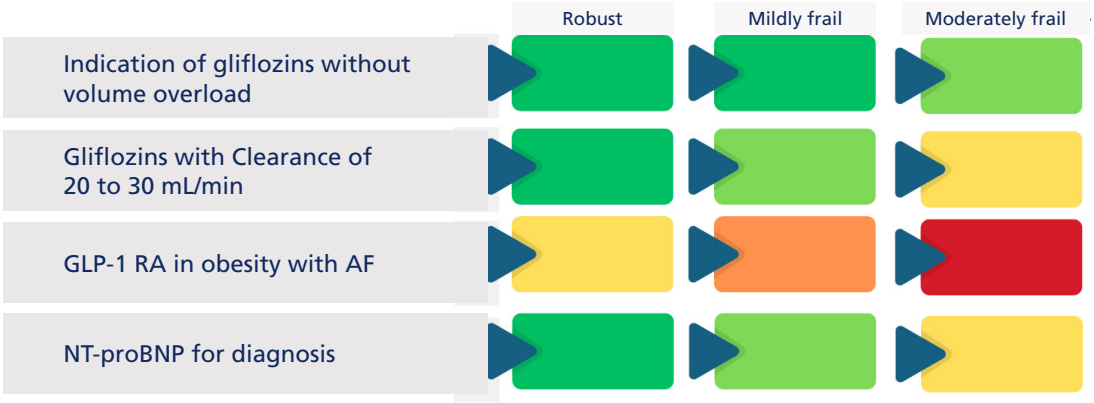
Frailty, unlike age, is a multidimensional and potentially reversible concept that is associated with poor clinical outcomes. To this end, it is crucial to approach frail patients with the necessary caution, but avoiding excessive care that may lead to unfairly denying them potentially beneficial treatments as in robust elderly patients.

Our goal is to incorporate frailty into the decision-making analysis and as part of the treatment strategy.

This meeting highlighted the need for a multicenter registry to know our population and to work on the development of a multidomain frailty score that combines the best tools. For this reason, the registry of frailty, multimorbidity and polypharmacy (RAFA) is under development.

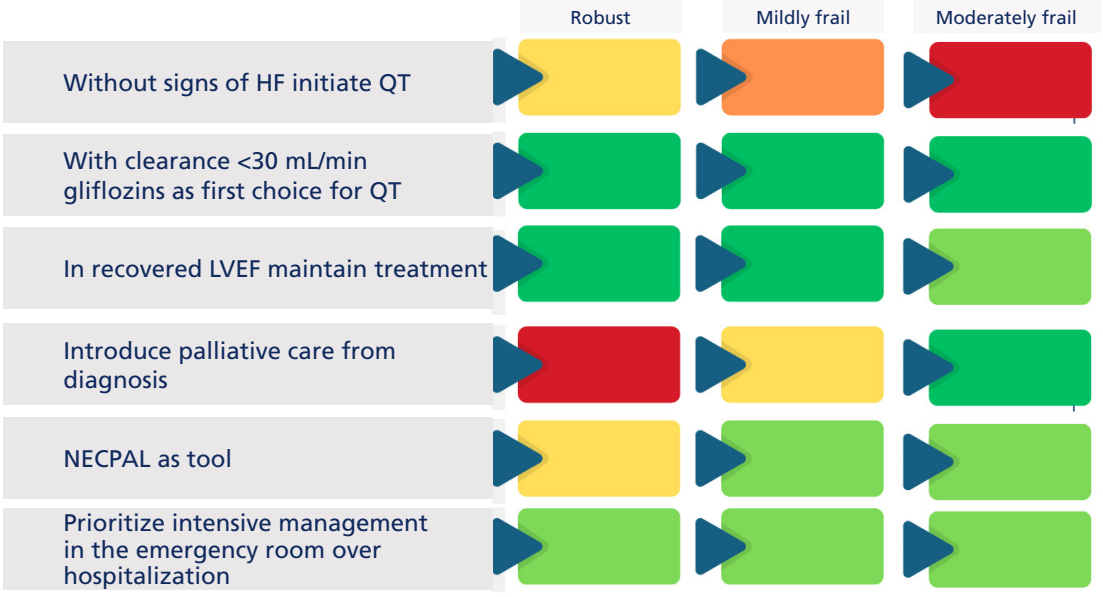
It was also proposed to develop our own criteria, based on existing criteria such as STOPP/START and BEERS, to address appropriate and inappropriate prescribing in patients with cardiovascular diseases.

Fig. 5. Heart failure with preserved left ventricular ejection fraction (HF-pEF)



AF, atrial fibrillation; GLP-1, glucagon-like peptide-1 receptor agonists; NT-proBNP: N-terminal pro-B-type natriuretic peptide

Fig. 6. Heart failure with reduced left ventricular ejection fraction (HF-rEF)



HF: heart failure; LVEF: left ventricular ejection fraction; NECPAL: need for palliative care; QT: quadruple therapy.

The Council is currently working on this registry proposal (MATE: Medication Appropriateness in Cardiovascular Therapeutics).

While progress is being made in more studies, consensuses from referent scientific societies can provide guidance in current practice. For this reason, we are planning the second Roundtable based on heart failure, with the aim of generating recommendations with expert opinion in this scenario.

Conflicts of interest

None declared.

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

Roundtable participants in alphabetical order:

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ANNEX 1.

The results are expressed in percentages

POLYPHARMACY	YES	I DOUBT	NO
Do you find extracardiological medication important?	100	0	0
Do you think about deprescribing drugs in follow-up?	97.5	2.5	0
Do you think the STOPP/START and BEERS criteria could be used in cardiology practice?	75	22.5	2.5
Is it of interest to you that we make our own criteria from the existing ones on inappropriate prescribing?	87.5	7.5	5

FRAILTY	YES	I DOUBT	NO
Do you think it is necessary to detect frailty in patients with cardiovascular pathology?	100	0	0
After the above, do you think it is more relevant to assess functional over multicomponent frailty?	32.5	22.5	45
Do you find it appropriate to use pathology-specific frailty tools?	55	22.5	22.5
Do you regularly perform any frailty screening?	50	15	35
If you had to choose one frailty screening tool, which one would you choose?			
Edmonton Frailty Scale	15		
FRAIL VIG Index	12.5		
CGA FI (Comprehensive Geriatric Assessment-Frailty Index)	20		
CFS (Clinical Frailty Scale)	35		
I would prefer to perform a simple screening of each domain.	17.5		
If we were to conduct a registry in search of a multidomain frailty tool, on polypharmacy and multimorbidity in people over 60 years of age, would you/center participate?	90	10	0

CARDIOVASCULAR PREVENTION	Robust			Mild fragile			Moderate fragile		
	YES	I DOUBT	NO	YES	I DOUBT	NO	YES	I DOUBT	NO
Do you consider cardiovascular risk scores to be useful?	66.7	20.5	12.8	46.2	28.2	25.6	25.6	30.8	43.6
Do you consider frailty as a modifier of CVR?	79.5	10.3	10.3	100	0	0	92.3	7.7	0
Do you consider RCV modifiers relevant for decision making?	84.6	10.3	5.1	84.6	12.8	2.6	64.1	33.3	2.6
Do you start treatment for dyslipidemia?	82.1	15.4	2.6	69.2	25.6	5.1	23.1	51.3	25.6
Does it make sense to screen for subclinical ASCVD?	64.1	17.9	17.9	56.4	30.8	12.8	20.5	43.6	35.9
Do you prescribe statins in primary prevention with subclinical ASCVD?	76.9	12.8	10.3	64.1	15.4	20.5	38.5	28.2	33.3
Do you deprescribe statins in primary prevention with subclinical ASCVD?	23.1	12.8	64.1	20.5	35.9	43.6	41	35.9	23.1

HEART FAILURE WITH PRESERVED LVEF	Robust			Mild fragile			Moderate fragile		
	YES	I DOUBT	NO	YES	I DOUBT	NO	YES	I DOUBT	NO
Without volume overload, would you indicate gliflozins?	94.6	5.4	0	86.5	13.5	0	54.1	40.5	5.4
Does a clearance of 20 to 30 indicate glyflozins?	78.4	16.2	5.4	45.9	43.2	10.8	24.3	51.4	24.3
Would you use GLP-1 RA in obese patients with AF?	40.5	29.7	29.7	16.2	45.9	37.8	5.4	32.4	62.2
NT-proBNP for Diagnostics?	59.5	21.6	18.9	48.6	29.7	21.6	40.5	29.7	29.7

HEART FAILURE WITH REDUCED LVEF	Robust			Mild fragile			Moderate fragile		
	YES	I DOUBT	NO	YES	I DOUBT	NO	YES	I DOUBT	NO
Without clinical signs of HF, do you simultaneously initiate quadruple therapy?	45.9	24.3	29.7	27	29.7	43.2	2.7	35.1	62.2
Which indicates 1st, 2nd and 3rd: Antialdosteronics Sacubitril valsartan Glyflozines									
Clearance < 30 ml/min: Antialdosteronics Sacubitril valsartan Glyflozines	 27 40.5 81.1			 18.9 40.5 81.1			 13.5 40.5 70.3		
In LVEF recovery, do you mantain the treatment?	91.9	8.1	0	73	24.3	2.7	59.5	21.6	18.9
Do you consider the introduction of palliative care from diagnosis?	32.4	13.5	54.1	43.2	43.2	13.5	89.2	0	10.8
Would tools such as NECPAL be useful to you?	43.2	29.7	27	51.4	35.1	13.5	64.9	24.3	10. 8
Do you prioritize intensive management in the emergency room over hospitalization?	62.2	2.7	35.1	59.5	24.3	16.2	62.2	10.8	27

AF: atrial fibrillation; ASCVD: atherosclerotic cardiovascular disease; CVR: cardiovascular risk; GLP-1 RA: glucagon-like peptide 1 receptor agonists; HF: heart failure; LVEF: left ventricular ejection fraction; NECPAL: need for palliative care.

ORIGINAL ARTICLE

Cardiovascular Risk Assessment in Primary Prevention in Patients with Type 2 Diabetes: Comparison of Multiple Scores and Detection of Subclinical Atheromatosis

Evaluación del riesgo cardiovascular en prevención primaria en pacientes con diabetes tipo 2: comparación de múltiples puntajes y detección de ateromatosis subclínica

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ABSTRACT

Background: Risk stratification in type 2 diabetes mellitus (DM2) patients constitutes a real clinical challenge.
Objectives: 1) To stratify cardiovascular risk in a population with DM2 in primary prevention, using different risk scores; 2) To describe the prevalence of atherosclerotic carotid plaque (ACP); 3) To analyze the correlation and concordance between the different risk scores; and 4) To evaluate the discriminative capacity of the different scores to identify the presence or absence of ACP.
Methods: Observational, cross-sectional, multicenter study. Patients with DM2 in primary prevention without lipid-lowering treatment were included. The following risk scores were calculated: Framingham scores for cardiovascular disease (FrCVD) and for coronary heart disease (FrCHD), the 2018 ACC/AHA (AHA2018), PREVENT (AHA2023) and Diabetes-2 (S2-DBT) scores, and UKPDS scores for fatal coronary heart disease (UKPDS-FCHD), non-fatal coronary heart disease (UKPDS-NFCHD), fatal stroke (UKPDS-FS) and non-fatal stroke (UKPDS-NFS). Correlation and concordance between them were evaluated. The discriminative capacity of the different scores for PAC prediction was analyzed using ROC curves.
Results: A total of 170 patients were included in the study, (mean age of 61.2±10.8 years, 58.8% men). The proportion of patients classified as at least high risk was 71.2%, 39.9%, 43.6%, 23.9%, 20.9%, 53.4%, 9.8% and 49.7% when the FrCVD, FrCHD, UKPDS-NFCHD, UKPDS-FCHD, UKPDS-NFS, AHA2018, AHA2023S and 2-DBT scores, respectively, were applied. No patient was classified with risk ≥20 % when using UKPDS-FS score. A good correlation was observed between all scores assessed (Spearman´s rho values between 0.64 and 0.98). The overall agreement between the scores was fair (Fleiss Kappa coefficient of 0.38). The prevalence of ACP was 50.6%, higher in the upper risk strata of all the scores evaluated. The analysis of the ROC curves showed a very good predictive capacity of all the scores for ACP detection.
Conclusion: Cardiovascular risk was considerable for most of the scores evaluated, with an adequate correlation, but a fair concordance between the different scores. A very good predictive ability of all scores for ACP detection was observed.

Key words: Diabetes mellitus - Cardiovascular risk - Cardiovascular risk factors - Atherosclerosis - Carotid artery disease - Data correlation

RESUMEN

Introducción: La estratificación de riesgo en el paciente con diabetes mellitus tipo 2 (DM2) constituye un verdadero desafío clínico.
Objetivos: 1) Estratificar el riesgo cardiovascular en una población con DM2 en prevención primaria, utilizando diversos puntajes de riesgo; 2) Describir la prevalencia de placa aterosclerótica carotídea (PAC); 3) Analizar la correlación y concordancia entre los diferentes puntajes de riesgo; 4) Evaluar la capacidad discriminativa de las distintas puntuaciones para identificar la presencia o ausencia de PAC.

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Material y métodos: Estudio observacional, de corte transversal y multicéntrico. Se incluyeron pacientes con DM2 en prevención primaria sin tratamiento hipolipemiante. Se calcularon los siguientes puntajes de riesgo: Framingham para enfermedad cardiovascular (PF-CV) y para enfermedad coronaria (PF-Cor); ACC/AHA 2018 P-AHA2018; PREVENT P-AHA2023; SCORE2-Diabetes (PE2-DBT); y los puntajes UKPDS para enfermedad coronaria fatal (P-UKPDS-ECF), enfermedad coronaria no fatal (P-UKPDS-ECNF), accidente cerebrovascular fatal (P-UKPDS-ACVF) y no fatal (P-UKPDS-ACVNF). Se evaluó la correlación y concordancia entre ellos. Se analizó mediante curvas ROC la capacidad discriminativa de los distintos puntajes para la predicción de PAC.
Resultados: Se incluyeron 170 pacientes [edad media 61,2 (10,8) años, 58,8% hombres]. La proporción de sujetos clasificados como de al menos alto riesgo fue del 71,2%, 39,9%, 43,6%, 23,9%, 20,9%, 53,4%, 9,8% y 49,7% cuando aplicamos los PF-CV, PF-Cor, P-UKPDS-ECNF, P-UKPDS-ECF, P-UKPDS-ACVNF, P-AHA2018, P-AHA2023 y PE2-DBT, respectivamente. Ningún paciente fue clasificado con un riesgo ≥20 % al utilizar el P-UKPDS-ACVF. Se observó una buena correlación entre todos los puntajes evaluados (valores de coeficiente rho de Spearman entre 0,64 y 0,98). La concordancia global entre los puntajes fue regular (coeficiente Kappa de Fleiss de 0,38). La prevalencia de PAC fue del 50,6 %, mayor en los estratos de mayor riesgo de todos los puntajes evaluados. El análisis de las curvas ROC mostró una muy buena capacidad predictiva de todos los puntajes para la detección de PAC.
Conclusión: El riesgo cardiovascular observado fue considerable para la mayoría de las puntuaciones evaluadas; con una adecuada correlación, pero una concordancia regular entre los distintos puntajes. Se observó una muy buena capacidad predictiva de todos los puntajes para la detección de PAC.

Palabras clave: Diabetes mellitus - Riesgo cardiovascular - Factores de riesgo cardiovascular – Aterosclerosis - Enfermedad de las arterias carótidas - Correlación de datos

INTRODUCTION

In 2021, the global prevalence of type 2 diabetes mellitus (DM2) in people aged 20-79 years was estimated to be 10.5%, representing approximately 537 million individuals. (1) By 2045, the prevalence is projected to increase by 12.2%, equivalent to 783 million people. Healthcare costs associated with DM2, were estimated at $966 billion in 2021, and are projected to increase to more than $1 trillion in 2045. According to the Fourth National Survey of Risk Factors (2018), the prevalence of DM2 in Argentina, based on self-reporting, is 12.7%, which represents a significant increase compared with previous editions of that report. (2) This increase seems to be closely related to the sustained growth in the prevalence of obesity in the population.

Atherosclerotic cardiovascular disease continues to be the main cause of morbidity and mortality associated with DM2, (3) approximately doubling the risk of developing a wide variety of vascular diseases, independently of conventional risk factors (4). In this context, the CAPTURE study revealed that about one in three patients with DM2 has established cardiovascular disease. (5)

Based on early studies, the cardiovascular risk associated with DM2 was considered for many years to be equivalent to that of coronary heart disease. (6,7) However, with the emergence of new data, some authors have questioned this premise. (8,9) Although it is clear that patients with DM2 constitute a higher-risk population, it is likely that not all of them present the same level of vulnerability. In this context, the use of various risk scores and additional tools, such as the detection of subclinical atheromatosis, could help to optimize cardiovascular risk stratification in this population. (10) A more accurate estimation of cardiovascular risk would allow better individualization of prevention strategies, focusing interventions of greater intensity (and greater costs) on subjects at higher risk. Although there are several tools used for cardiovascular risk estimation, and many of them have been evaluated in our population, (11) two new tools derived from the most widely used cohorts were published in mid-2023. The first is the updated 2023 American College of Cardiology (ACC) and American Heart Association (AHA) cardiovascular risk scores designed for the general population (called PREVENT, which we will refer to as AHA2023). The second is a specific tool for the diabetic population, developed in Europe, called SCORE2-Diabetes (which we will refer to as S2-DBT). (12-14) So far, we do not know how these tools would classify our patients with DM2, their relationship with other tools, and their ability to predict subclinical atherosclerotic disease.

Considering the above, the objectives of this work were: 1) To stratify cardiovascular risk in a population with DM2 in primary prevention, using different risk scores; 2) To describe the prevalence of atherosclerotic carotid plaque (ACP) in the different risk categories defined by the scores used; 3) To analyze the correlation and concordance between the different risk scores; 4) To evaluate the discriminative capacity of the different scores to identify the presence or absence of ACP.

METHODS

An observational, cross-sectional, multicenter cohort study was carried out, consecutively evaluating patients attending the cardiovascular prevention clinics of five centers located in the Autonomous City of Buenos Aires and the Province of Buenos Aires.

Patients with a diagnosis of DM2, defined by at least two fasting blood glucose values ≥126 mg/dl, blood glucose ≥200 mg/dl at 2 hours after the oral glucose tolerance test, or a glycosylated hemoglobin (HbA1c) value >6.4%, were included. (15,16) Patients with a history of acute myocardial infarction, coronary angioplasty, myocardial revascularization surgery, stroke, peripheral vascular disease, as well as patients receiving statin treatment were excluded. This last exclusion was intended to allow baseline risk stratification before any modification of the lipid profile, since this profile is a key component in the calculation of cardiovascular risk. Patients who were not receiving statins could have no medical indication or, more likely, could not be complying with the treatment despite having an indication for their use.

Laboratory data, clinical history, and usual medica-

tion were collected. Based on this information, the following 10-year cardiovascular risk scores were calculated: the Framingham score for cardiovascular disease (FrCVD) (17) and for coronary heart disease (FrCHD); (18) the ACC/AHA 2018 (AHA2018) (19) and AHA2023 risk scores; (12,13,20) the S2-DBT for low-risk population score; (14) and the United Kingdom Prospective Diabetes Study (UKPDS) scores for fatal coronary heart disease (UKPDS-FCHD), nonfatal coronary heart disease (UKPDS-NFCHD), fatal stroke (UKPDS-FS), and nonfatal stroke (UKPDS-NFS). (21,22)

Given the availability of the method in all participating centers and the evidence supporting the presence of ACP as an independent predictor of coronary events, this tool was chosen as a surrogate marker of clinical atherosclerotic disease. (23) Ultrasound was used as a noninvasive method for ACP detection. Plaque characterization was based on the presence of the following criteria: 1) abnormal wall thickening (intima-media thickness >1.5 mm), 2) structural alteration (protrusion into the lumen or loss of alignment with the adjacent wall), and 3) abnormal wall echogenicity. The prevalence of ACP was compared between the different risk strata (quartiles) according to each of the scores used.

A Receiver Operating Characteristic (ROC) curve analysis was performed to determine the area under the curve (AUC), with the aim of evaluating the discriminative capacity of the different scores to identify the presence or absence of ACP. To establish the optimal cut-off point (OCP) for each score, the Youden index, defined as the maximum vertical distance between the ROC curve and the statistical probability line, was used.

Statistical analysis

Continuous variables with normal distribution were expressed as mean and standard deviation (SD,) and as median and interquartile range (IQR) for non-normal distribution. Comparison between groups was performed using Student's test in the case of normal distribution or the Mann-Whitney-Wilcoxon test when this condition was not met. Categorical variables were presented as percentages, and their comparison between groups was performed using the chi-square test. Due to the non-normal distribution of the scores evaluated, the correlation between the different risk scores was evaluated using Spearman's rho correlation coefficient, and was defined as null, poor, low, moderate, good or very good, if this coefficient was 0.0-0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80, 0.81-1. The overall and pairwise concordance between risk scores was estimated according to the classification of patients into categories of "low/moderate" or "high/very high" cardiovascular risk, using the specific cut-off points defined for each score. The Fleiss Kappa coefficient was used to determine overall concordance and Cohen's Kappa coefficient for pairwise concordance, and were considered low, fair, moderate, good and very good, if the coefficients were <0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80, or 0.81-1, respectively. A value of two tailed p<0.05 was considered statistically significant. Statistical analysis was performed using R v 4.4.2 software. (24)

Ethical considerations

The present study was performed in accordance with the ethical standards of the declaration of Helsinki (25), and the law on personal data protection 25326. (26)

RESULTS

A total of 170 patients were included in the study, mean age of 61.2 (10.8) years, 58.8% men. Mean HbA1c was 7.1 (1.3) and 14.9% were receiving insulin treatment. Median time of DM2 evolution was 5 (2-10) years. A total of 31.7% patients were overweight, 51.1% had some degree of obesity, and only 1 out of 5 was at a healthy weight. A total of 73.4 % had low-density lipoprotein cholesterol (LDL-C) levels above 100 mg/dl. In addition, 64.1 % of the patients had hypertension, 18.8 % were smokers and 3.6 % had a history of atrial fibrillation. Table 1 shows population characteristics.

Median (IQR) values of FrCHD, FrCVD, S2-DBT, AHA2018, and AHA2023 scores were 18 (10.3-27.0), 29 (16.5-47.8), 9.8 (6.7-13.0), 21.7 (9.5-37.0), and 10.0 (5.8-15.0), respectively. Similarly, according to the UKPDS scores, the median values for coronary heart disease (fatal and nonfatal), fatal coronary heart disease, stroke (fatal and nonfatal), and fatal stroke were 18 (10.5-29.1), 10.7 (5.2-19.3), 8.0 (3.7-15.9), and 1.1 (0.5-2.2), respectively.

The proportion of subjects classified as at least high risk was 71.2%, 39.9%, 53.4%, 9.8%, and 49.7% when applying the FrCVD, FrCHD, AHA2018, AHA2023, and S2-DBT scores, respectively. Regarding the UKPDS models, the proportion of patients so categorized was 43.6%, 23.9% and 20.9% when using UKPDS-NFCHD, UKPDS-FCHD and UKPDS-NFS scores, respectively. Of note, no patient was classified with a risk ≥ 20% when applying the UKPDS-FS score.

A significant correlation was observed between all the scores assessed, with Spearman´s rho coefficient values ranging from 0.64 to 0.98 (Figure 1A). However, despite this correlation, the overall concordance between scores was fair, with a Fleiss Kappa coefficient of 0.38. Pairwise agreement was evaluated for all the scores, with the exception of the UKPDS-FS score, because it classified all patients as "low/moderate risk" and the categories could not be compared. Cohen's Kappa coefficients are presented in Figure 1B.

Overall, the prevalence of ACP was 50.6%, with a higher proportion in men than in women (60% vs. 37.1%, p=0.005). This prevalence increased progressively in the higher risk strata (quartiles) in all scores assessed. Although the highest prevalence was recorded in the upper quartile with the UKPDS-NFCHD and AHA2023 scores (95.2% and 95.1%, respectively), the range of variation within this quartile was relatively narrow (81.4% - 95.2%) (Figure 2). Patients with the presence of ACP were significantly older 62.7(7.7) vs. 55.1 (10.0) years, p <0.001, and with a lower proportion of women (30.2% vs. 52.4%, p=0.005). In addition, they had more frequent hypertension, smoking habit and a longer time of DM2 evolution compared with the group without ACP. All cardiovascular risk scores assessed showed significantly higher mean values in patients with ACP (Table 2).

Analysis of ROC curves showed a very good predictive ability of all scores for plaque detection. The UKPDS scores presented practically identical AUC values (≈ 0.88). Among the remaining scores, those that best classified patients were the AHA2018, AHA2023, and

Table 1. Total population characteristics, stratified by sex.

Continuous variables, mean (SD) or median (IQR)	Overall n=170	Male n = 100	Female n = 70	p
Age, years	61.2 (10.8)	61.0 (11.3)	61.5 (10.1)	0.761
Total cholesterol, mg/dL	200.7 (36.2)	202.7 (40.2)	197.8 (29.6)	0.384
LDL-C, mg/dL	121.1 (34.1)	126.3 (37.5)	113.9 (27.4)	0.021
HDL-C, mg/dL	45.7 (13.4)	41.8 (10.4)	51.3 (15.2)	<0.001
Triglycerides, mg/dL	172.4 (101.2)	184.3 (115.7)	155.4 (73.3)	0.067
Body mass index, Kg/m^2	30.6 (5.7)	29.9 (5.2)	31.7 (6.1)	0.043
HbA1c, %	7.1 (1.3)	7.1 (1.2)	6.9 (1.4)	0.328
DM2 evolution, years	5 (2-10)	6 (2-10)	4 (2-8)	0.101
Categorical variables, n (%)	**n = 170**	**n = 100**	**n = 70**	
Hypertension	109 (64.1)	70 (70.0)	39 (55.7)	0.084
Active smoking	32 (18.8)	25 (25.0)	7 (10.0)	0.001
Atrial fibrillation	6 (3.6)	6 (6.1)	0 (0.0)	0.097
Family history of early coronary artery disease	30 (17.6)	23 (23.0)	7 (10.0)	0.047
ACP	86 (50.6)	60 (60.0)	26 (37.1)	0.005
Insulinized	25 (14.9)	18 (18.2)	7 (10.1)	0.223

ACP: atherosclerotic carotid plaque; DM2: type 2 diabetes mellitus; HbA1c: glycosylated hemoglobin; HDL-C: high-density lipoprotein cholesterol; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; SD: standard deviation

S2-DBT, with AUC values of 0.86, 0.86, and 0.87, respectively. As shown in Figure 3, the OCPs varied according to the score evaluated.

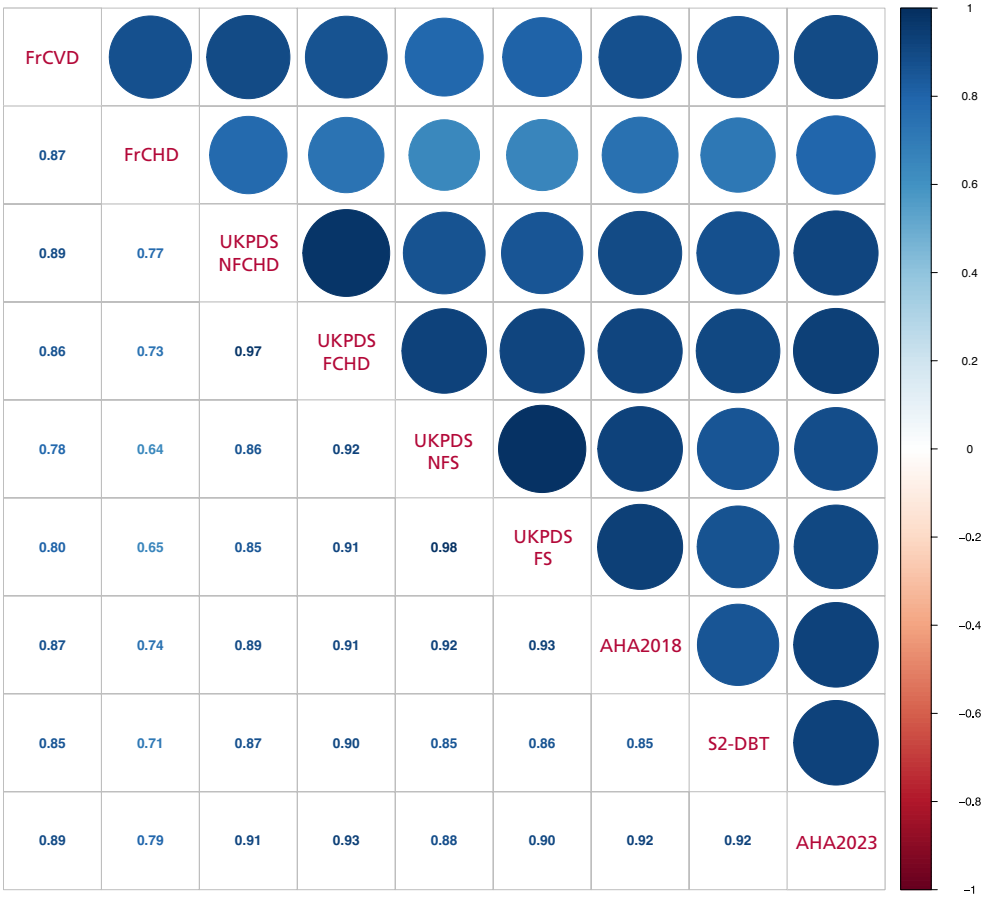
DISCUSSION

The identification of patients at risk of developing cardiovascular events represents one of the most complex challenges in clinical practice. Over time, various tools have been proposed to estimate the risk of future events in patients with DM2, although new cardiovascular risk calculators have recently been introduced. In our study, we compared eight predictive scales in a group of patients with DM2 without history of cardiovascular disease and analyzed their relationship with the presence of ACP.

A key point for discussion is the role of risk scores in patients with DM2 in primary prevention. The 2018 AHA/ACC guidelines for lipid management recommend administration of moderate-intensity statins in patients aged 40-75 years with DM2, and no cardiovascular history. (19) However, they suggest stratifying cardiovascular risk (AHA18S) to administer high-intensity statins in those at higher risk. An expert consensus on the role of non-statin therapies, published in 2022 by the same scientific societies, recommends in this population the administration of high-intensity statins when the calculated cardiovascular risk is equal to or greater than 7.5% at 10 years, and the addition of ezetimibe when the risk exceeds 20% and LDL-C is >70 mg/dL. (27) On the other hand, the 2023 European guidelines for the management of cardiovascular disease in patients with DM2 suggest using the S2DBT to classify patients into the following categories: low risk (<5%), moderate risk (5-10%), high risk (>10% and <20%), and very high risk (≥20%). (28) Lipid-lowering medication, the choice of antidiabetic drugs, and therapeutic targets vary according to the risk of each patient. Similarly, the latest Cardiovascular Prevention Consensus of the Argentine Society of Cardiology (SAC) follows this approach, endorsing cardiovascular risk stratification as the basis for defining the type and intensity of treatments in the patient with DM2. (29) Our study revealed that a significant proportion of persons with DM2 were classified as at least high cardiovascular risk according to most of the scores evaluated. However, this proportion varies, being lower when scores assessing a reduced number of clinical events are analyzed and, even more, if only fatal events are considered. Such is the case of the UKPDS-FS, where no patient showed a risk ≥20%. On the other hand, the scores used do not always consider the same variables. A particular case is that of the-AHA2018 and AHA2023 scores, where the difference in the classification of patients as high risk was notably greater in the former (50.4% vs. 9.8%). Unlike the 2018 calculator, PREVENT includes body mass index, estimated glomerular filtration rate, and optionally HbA1c and urinary albumin-to-creatinine ratio.

Fig 1. Correlation and concordance between the different scores assessed. **A:** Correlation coefficient between the different cardiovascular risk scores. **B:** Overall and pairwise concordance of the different cardiovascular risk scores. The UKPDS-FS score was not evaluated since no patient was categorized as high risk. For score abbreviations see the Methods section

A



B

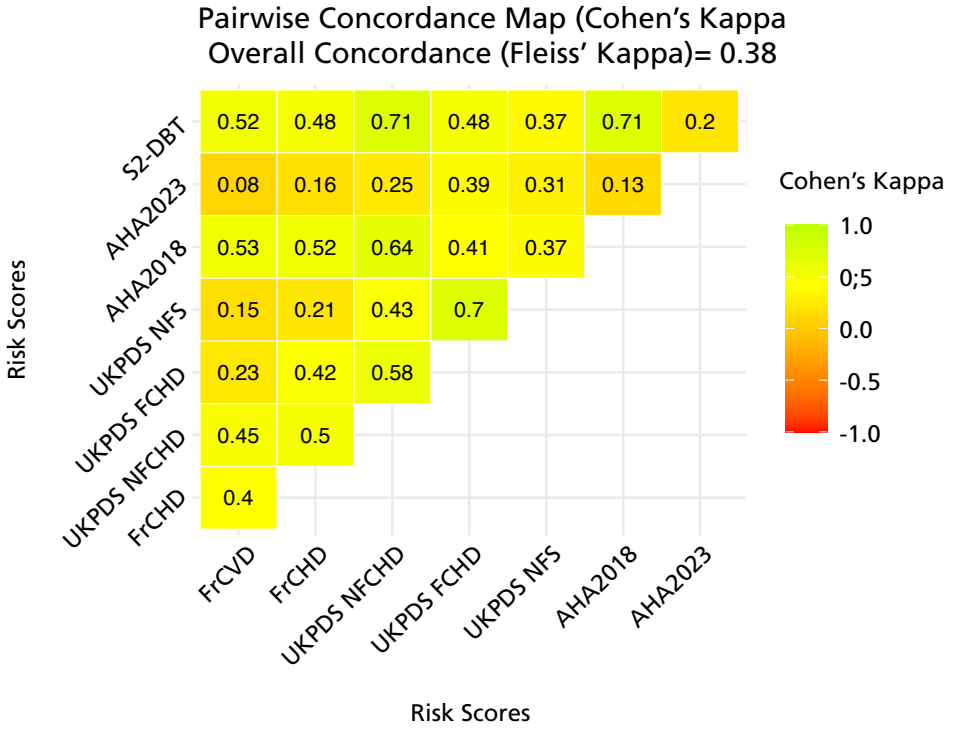
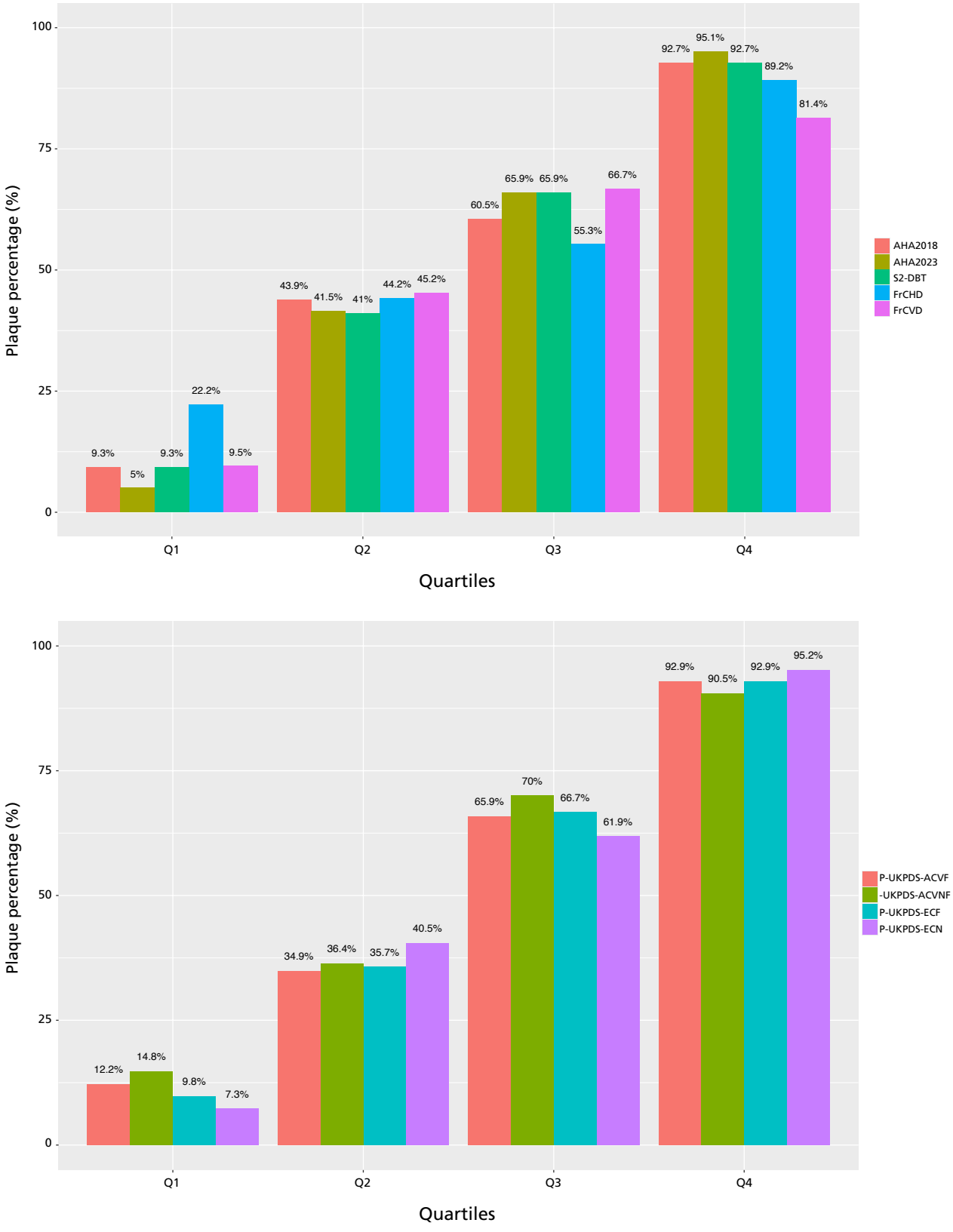


Fig. 2. Prevalence of plaque, according to the cardiovascular risk quartiles of the different scores evaluated.



For score abbreviations see the Methods section.

Table 2. Patient characteristics according to the presence or absence of ACP

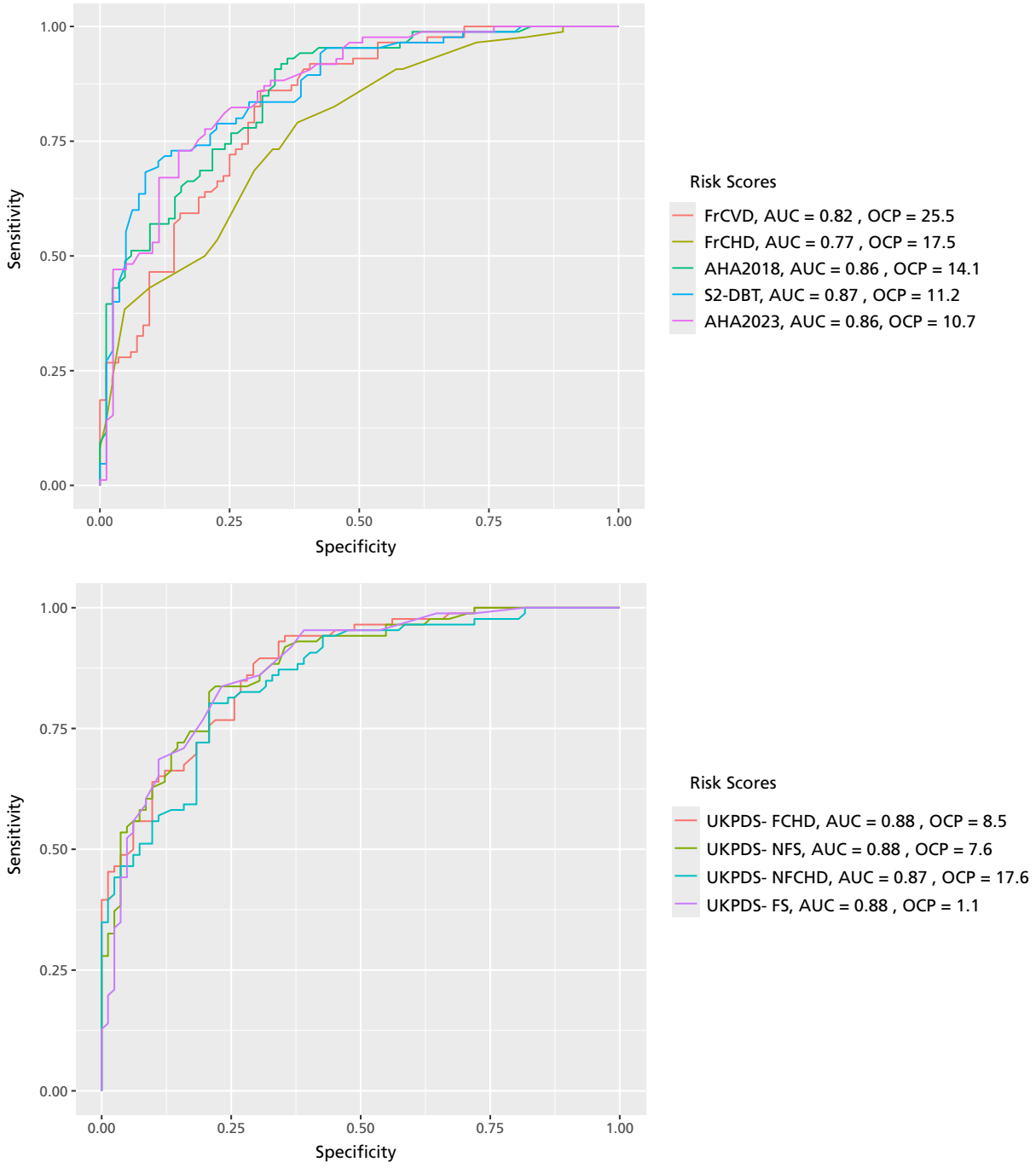
Continuous variables, mean (SD) or median (IQR).	Without ACP n=84	With ACP n=86	p
Age, years	55.1 (10.0)	67.2 (7.7)	<0.001
Total cholesterol, mg/dl	199.0 (35.9)	202.4 (36.6)	0.542
LDL-C, mg/dl	115.7 (32.7)	126.4 (34.9)	0.043
HDL-C, mg/dl	47.3 (14.7)	44.2 (11.8)	0.13
Triglycerides, mg/dl	185.6 (125.2)	159.4 (68.6)	0.092
Body mass index, Kg/m^2	31.3 (5.8)	30.0 (5.5)	0.158
HbA1c, %	6.9 (1.4)	7.2 (1.1)	0.138
DM2 evolution, years	4 (1.25-6)	8 (3-12)	<0.001
FrCVD,%	19.6 (9.4-30.4)	42.4 (27.4-56,8)	<0.001
FrCHD,%	13,0 (8.0-20.0)	24.5 (16.0-31.0)	<0.001
AHA2018,%	10.1 (4.6-21.2)	34.4 (21.6-48.7)	<0.001
UKPDS-NFCHD,%	10.7 (6.4-16.3)	26.5 (18.6-44.1)	<0.001
UKPDS-NFS,%	4.3 (1.6-6.8)	14.5 (8.3-29.4)	<0.001
UKPDS-FCHD,%	5.5 (2.5-10.4)	17.8 (10.9-34.9)	<0.001
UKPDS-FS,%	0.6 (0.2-1.0)	2.0 (1.20-4.0)	<0.001
S2-DBT,%	6.8 (4.4-9.5)	12.9 (10.1-16.5)	<0.001
AHA2023,%	6.0 (3.8-9.4)	13.9 (10.3-19.1)	<0.001
Categorical variables, n (%)	**Without ACP n=84**	**With ACP n=86**	**p**
Women	44 (52.4)	26 (30.2)	0.005
Hypertension	41 (48.8)	68 (79.1)	<0.001
Active smoking	10 (11.9)	22 (25.6)	0.002
Atrial fibrillation	1 (1.2)	5 (5.8)	0.235
Family history of early coronary artery disease	15 (17.9)	15 (17.4)	1
Insulinized	10 (12.2)	15 (17.4)	0.46

ACP: atherosclerotic carotid plaque; DM2: type 2 diabetes mellitus; HDL-C: high-density lipoprotein cholesterol; IQR: interquartile range. LDL-C: low-density lipoprotein cholesterol; SD: standard deviation. For score abbreviations see the Methods section.

In addition, PREVENT omits ethnicity, which was included in the 2018 calculator. In fact, in other populations it has also been observed that the AHA18S tends to overestimate risk compared to the AHA2023. (30)

The concepts of concordance and correlation are widely used to assess the association between variables, but, although related, they represent different approaches. (31) Correlation focuses on the relationship between observed changes in two variables, i.e., how one varies as a function of the other. In contrast, concordance focuses on the degree of coincidence between two methods of measuring or classifying the same variable. Thus, while correlation measures association, concordance evaluates the degree of agreement between the results. In this sense, our study showed a high correlation between the different models analyzed. Previously, our research group had reported similar results in a population with DM2, though without including the new cardiovascular risk scales. (32) However, in our study, the concordance in the classification of patients as "high risk" was low or moderate among the different scores evaluated. In the general population, several studies have shown that the application of different cardiovascular risk prediction models in the same group of patients can generate discrepancies in risk classification in about 30% of cases. (33) In particular, when comparing the Framingham model with the European SCORE model, the concordance reported was mild to moderate. (34,35) Similar data have been reported in our region. For example, in Colombia, the kappa coefficient of concordance between the Framingham model and SCORE for the classification of patients as high risk was 0.28, indicating low concordance. (36) Similarly, in Peru, limited agreement was observed between the AHA/ACC equations and six different cardiovascular

Fig. 3. ROC curves, AUC and OCP of the different cardiovascular risk scores evaluated.



For score abbreviations see the Methods section.

risk estimation scales. (37)

A recent analysis by Dziopa et al. compared the performance of 22 cardiovascular risk models, including both those designed specifically for persons with DM2 and others originally developed for the general population. The study evidenced remarkable variability in the predictive ability of these models. Surprisingly, the results indicated that models based on the general population did not necessarily underperform compared with DM2-specific models. (38) Even the non-specific scores included a small percentage of patients with DM2 in their derivation cohorts (e.g., FrCVD score 5%, FrCHD score 5.2%, and AHA2018 score between 1% and 14%, depending on the cohort evaluated). This unexpected result highlights that DM2-specific models do not necessarily outperform general models in predicting cardiovascular events. In other words, these findings challenge the assumption that incorporating DM2-related

variables-such as HbA1c and disease duration-always improves risk predictive ability. (39) After adjusting for differences in population characteristics and baseline risk, recalibration significantly improved the performance of many models. This emphasizes the importance of making local adaptations of widely used models (recalibration). (40) Overall, the global prevalence of ACP in people aged 30-79 years in 2020 was estimated to be 21.1%, equivalent to approximately 816 million people affected, with 59% increase since 2000. (41) As expected, DM2 proved to be one of the risk factors most closely associated with the increased likelihood of developing ACP. In our study, we found that approximately 1 in 2 patients with DM2 had ACP. These results are consistent with previous reports. For example, a study conducted in Taiwan (42) reported a prevalence of 53.6%, whereas another conducted in China found 44.9%. (43) In the latter case, and as in our study, the authors reported that subjects with ACP were older, had longer evolution of DM2, and had a higher prevalence of hypertension. Finally, and in line with the current findings, the study previously conducted by this group of investigators showed a prevalence of ACP of 51%. (32) These findings have notable clinical implications. According to the SAC Consensus on the management of patients with DM2 and cardiovascular disease in patients with low or intermediate risk (<20%), it could be useful to screen for subclinical atheromatosis, since its presence would allow the patient with DM2 to be recategorized as very high risk. (44) Furthermore, this finding justifies the intensification of lipid-lowering treatment, also prioritizing the use of antidiabetic drugs with proven cardiovascular efficacy.

Finally, in our investigation, all the scores evaluated demonstrated a very good ability to predict the presence of ACP, with AUC above 0.75. However, the OCP varied considerably among the different scores evaluated. Some showed values close to the high-risk threshold (20%) established by the guidelines recommending their use, such as the FCVS and FCDS. Similarly, S2-DBT score presented an OCP close to 10%, the threshold considered by the respective guidelines to define high cardiovascular risk. In contrast, other scores, such as the AHA2018 score and, especially, the AHA2023 score showed significantly lower OCP than the commonly used high-risk thresholds, suggesting that many patients with scores that were not as high could nevertheless present ACP.

This study has several limitations. First, it was a cross-sectional study with a small number of patients. Consequently, our findings should be confirmed in larger studies. Secondly, all participants were recruited from outpatient cardiovascular prevention clinics belonging to cardiology centers, which could have introduced a selection bias. Furthermore, this conditions its extrapolation to daily health care practice. Finally, this study did not aim to evaluate the validity of the risk scores analyzed in our country. However, we consider that our findings highlight the difficulties inherent to cardiovascular risk stratification in this population, as well as the relevance of having local adaptations of the predictive models usually employed.

CONCLUSIONS

The observed cardiovascular risk was considerable according to most of the scores assessed; however, risk stratification was heterogeneous, with adequate correlation but only modest concordance between the different scores. In other words, these findings reflect that our patients with DM2 are not uniformly classified when applying different predictive tools. The prevalence of ACP was significantly increased in strata with higher estimated risk. Understanding the relationship between the presence of ACP and different estimation tools could improve the accuracy of cardiovascular risk assessment in patients with DM2 and optimize treatment in those most likely to have an event.

Funding

None.

Conflicts of interest

None declared.

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

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BRIEF ARTICLE

Eligibility for Icosapent Ethyl in a Real-World Population of Patients with Type 2 Diabetes in Argentina

Elegibilidad para icosapento de etilo en una población de mundo real de pacientes con diabetes tipo 2 en la República Argentina

AUGUSTO LAVALLE COBO[1, MTSAC], JOSEFINA DESTAVILLE[1], EMILIANO SALMERI[1], EZEQUIEL FORTE[1, MTSAC], PAOLA HARWICZ1, PABLO CORRAL[2]

ABSTRACT

Background: Patients with type 2 diabetes mellitus (DM2) are at increased cardiovascular risk even when they receive lipid-lowering treatment with statins and achieve low-density lipoprotein-associated cholesterol (LDL-C) levels < 55 mg/dL. Moderate hypertriglyceridemia is common in this population and constitutes an additional risk factor. The REDUCE-IT study demonstrated that icosapent ethyl (IPE) reduces cardiovascular events by 25% in patients with atherosclerotic cardiovascular disease (ASCVD) or DM2 with risk factors and elevated triglycerides, which led to its incorporation into clinical guidelines.
Objective: The aim of this study was to assess eligibility IPE in patients with DM2 in the real world.
Methods: We conducted a descriptive and retrospective study of the patients included in the registry of Cardiometabolism of the Argentine Society of Cardiology. Patients were defined as eligible for IPE if they were between 40 and 75 years of age, had a history of ASCVD or 2 associated risk factors, were receiving statin therapy, and had a LDL-C < 100 mg/dL and triglycerides between 150 and 499 mg/dL.
Results: A total of 694 patients with DM2 were included, of whom 601 had a complete lipid profile; 51.7 % had AVCD, and 48.3 % were in primary prevention. After applying the eligibility criteria, 19.3 % of patients were eligible to receive IPE, with a higher proportion of patients in secondary prevention (22.8 %) compared to those in primary prevention (15.5 %), OR 1.61, 95% CI 1.04-2.49; p=0.029
Conclusions: A significant proportion of patients with DM2 are eligible for treatment with IPE. These findings underscore the importance of identifying patients with DM2 who could benefit from this treatment to reduce residual cardiovascular risk.

Keywords: Cardiovascular risk - Residual cardiovascular risk - Hypertriglyceridemia - Icosapent ethyl -Diabetes mellitus - Cardiovascular disease.

RESUMEN

Introducción: Los pacientes con diabetes mellitus tipo 2 (DM2) tienen un mayor riesgo cardiovascular, incluso cuando reciben tratamiento hipolipemiante con estatinas y alcanzan niveles de colesterol asociado a lipoproteínas de baja densidad (c-LDL) < 55 mg/dL. La hipertrigliceridemia moderada es frecuente en esta población y constituye un factor de riesgo adicional. El estudio REDUCE-IT demostró que el icosapento de etilo (IPE) reduce un 25 % los eventos cardiovasculares en pacientes con enfermedad cardiovascular aterosclerótica (ECVA) o DM2 con factores de riesgo y triglicéridos elevados, lo que llevó a su incorporación en guías clínicas.
Objetivo: Evaluar la elegibilidad para IPE en el mundo real en pacientes con DM2.
Material y métodos: Estudio descriptivo y retrospectivo del Registro de Cardiometabolismo de la Sociedad Argentina de Cardiología. Se definió que los pacientes eran elegibles para IPE si presentaban edad entre 40 y 75 años, antecedentes de ECVA o 2 factores de riesgo asociados, estaban recibiendo tratamiento con estatinas, y tenían un valor de c-LDL < 100 mg/ dL y triglicéridos entre 150 y 499 mg/dL.
Resultados: Se incluyeron 694 pacientes con DM2, de los cuales 601 tenían perfil lipídico completo. El 51,7 % tenía ECVA, y el 48,3 % estaba en prevención primaria. Tras aplicar los criterios de elegibilidad, el 19,3 % de los pacientes calificaban para recibir IPE, con mayor proporción en prevención secundaria (22,8 %) que en primaria (15,5 %), OR 1,61, IC 95% 1,04-2,49; p=0,029.
Conclusiones: Una proporción significativa de pacientes con DM2 es elegible para recibir tratamiento con IPE. Estos hallazgos resaltan la relevancia de identificar a los pacientes con DM2 que podrían beneficiarse con este tratamiento para reducir el riesgo cardiovascular residual.

Palabras clave: Riesgo cardiovascular - Riesgo cardiovascular residual - Hipertrigliceridemia - Icosapento de etilo - Diabetes mellitus - Enfermedad cardiovascular

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INTRODUCTION

Patients with type 2 diabetes mellitus (DM2) are at a higher risk for cardiovascular disease than other population groups with similar characteristics without DM2. (1,2) The administration of lipid-lowering medications, aimed at reducing plasma levels of low-density lipoprotein cholesterol (LDL-C), has been demonstrated to result in a reduction in major cardiovascular events in various clinical trials, irrespective of the presence of DM2. However, the risk of developing new cardiovascular events persists even when LDL-C levels drop below 55 mg/dL. (3-4) The presence of moderate hypertriglyceridemia is a common characteristic of patients with DM2. (5) The use of icosapent ethyl (IPE) in patients with atherosclerotic cardiovascular disease (ASCVD) or DM2 associated with another cardiovascular risk factor and elevated triglycerides was associated with a 25% reduction in the risk of major cardiovascular events in the REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) study. (6) These results led to the incorporation of this new therapeutic option in clinical practice guidelines to reduce residual risk in this population. (7,8) Although this treatment has recently been approved in Argentina, the proportion of patients with DM2 who could be considered candidates to receive it is unknown. The aim of this study is to evaluate the eligibility of patients with DM2 who could benefit from treatment with icosapent ethyl (IPE) in terms of cardiovascular risk reduction.

METHODS

We conducted a descriptive and retrospective study. Patients with DM2 who were included in the registry of the Council on Cardiometabolism of the Argentine Society of Cardiology between May and July 2019 were included. Patients hospitalized were excluded from the study, as well as those with type 1 diabetes, secondary DM, pregnancy and those who refused to be included in the protocol. The clinical characteristics and the laboratory findings were evaluated. Patients were considered eligible for IPE if they were between 40 and 75 years of age, had a history of ASCVD or 2 associated risk factors, were receiving statin therapy, and had LDL-C levels < 100 mg/dL and TG levels between 150 and 499 mg/dL. Eligibility for IPE was assessed in the total population, in the population of patients with ASCVD (history of coronary artery disease, cerebrovascular disease, or peripheral vascular disease), and in those without ASCVD. The study was conducted following the recommendations of the Declaration of Helsinki revised in 2003. (9) The participation was voluntary and all the patients signed an informed consent form to be included in the study. Qualitative variables are presented as frequency and percentage, and quantitative variables as mean and standard deviation (SD). Statistical significance was considered with a 2-tailed p-value < 0.05.

RESULTS

A total of 694 patients included in the registry of Cardiometabolism of the Argentine Society of Cardiology were evaluated. Of these, 601 had a complete lipid profile, 51.7% (311 patients) had ASCVD and 48.3% (290 patients) were in primary prevention. Mean age was 67.2 ± 9.3 years; 60.1% were male and 91.7% had hypertension. The mean body mass index was 32 kg/m2. Mean glycated hemoglobin was 7.3 %, mean LDL-C was 95 mg/dL, mean TG was 166.5 mg/dL and mean glomerular filtration rate was 78.6 mL/min/1.73m2; 72.4% were receiving statins, and 7.1% were receiving ezetimibe. The differences between patients with and without ASCVD are presented in Table 1. Patients with ASCVD were predominantly male, older and were using statins and ezetimibe, which explains the lower total and LDL cholesterol values. After applying the eligibility criteria for IPE, 19.3% of the patients were deemed eligible (Figure 1). When these patients were divided according to the history or absence of ACVD, 22.8% (71 patients) in secondary prevention and 15.5% (45 patients) in primary prevention met criteria for receiving IPE (OR 1.61, 95% CI 1.04-2.49; p= 0.029). (Figure 2).

DISCUSSION

This study showed that, in a cohort of patients with DM2 with high and very high cardiovascular risk, one out of five patients met the criteria for eligibility to receive IPE. Rawshani et al. showed a reduction in both death from cardiovascular disease and death from coronary artery disease and hospitalizations for cardiovascular disease over the last 20 years, with a smaller reduction in patients with DM2. This finding suggests the presence of a notable increase in residual risk within this patient population. (10) The emergence of novel pharmacological groups that have shown a reduction in major cardiovascular events, risk of hospitalization for heart failure and even cardiovascular mortality in some patient subgroups across various clinical studies, shows that this residual risk exists and that it can be reduced through the incorporation of novel therapeutic options. (11,12) However, beyond these interventions, the high incidence of cardiovascular events observed, especially in studies that included patients with DM2 at very high cardiovascular risk, makes it necessary to address other variables in order to achieve a greater reduction. Despite the above, the use of drugs with proven cardiovascular benefits remains suboptimal, (13) if we consider that only 25.9% of patients in this registry received medications with documented cardiovascular benefits. Hypertriglyceridemia and remnant cholesterol emerge as therapeutic targets of interest, particularly in patients with DM2 who have a higher prevalence of elevated triglyceride levels than other patient subgroups. Omega-3 fatty acids are among the drugs evaluated in patients with these characteristics. The JELIS (Japan EPA Lipid Interventional Study) study, conducted in Japan, included patients with total cholesterol levels ≥ 250 mg/dL. Treatment with 1,800 mg of eicosapentaenoic acid (EPA) combined with statins reduced the risk of major cardiovascular events by 19%, compared to treatment with statins alone. (14) In the same line, the REDUCE-IT study compared the use of 4 g/day of EPA

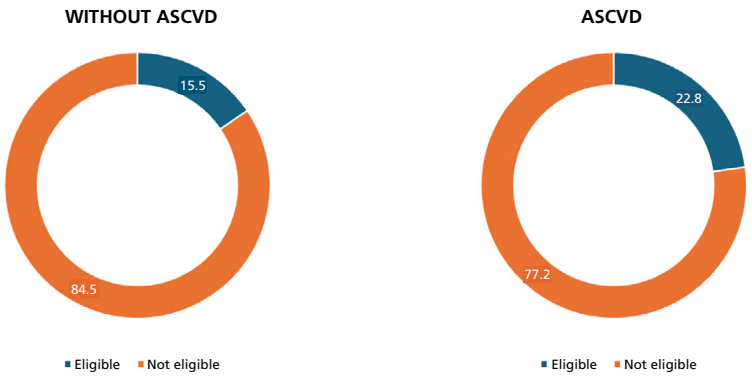
Table 1. Baseline characteristics

	Without ASCVD (n = 290)	With ASCVD (n = 311)	Total (n = 601)	p*
Age, years (mean ± SD)	63 ± 9.6	67 ± 9.7	65 ± 9.8	<0.001
Male sex, (%)	45	69	57.6	<0.001
HTN (%)	90	93	91.7	0.241
BMI (mean ± SD)	32.5 ± 5.9	31.5 ± 6.1	32 ± 6	0.041
DM2 diagnosis > 10 years (%)	34.5	43	38.9	0.036
HbA1c,% (mean ± SD)	7.3 ± 1.7	7.2 ± 1.4	7.3 ± 1.6	0.430
Total cholesterol, mg/dL (mean ± SD)	181 ± 45.8	159 ± 43	170 ± 45.7	<0.001
HDL-cholesterol, mg/dL (mean ± SD)	45 ± 11.7	44 ± 24.13	44.5 ± 26	0.523
LDL-cholesterol, mg/dL (mean ± SD)	105 ± 40	85 ± 36.2	95 ± 39.3	<0.001
Triglycerides, mg/dL (mean ± SD)	173 ± 103.6	160 ± 79.8	166.5 ± 92.1	0.084
GFR, mL/min/1.73m^2 (mean ± SD)	84 ± 20	73 ± 21.6	78.5 ± 21	<0.001
Statins (%)	62.4	81.6	72.4	<0.001
Ezetimibe (%)	4.5	9.6	7.1	0.017
Insulin (%)	19	25.6	22.5	0.062
GLP-1 RA (%)	2.4	3.5	5.9	0.478
SGLT2i (%)	6.2	12.8	20	0.006

*: without ACVD vs. with ACVD
ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; DM2: type 2 diabetes mellitus; GFR: glomerular filtration rate; GLP-1 RA: glucagon-like peptide 1 receptor agonists; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; HTN: hypertension; LDL: low-density lipoprotein; SD: standard deviation; SGLT2i: sodium-glucose co-transporter 2 inhibitors

Fig. 1. Patients eligible for icosapent ethyl.

Fig. 2. Percentage of patients eligible for icosapent ethyl according to the history of atherosclerotic cardiovascular disease (ASCVD)



associated with statins with or without ezetimibe versus treatment with statins with or without ezetimibe. Once again, there was a reduction in major cardiovascular events, this time by 25%, as well as a reduction in most of the evaluated secondary endpoints. (6) It is important to highlight that in this study 57.8% of the patients had DM2. Subsequently, the EVAPORATE study demonstrated that the use of 4 g/day of IPE was associated with changes consistent with atheroma plaque regression. (15) The exact mechanisms by which this benefit occurs are still under discussion. However, it is suggested that the risk reduction with IPE treatment exceeds the observed reduction in TG levels. (16,17) Based on these results, clinical practice guidelines have recommended considering the use of IPE for patients with DM2 or ASCVD who are receiving statins and have TG between 150 and 499 mg/dL, in order to reduce cardiovascular risk.

One limitation of our study is that eligibility was defined based on the treatment received by the patients, without specifying the dose of statins used or the proportion of patients receiving other drugs such as fibrates for the treatment of hypertriglyceridemia. We must also consider the fact that 70% of patients were receiving statins, which can lead to an underestimation or overestimation of the actual triglyceride value and thus influence eligibility. Likewise, the population evaluated may not represent the total number of patients with DM2 but rather the one evaluated in a cardiology office.

In conclusion, in a real-world population of patients with DM2 who are monitored by cardiologists in Argentina, 1 out of 5 patients is eligible for treatment with IPE, which has the potential to reduce cardiovascular events.

Conflicts of interest

None declared.

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

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CONTROVERSY

In Non-ischemic Dilated Cardiomyopathy, the Implantable Cardioverter-Defibrillator Remains the First Choice for Primary Prevention of Sudden Death.

En la miocardiopatía dilatada no isquémica el cardiodesfibrilador implantable sigue siendo la primera elección para la prevención primaria de la muerte súbita

AGONIST

CARLOS LABADET[1], MTSAC,

The indication for implantable cardioverter defibrillator (ICD) for primary prevention of sudden death (SD) in patients with non-ischemic dilated cardiomyopathy (NIDCM) has been supported by multiple randomized studies. (1-5) The development of these complex studies was not simple, and initially those with more patients included ischemic and non-ischemic cardiomyopathy, with fewer non-ischemic patients. Some studies individually showed only a trend toward improved survival with ICD implantation, while others lacked the statistical power to meet their outcomes. (1-3)

The methodology used to address this issue was the meta-analysis.

Desai published one of the first studies that pooled data from the initial five studies on this subject: AMIOVIRT, CAT, DEFINITE, SCD-HeFT and COMPANION. (6) The analysis showed lower all-cause mortality: relative risk (RR) 0.69; 95% confidence interval (95% CI) 0.55-0.87; p = 0.002. The meta-analysis result remained consistent even when excluding the COMPANION study, which included cardiac resynchronization therapy (CRT). These findings, together with others, supported the Class I indication for ICD in primary prevention in both American and European guidelines. (7,8)

However, several important factors weakened this indication: the studies enrolled few patients, follow-up periods were short, and, most importantly, the studies were conducted at a time when therapeutic options for heart failure (HF) were limited, including CRT or subsequent pharmacological advances, which have consistently demonstrated a reduction in cardiovascular mortality. Some reports show a reduction in SD of up to 44% between 1995 and 2014. (9)

The Denmark factor

In 2016, the DANISH study was published. After a 5-year follow-up, it demonstrated a 50% relative risk reduction in SD in the ICD group compared to the control group in NIDCM patients: 4.3% vs. 8.2%; hazard ratio (HR) 0.50; 95% CI 0.31-0.82; p = 0.005, confirming the benefit of ICD in reducing SD. There was a trend toward lower cardiovascular mortality; however, all-cause mortality was similar between the two groups. (10)

Therefore, the DANISH study introduced a wake-up call regarding the previously accepted concept of the benefit of ICD in reducing all-cause mortality. Several factors may account for this finding, namely:

- The population was quite specific, exceptionally treated with a very high rate of drug use that is not replicated in daily clinical practice. The CHAMP HF study, a registry of over 3000 patients with HF, reported that 23%, 33% and 67% of the population were not receiving angiotensin-converting enzyme inhibitors, beta-blockers or aldosterone antagonists, respectively, compared to 4%, 8% and 41% in DANISH. (11)

- In 58% of overall population and in 65% of patients over 70 years old, CRT was implanted, indicating the extensive use of this therapy. In addition, 10% of patients had previous CRT or pacemaker implantation. Studies published at that time, such as PARADIGM-HF and DAPA-HF, reported only 7% of patients with CRT. Even in the OFFICE-IC AR registry of the Argentine Society of Cardiology (SAC) published six years later, 1.8% received CRT and 10.7% CRT with defibrillator (CRT-D), confirming that the DANISH study population was highly selected. (12-14)

Following this reasoning, the proper indication

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for CRT, the prevalence of left bundle-branch block (LBBB) in the DANISH study would be at least twice as high as that reported in other studies: 60% in DANISH vs. 30% in OFFICE-IC AR, which included 644 patients with HF and reduced left ventricular ejection fraction (LVEF). (14)

- With such a high rate of use of CRT, and probably of LBBB as well, it is logical to suggest that much of the observed benefit may have been attributable to this therapy. There are no randomized studies demonstrating superiority in terms of mortality when comparing CRT and ICD. Moreover, as shown in the MADIT CRT study, if resynchronization increases LVEF above 35%, the rate of appropriate ICD therapies is significantly reduced (HR 0.44; 95% CI 0.28-0.68; $p < 0.001$). (15) Although excluding these patients in the DANISH analysis did not change the results, the number of cases is undeniably reduced and, thus, the statistical power to analyze the outcome. In other words, ICD was compared to medical therapy in 40% of the population, while CRT-D was compared to CRT in 60%.

- It is interesting to observe that during the first five years, the mortality curves diverged in favor of ICD but converged in a longer follow-up. The DANISH population was older than that included in the DEFINITE and SCD-HeFT studies. (16,17) Therefore, although ICD may have initially reduced mortality, with longer follow-up in an older population, it is reasonable to observe an increase in non-cardiovascular or HF-related mortality, for which ICD has no effect. Indeed, non-cardiovascular mortality accounted for 31% of deaths in DANISH.

- A *post hoc* analysis of the DANISH study confirmed that patients >70 years of age had a significantly longer history of HF (twice as long), worse functional class , higher levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide), greater renal impairment, and a higher prevalence of atrial fibrillation. (18) These findings help explain why the non-sudden mortality was twice as high compared to patients <70 years of age. It is not surprising, then, that the authors highlighted the benefit of ICD implantation in younger patients, in whom the ICD significantly reduced both sudden and all-cause mortality (HR 0.70; 95% CI 0.51-0.96 ; $p = 0.03$).

However...

Immediately after the publication of the DANISH study, nine meta-analyses were published, all of which included DANISH (Table 1). Using all possible combinations, the result was conclusive: ICD significantly reduced all-cause mortality in NIDCM. (19-27)

- Recent prospective registries, such as BIO-LIBRA—presented this year and including 1,000 patients across 50 sites—continue to report a high rate of ventricular tachycardia/ventricular fibrillation (VT/VF) or death during follow-up in patients with NIDCM receiving ICD with or without CRT in primary prevention. At 3-year follow-up, the rate of VT/VF or death remained high: 28% in men and 17% in women. A lower rate of shock was confirmed in patients with CRT and in women. (28)

Like other studies, DANISH did not consider the etiology of NIDCM. This diagnosis includes heterogeneous populations with potentially distinct clinical courses. Indeed, it is well established that certain conditions are associated with a higher rate of SD, such as arrhythmogenic genetic mutations (e. g., lamin, phospholamban, or filamin) or sarcoidosis. (29) Conversely, ventricular dysfunction due to amyloidosis often leads to death from HF or pulseless electrical activity. It is also worth noting that some forms of dilated cardiomyopathy may be caused or worsened by atrial fibrillation or ventricular ectopic beats, whose progression could be modified with appropriate arrhythmia treatment.

Among the risk markers not evaluated in these studies, the presence of left ventricular fibrosis assessed by cardiac magnetic resonance imaging stands out. Observational studies have shown that this finding is associated with a higher incidence of VT/VF, and it may even help identify patients with lower mortality when treated with CRT-D compared to CRT alone. (30) Therefore, several factors beyond LVEF remain to be assessed to refine patient selection for ICD implantation in the setting of primary prevention.

The risks of implanting an ICD

The complications associated with ICD implantation have become increasingly rare. For instance, with modern programming, the annual rate of inappropriate shocks is now below 2%. Moreover, the advent of subcutaneous ICD—which has no endocardial leads and provides efficacy comparable to conventional ICD—has significantly reduced catheter-related infections and late complications. These advancements further support the consideration of ICD implantation for primary prevention in this patient population.

CONCLUSIONS

The latest guidelines from the American Heart Association (AHA), the American College of Cardiology (ACC), and the Heart Failure Society of America (HFSA) for the management of HF assign a Class I recommendation to ICD implantation for the primary prevention of sudden death in patients with NIDCM, whereas the European and Argentine guidelines classify it as Class IIa. Interestingly, all of these guidelines are based on exactly the same studies. (31- 33)

Given the strong support in both national and international guidelines, primary prevention with an ICD in NIDCM should always be considered as indicated. There is no doubt regarding this indication in patients under 70 years of age, and it should also be considered in those over 70, unless reduced life expectancy, advanced HF or severe comorbidities suggest a higher risk of non-arrhythmic mortality.

Table 1. Meta-analysis of the different studies in primary prevention including patients with non-ischemic dilated cardiomyopathy

Author	Studies	Patients (ICD/MT)	Effect on all-cause mortality	Study conclusion
Al-Khatib et al. 2017 (19)	CAT, DEFINITE, SCD-HeFT, DANISH	1874 (937/937)	HR 0.75 95% CI 0.61-0.93 p = 0.008	PP with ICD is effective in reducing all-cause mortality in NIDCM
Narayanan et al. 2017 (20)	CAT, AMIOVIRT, DEFINITE, SCD-HeWWWFT, COMPANION, DANISH	2347 (962/1385)	RR 0.76 95% CI 0.63-0.91 p = 0.003	Significant decrease in all-cause and sudden mortality in NIDCM
Golwala et al. 2017 (21)	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, COMPANION, DANISH	2970	HR 0.77 95% CI 0.64-0.91	Significant decrease in all-cause mortality in PP in patients with NIDCM
Kołodziejczak et al. 2017 (22).	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH	2992 (1284/1708)	HR 0 .81 95% CI 072-0.91 p = 0.006	Significant decrease in all-cause mortality in NIDCM
Barakat et al. 2017 (23)	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH	2573 (1284/1289)	HR. 0.79 95% CI 0.64-0.93 p < 0.001	ICD was associated with significant decrease in all-cause mortality in NIDCM
Stavrakis et al. 2017 (24)	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, COMPANION, DANISH	2967 (1553/1414)	HR. 0.78 95% CI 0.66-0.92 p = 0.003	ICD reduced all-cause mortality by 22% in NIDCM
Romero et al. 2017 (25)	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH	2573	RR 0.84 95% CI 0.71-0.99 p = 0.03	Significant decrease in all-cause and sudden mortality with ICD in NIDCM
Akel et al. 2017 (26)	CAT, AMIOVIRT, DEFINITE, SCD-HeFT, DANISH	2573	HR 0.80 95% CI 0.67-0.96 p = 0.02	ICD reduced all-cause mortality in NIDCM
Masri et al. 2017 (27)	CAT, DEFINITE, SCD-HeFT, COMPANION, DANISH	2867 (1503/1364)	RR 0.76 95% CI 0.64-0.91 p = 0.002	ICD reduced all-cause and sudden mortality in NIDCM

ICD: implantable cardioverter defibrillator; MT: medical treatment; NIDCM: non-ischemic dilated cardiomyopathy; PP: primary prevention; Remaining abbreviations in the text.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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ANTAGONIST

ARTURO CAGIDE[1], MTSAC,

Non-ischemic dilated cardiomyopathy (NIDCM) is defined as a structural abnormality of the myocardium not attributable to coronary artery disease, characterized by impaired contractility and a variable prognosis that includes a varying risk of sudden death (SD). It may result from multiple causes, such as tachycardia-induced cardiomyopathy, postpartum cardiomyopathy, Chagas disease, post-myocarditis, and cardiomyopathies associated with certain genetic variants, among other etiologies.

In many of these conditions, the indication for implantable cardioverter defibrillator (ICD) implanta-

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tion for the prevention of SD is supported by limited evidence, generally arising from observational studies with small patient populations. In most cases, the decision is based on the presence of a left ventricular ejection fraction (LVEF) ≤35% along with other risk factors for SD. In this context, it is worth noting that a high proportion of cases of lymphocytic myocarditis, tachycardia-induced cardiomyopathy and postpartum cardiomyopathy show recovery of ventricular function once the acute phase or the underlying condition resolves.

Beyond these entities, NIDCM is likely the result of a prior viral infection or various genetic variants, although in a large proportion of cases, the etiology remains unknown.

For the purposes of this discussion, focus will be limited to the latter group, which also represents the most prevalent form of the condition.

CLINICAL TRIALS AND EVIDENCE

For the primary prevention of SD in NIDCM, Table 1 summarizes the results of clinical trials comparing the ICD group with the control group. The studies included are AMIOVIRT, CAT, DEFINITE, DANISH, and SCD-HeFT. (1-5) None of them demonstrated a statistically significant reduction in all-cause mortality, which remains the only clinically relevant endpoint.

By contrast, in ischemic cardiomyopathy, the MADIT, MUSTT and MADIT II trials showed statistically significant difference in favor of the ICD group compared to the control group, although the DINAMIT and CABG-PATCH trials yielded neutral results. (6-10)

The SCD-HeFT study, which included patients with ischemic and non-ischemic cardiomyopathy in equal proportions, demonstrated a significant difference in the overall population but not in the subgroups analyzed by etiology. (5)

However, to complete the analysis, two other relevant publications should be considered.

A meta-analysis that included the five studies shown in Table 1 demonstrated a significant difference in favor of ICD implantation: odds ratio (OR) 0.78, 95% CI 0.66-0.93, $p < 0.05$. (11)

The other publication refers to the DEFINITE trial. A substudy demonstrated that, in patients recently diagnosed with NIDCM, ICD significantly reduced mortality at 3 months post-implantation. (12)

These findings do not strengthen but rather weaken the evidence supporting ICD. A meta-analysis based on negative trials does not carry the same clinical relevance as one that includes at least a single positive trial. In the case of DEFINITE, this is a post hoc analysis with limited statistical value, which also contradicts current guideline recommendations that state that ICD implantation should only be considered after at least three months of optimal medical therapy.

GUIDELINES AND RECOMMENDATIONS

Although not mandatory for medical decision-making, guidelines provide essential support for healthcare professionals. In general, guidelines developed by subspecialties, such as those for electrophysiology or cardiac pacing, tend to be more likely to indicate interventions than general clinical guidelines.

Table 2 summarizes the recommendation levels for ICD implantation in NIDCM compared to ischemic cardiomyopathy, according to the guidelines of the Argentine Society of Cardiology (SAC), (13) the European Society of Cardiology (ESC), (14) and a recent consensus of the American societies on the appropriate use criteria for ICD, cardiac resynchronization therapy and pacing. (15)

In summary:

- In NIDCM, the indication for ICD implantation can only be considered after three months from the initial diagnosis, provided the patient has received optimal medical therapy and has a life expectancy greater than one year.
- Unlike ischemic cardiomyopathy, there is no Class I recommendation for NIDCM, either in the SAC consensus or the ESC guideline. In the American consensus document, although ICD is listed as an "appropriate option", the score on the appropriateness scale is lower.
- In patients with LVEF ≤35% and functional class I (FC I), the ESC does not consider ICD implantation, and the SAC assigns it a Class IIb recommendation, which—on the ordinal scale of recommendations—is closer to Class III than to Class I.
- In patients with LVEF ≤35% and FC II/III, the Class IIa recommendation indicates that ICD implantation "*should be considered*", which is far from a Class I recommendation, where the intervention is forcefully stated to be "*indicated*".

FROM GUIDELINES TO DECISION-MAKING

How, then, can the above conclusions be translated into clinical practice?

Table 1. Controlled clinical trials in non-ischemic dilated cardiomyopathy. Result expressed as hazard ratio (ICD vs. control) and 95% confidence interval.

AMIOVIRT (1)	CAT (2)	DEFINITE (3)	DANISH (4)	SCD-HeFT (5)
0.69 (0.48-1.00)	0.81 (0.33-1.91)	0.65 (0.40-1.06)	0.87 (0.68-1.12)	0.73 (0.50-1.07)

Table 2. Comparison of recommendations in non-ischemic dilated cardiomyopathy and ischemic cardiomyopathy according to the guidelines from the Argentine Society of Cardiology (SAC), the European Society of Cardiology (ESC) and the consensus statement from American College of Cardiology/American Heart Association (ACC/AHA) on the appropriate use criteria for ICD, CRT and pacing.

NIDCM	SAC	ESC	ACC/AHA
LVEF ≤35%, FC I	IIb	NC	A7
LVEF ≤35%, FC II/III	IIa	IIa	A8
Ischemic cardiomyopathy	**SAC**	**ESC**	**ACC**
LVEF ≤30%, FC I	I	IIa	A8
LVEF ≤35%, FC II/III	I	I	A9

Note: Members of the consensus panel of the American societies rated each clinical scenario using an appropriateness scale from A1 to A9. Scores A7-A9 indicate an appropriate behavior for the specific indication: reasonable, generally accepted, with benefits outweighing risks, and suitable to be included in the treatment plan, although its necessity depends on clinical judgment and patient preferences. FC: functional class; LVEF: left ventricular ejection fraction; NC: not considered; NIDCM: non-ischemic dilated cardiomyopathy

One possible approach is as follows: in the case of a Class I recommendation, the clinician may ask: "*Is there any reason not to indicate this procedure?*". In contrast, with a Class IIa recommendation, the question is definitely different: "*Is there any additional finding that supports the indication*?

From this perspective, the possible factors to consider in patients with LVEF ≤35% and FC II/III (Class IIa) may include:

- Syncope of unknown cause
- Positive electrophysiological study
- Other clinical conditions indicating a high risk of SD
- Late gadolinium enhancement or high-risk genetic variants

The last three factors require further consideration.

What is referred to as "*high-risk clinical conditions*" stems from post hoc analyses, which carry lower statistical value.

Regarding late gadolinium enhancement on cardiac MRI, although observational studies have shown an association with SD, ICD implantation in these patients did not reduce mortality. (16) This may explain why the guidelines do not consider it. (17)

Finally, in patients with LVEF >35%, certain genetic variants *(LMNA, FLNC-truncating variants, TMEM43, PLN, DSP, RBM20)*, associated with a higher incidence of SD are considered for a Class IIa recommendation only if additional risk factors are present. (17) This conclusion reflects the fact that some variants initially thought to indicate a poor prognosis have since been reevaluated. For example, in the case of sarcomeric variants in hypertrophic cardiomyopathy, their prognostic value was questioned in the ESC guideline, which states: "*Variants classified as malignant or benign have different phenotypic expression and variable prognosis*", *("...multiple sarcomeric variants suggested to be associated with a worse prognosis, other cohorts have not consistently reported this association...")*, which then modified the assumption with respect to previous documents *("Task Force does not recommend the use of the presence of sarcomeric variant (s) to guide decisions around ICD implantation for primary prevention")*. (14) Could a similar change in the original positioning be applied in the near future to genetic variants associated with NIDCM?

CONCLUSION

This antagonistic position regarding the use of ICD implantation in patients with NIDCM does not support the notion of an absolute contraindication; however, it is sufficient to consider the indication as non-systematic. As previously discussed, certain associated factors should be present to justify the recommendation. Moreover, in the absence of such factors or if the complementary studies are unavailable, ICD implantation may not be appropriate.

Finally, a reflection on the indication of ICD tailored to the economic conditions of the Argentine healthcare system.

In necrotic ischemic cardiomyopathy, the SAC consensus states that *"the appropriate indication of ICD... in our setting requires the need to select higher-risk groups in which to use this valuable therapeutic resource"*. (13)

If such a conclusion is reached in the context of ischemic cardiomyopathy—where the level of evidence is higher—then the concept must necessarily be extended and reinforced in the context of NIDCM, where both the evidence and the strength of guideline recommendations are clearly lower.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

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AGONIST REPLY

I congratulate Dr. Cagide for his analysis and his excellent role of antagonist in this controversy. I agree with several of the points raised, particularly those highlighting the need to identify clinical risk factors that may support or not the decision to indicate an ICD. Non-ischemic dilated cardiomyopathy represents a final common pathway for many conditions, each associated with a different risk of SD. Genetic testing is likely to play a more important role as it becomes more accessible, as highlighted in the latest European guideline recommendations. Although not yet conclusive, myocardial fibrosis analysis may provide more insight in the future.

I believe that the suspected ventricular dysfunction caused by arrhythmias should always be considered by clinical cardiologists. There are reports of LVEF above 35% after ablation of frequent ventricular ectopic beats and atrial fibrillation AF, excluding the patient from the formal indication for ICD implantation.

It is also essential to evaluate the relevant causes of SD, i.e., many patients present with comorbidities or advanced heart failure, making it clear that ICD implantation would not alter the overall prognosis. In this regard, the impact of advanced age in NIDCM is particularly noteworthy, as highlighted by the DANISH study.

Finally, I agree with your comment: "In NIDCM, the indication for ICD can only be considered after three months from the initial diagnosis, provided that the patient has received full medical treatment and life expectancy exceeds one year", to which I would add: after a clinical assessment that weighs other potential risk factors for SD and comorbidities affecting overall prognosis.

Carlos Labadet

ANTAGONIST REPLY

A common point emerging from the arguments presented throughout this document is that the recommendation for ICD implantation for the primary prevention of SD in NIDCM is weaker than in ischemic cardiomyopathy, reflecting a definitively lower level of evidence.

In recent years, international guidelines have incorporated, alongside the strength of recommendation and level of evidence, the concept of cost-effectiveness, based on the economic impact of the proposed intervention on healthcare system. These considerations have recently prompted editorials and updates in specialty journals. In our setting, this issue is undoubt

edly even more relevant.

However, if we now combine both conclusions, it becomes clear that routinely recommending ICD implantation for all patients with NIDCM is clearly unsustainable in our country.

Thus, the conclusion of the Argentine Society of Cardiology guidelines is once again reaffirmed when it recommends "adjusting" the indication for ICD implantation in primary prevention in ischemic cardiomyopathy. This leads us to apply the same reasoning in NIDCM, where, as repeatedly noted, the level of evidence is even lower.

Arturo Cagide

REVIEW ARTICLE

The Arterial Biomechanics and Traslational Medicine Saga

La saga de la biomecánica arterial y la medicina traslacional

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ABSTRACT

Translational medicine can be described as the interdisciplinary application of biomedical research for the improvement of health of patients and the society.
This article describes the translational medicine activities related to arterial biomechanics carried out by a group of researchers from the IMETTYB (Instituto de Medicina Traslacional, Trasplante y Bioingeniería) CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas)-Favaloro University.

Key words: Arterial biomechanics – Translational medicine - Arterial stiffness - Pulse wave velocity - Arterial thickness - Related drugs

RESUMEN

La medicina traslacional puede ser definida como la aplicación de la investigación biomédica para la recuperación de la salud, tanto de los pacientes como de la comunidad en un amplio campo interdisciplinario.
En este artículo se describe la actividad en medicina traslacional circunscripta a temas de biomecánica arterial llevada adelante por un grupo de investigadores del IMETTYB (Instituto de Medicina Traslacional, Trasplante y Bioingeniería) - Universidad Favaloro.

Palabras clave: Biomecánica arterial - Medicina traslacional - Rigidez arterial - Velocidad de onda de pulso - Espesor arterial - Fármacos relacionados

INTRODUCTION

In 1996 Dr. Alberto Agrest wrote The Renin Saga. (1) Renin, a chemical mediator, was discovered by Tigerssted in the 19th century. Interestingly, it was the Finnish researcher mentioned above who developed the first quantification of arterial elasticity. (2) Renin and pulse wave velocity (PWV), a benchmark of arterial wall stiffness, are closely related to hypertension. Although it took a century for the study of PWV to be applied to large populations of hypertensive patients, it is undeniable that this step from the experimental stage to medical practice is an example of translational medicine, according to current criteria. (3)

According to Rodolfo Rey, principal researcher at CONICET and the director of CEDIE (Centro de Investigaciones Endocrinológicas "Dr. César Bergadá"), CONICET-FEI-GCABA (Fundación Endocrinológica Infantil-Gobierno de la Ciudad Autónoma de Buenos Aires), "There are few institutions in Argentina that have traditionally conducted translational research in medicine because the groups that did basic research and those that did clinical research were distant. Very few places had both."

This article describes the translational medicine activities related to arterial biomechanics carried out by a group of researchers from the IMETTYB (Instituto de Medicina Traslacional, Trasplante y Bioingeniería) CONICET-Favaloro University.

About translational medicine

A definition accepted by the scientific community mentions that translational medicine would be the interdisciplinary application of biomedical research for the improvement of health of patients and the society. (3)

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Biomedical research at the institution of the authors of this article began as an isolated initiative that later became associated with institutions such as CONICET and INSERM (Institut National de la Santé et de la Recherche Médicale, France). Research was generated within the framework of cooperation agreements, the most notable of which are those with INSIBIO-CONICET (Instituto Superior de Investigaciones Biológicas de San Miguel de Tucumán) and the Department of Physiology at the Faculty of Medicine of the University of the Republic (Uruguay).

The original lines of research and subsequent studies covered numerous areas of biomedical knowledge. This article only mentions those related to arterial biomechanics.

The experimental stage of knowledge that was later applied in clinical practice included basic and applied research. In this regard, it is important to adhere to the definitions of the Frascati Manual. (4)

Since we are dealing with more than four decades of scientific production published at the regional level and in peer-reviewed scientific journals, we will make a synthesis considering only two main areas:

1. Indices and indicators of arterial function used in biomedical laboratory research that were later incorporated into medical practice, and
2. Experimental models in which arterial function was analyzed in a laboratory setting to characterize physiological and abnormal states.

Objectives

This article describes:

a. General aspects of how arterial biomechanics evolved,
b. The beginnings of experimental laboratory research,
c. A synthesis of experimental vascular function indices, and
d. The implementation and use of these indices in clinical cardiology.

A brief history of the beginnings of arterial mechanics

The first scientific contribution to show a variable involved in arterial mechanics was the measurement of intra-arterial pressure in an equine performed by Hales in 1733. (5) More than a century later, in 1847, Karl Ludwig plotted the temporal pressures of a canine carotid artery. (6) A significant advance occurred soon after, when Tigerstedt quantified the elasticity of the vascular wall and determined the PWV for the first time in 1893. (2) By 1933, Schretzenmayr (7) experimentally demonstrated that increases in arterial flow produced an increase in vascular diameter.

Intraluminal pressures and arterial diameters are variables used to characterize arterial mechanics. However, these contributions were not incorporated into medical practice until the second half of the 20th century. Moreover, the noninvasive blood pressure measurement technique developed by Riva Rocci in 1896 (8) did not significantly impact medical practice, despite the publication by John Welton Fisher in JAMA in 1914 demonstrating the consequences of hypertension. (9)

In 1922 Bramwell and Hill published an analysis of arterial PWV and emphasized its dependence on the elasticity of the vascular wall. (10) Then, in the second half of the 20th century, the study of arterial mechanics gained momentum when Hardung measured arterial elasticity in 1953. (11)

First Argentine contributions to arterial biomechanics

The IMETTYB includes topics that began to be developed in 1983, as the line of research "Cardiovascular Dynamics and Circulatory Support".

Since the 1980s, it has been possible to characterize the contributions of the components of the arterial wall in chronically instrumented, conscious animal models. (12-15) In this initial stage, the roles of collagen, elastin, and vascular smooth muscle could be identified in arterial pressure-diameter curves. This information can currently be found in articles included in PubMed. These investigations were conducted in an experimental laboratory in Argentina, and the data were analyzed in collaboration with French researchers from INSERM led by Dr. Alain Simon.

Based on these investigations, our goal was to analyze the contributions of each of the three layers that make up the arterial wall. For this purpose, we chose an in vitro model to study the arterial wall dynamics. And that is how we demonstrated for the first time that variations in hematocrit caused changes in vascular smooth muscle dynamics. (16) Next, we incorporated an anesthetized in vivo animal model to characterize the role of the adventitia (17). Finally, we used an in vivo animal model with heart failure that was treated with intra-aortic balloon pumping to demonstrate the role of the adventitia in the smooth muscle dynamics of the arteries. (18)

At this stage, the experimental research carried out at Favaloro University with a group of researchers from University of the Republic (Uruguay) analyzed the role of the endothelium in heart failure treated with intra-aortic balloon pumping. (19)

Finally, we analyzed the dynamics of the isolated media (muscular) layer (i.e., without the intima and adventitia layers) under the same conditions. (20)

Summary of indices and indicators incorporated in translational medicine

One of the criteria used to show the scientific activity in translational medicine was to compile a list of a dozen indices and indicators of arterial dynamics derived from publications in the experimental stage and reports on their implementation in medical practice (Table 1)

Since the authors are part of an interdisciplinary group and of other biomedical research associations, the bibliographic references include works with at

Table 1. Vascular indices and indicators used at different stages of the process

INDICATOR	EXPERIMENTAL STAGE	MEDICAL PRACTICE STAGE
Arterial compliance	Chau 1992 (21), Cabrera Fischer 2010 (17), Cabrera Fischer 2013 (18)	Chau 1992 (21), Christen 1997 (22), Brandani 2000 (23)
DABAC/SABAC	Cabrera Fischer 2004 (24)	Cabrera Fischer 2001 (25), Camus 2004 (26)
Arterial diameter	Cabrera Fischer 1987 (12)	Gamero 1999 (27)
Arterial distensibility	Armentano 1994 (28), Cabrera Fischer 2010 (17), Cabrera Fischer 2013 (18)	Armentano 1995 (29)
Arterial thickness	Cabrera Fischer 1988 (13)	Gamero 1999 (27)
AIx index	Wray 2021 (30)	Díaz 2018 (31)
Peterson's module	Cabrera Fischer 1991 (14), Cabrera Fischer 2005 (32), Cabrera Fischer 2009 (33)	Armentano 2006 (34)
Blood pressure	Cabrera Fischer 1987 (12), Cabrera Fischer 1988 (35)	Pessana 2021 (36), Sánchez 2020 (37), Sánchez 2022 (38)
Arterial viscosity	Barra 1997 (39)	Christen 2010 (40)
Pulse wave velocity	Armentano 1994 (28), Cabrera Fischer 2010 (17)	Christen 1997 (22), Cabrera Fischer 2009 (41), Cabrera Fischer 2018 (42)

AIx: augmentation Index; DABAC/SABAC: index that quantifies the effects of intra-aortic balloon pumping (diastolic area beneath the aortic curve/ systolic area beneath the aortic curve).

Table 2. Contributions of research to medical practice

ENTITY	EXPERIMENTAL STAGE	MEDICAL PRACTICE STAGE
Endothelium	Cabrera Fischer 2002 (16)	Christen 2010 (40)
Vascular smooth muscle	Barra 1997 (39)	Armentano 2006 (43)
HTN	Cabrera Fischer 1993 (44)	Gamero 1999 (27)
HF	Cabrera Fischer 1985 (45), Cabrera Fischer 2004 (46)	Cabrera Fischer 2001 (25)
Atherosclerosis	Cabrera Fischer 1991 (14)	Christen 2006 (47)
Renal function	Fischer P 2000 (48)	Sánchez 2007 (49)
ANS control	Risk 2004 (50)	Ramírez 2003 (51)
ACEI	44-Cabrera Fischer 1993 (44), Barra 1997 (39)	Ramírez 2019 (52)
Beta blockers	Crottogini 1987 (53)	Armentano 2001 (54)
Calcium channel blockers	Crottogini 1985 (55)	Ramírez 2019 (56)

Clinical situations of normality, disease and therapeutics that ventured from the experimental stage at the biomedical laboratory to medical practice.
ACEI: angiotensin-converting enzyme inhibitor. ANS: autonomic nervous system; HF: heart failure; HTN: hypertension.

least one author from the institution. On the other hand, it should be noted that not all indices or indicators of arterial function have been included, as the quantification of atherosclerotic plaque by fractal dimension analysis.

Table 1 includes the controversial blood pressure augmentation index (AIx), which has been analyzed experimentally since 2008 as part of a scientific and technological research project funded by the National Ministry of Science and Technology. Due to the lack of convincing evidence regarding the sensitivity and specificity of AIx, the decision was made to submit two manuscripts summarizing the experimental and clinical analyses.

Summary of the contributions of medical practice to translational medicine

Table 2 lists the clinical conditions (normal and abnormal) that were analyzed in the experimental laboratory and in medical practice, in parallel to the reported uses of indices and indicators of function and structures related to vascular biomechanics. Table 2 includes the treatments used in patients with specific conditions for which biomechanical analysis is performed or is under development.

Considerations on translational medicine in arterial biomechanics

The study of cardiovascular pathophysiology in the experimental laboratory is supported by animal models that replicate those published in the specialized literature. When there is a gap in the literature, new models are developed, such as those published by the authors. (45,18) This does not mean that experimental laboratory developments will always be transferred to medical practice. For example, the numerous works on adventitial function carried out by the IMETTYB group are not cited because they have not ventured into the field of patients. This fact underscores the wealth of knowledge generated by the laboratory and the underutilization of this knowledge in medical practice.

Just as the study of left ventricular function analyzes the dynamics of the ventricular wall, arterial mechanics focuses on the vascular walls. In both structures, mechanical analysis provides functional indices of significant diagnostic value. However, the study of arterial biomechanics has been recently introduced. This underscores the importance of using and analyzing new vascular function indices in different experimental models of various conditions.

In summary, the objectives of this article have been developed using part of the analyses that have been carried out and published over a period of four decades.

Conflicts of interest

None declared.

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

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REVIEW ARTICLE

Obstructive Sleep Apnea Syndrome: A Cardiovascular Risk Factor

Síndrome de apneas obstructivas del sueño: un factor de riesgo cardiovascular

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ABSTRACT

Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by repeated episodes of complete or partial upper airway obstruction during sleep. This condition is associated with a high prevalence of cardiovascular disease, including hypertension, arrhythmias, heart failure, and cerebrovascular events. The underlying pathophysiology involves intermittent hypoxia, sympathetic activation and oxidative stress, leading to endothelial dysfunction and cardiovascular remodeling.
Clinically, patients with OSAS usually present with excessive daytime sleepiness, snoring and morning headaches. Diagnosis is confirmed by polysomnography. The treatment of choice is continuous positive airway pressure (CPAP), a device that keeps the airway open during sleep.
Numerous studies have demonstrated a causal relationship between OSAS and increased cardiovascular risk. Despite advances in diagnosis and treatment, OSAS remains underdiagnosed and undertreated. Early identification and appropriate treatment with CPAP are critical to improve the cardiovascular prognosis and quality of life of patients.

Keywords: Cardiovascular risk factors - Hypercapnia - Hypoxia - Polysomnography - Obstructive sleep apnea syndrome

RESUMEN

El síndrome de apneas obstructivas del sueño (SAOS) es un trastorno caracterizado por episodios repetidos de obstrucción completa o parcial de las vías aéreas superiores durante el sueño. Esta condición se asocia con una alta prevalencia de enfermedades cardiovasculares, que incluyen hipertensión, arritmias, insuficiencia cardíaca y eventos cerebrovasculares. La fisiopatología subyacente involucra hipoxia intermitente, activación simpática y estrés oxidativo, lo que conduce a disfunción endotelial y remodelación cardiovascular.
Clínicamente, los pacientes con SAOS suelen presentar somnolencia diurna excesiva, ronquidos y cefaleas matutinas. El diagnóstico se confirma mediante polisomnografía. El tratamiento de elección es la presión positiva continua en las vías respiratorias (CPAP), un dispositivo que mantiene abiertas las vías aéreas durante el sueño.
Numerosos estudios han demostrado una relación causal entre el SAOS y el aumento del riesgo cardiovascular. A pesar de los avances en el diagnóstico y tratamiento, el SAOS sigue siendo subdiagnosticado y subtratado. La identificación temprana y el tratamiento adecuado con CPAP son fundamentales para mejorar el pronóstico cardiovascular y la calidad de vida de los pacientes.

Palabras clave: Factores de riesgo cardiovascular - Hipercapnia- Hipoxia - Polisomnografía -Síndrome de apneas obstructivas del sueño

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a complex disease with multiple symptoms and associated comorbidities, characterized by the intermittent presence of apneas and hypopneas, i.e. total or partial obstruction of the airway, during sleep. This leads to a state of hypoxemia, autonomic fluctuation, and sleep fragmentation. (1)

Daytime and nocturnal symptoms or cardiometabolic comorbidities are caused by obstructive sleep apnea (OSA). Both terms (OSA and OSAS) are often used interchangeably in the literature. (2)

The estimated prevalence of this disease is 3% in women and 10% in men between 30 and 49 years of age, and 9% in women and 17% in men between 50 and 70 years of age, (3) but among patients with hyper-

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tension (HTN), heart failure (HF), atrial fibrillation (AF), coronary heart disease, pulmonary hypertension and stroke, the prevalence increases significantly. (4)

Most patients are unaware of the disease and, what is worse, do not consider sleep disturbances relevant, so they do not consult and are not diagnosed.

Currently, OSA is recognized as a problem that generates a high cost to health systems worldwide. The aim of this review is to understand the pathophysiology, its importance as a risk factor and its relationship with cardiovascular disease (CVD).

Pathophysiology

The pathophysiology of OSA is the result of the interaction between alterations in upper airway anatomy and upper airway function during sleep.

Morphologic abnormalities are the most common factors contributing to upper airway obstruction (e.g., retrognathia, enlarged tonsils, and increased soft tissue in the neck). In patients with decompensated HF, jugular distention during supine decubitus may exacerbate OSA by increasing pressure in the hypopharynx. (5)

Regarding the pathophysiological effects on the cardiovascular system, apnea-hypopnea episodes cause periodic hypercapnia and hypoxemia, with activation of the sympathetic nervous system and elevation of serum catecholamines. Both factors increase heart rate and systolic blood pressure, and thus myocardial oxygen consumption. Similarly, frequent awakenings and lack of sleep due to periodic asphyxia also activate the sympathetic nervous system. (6) Over time, these hemodynamic changes eventually lead to left ventricular hypertrophy and HF. In addition, hypoxemia promotes oxidative stress, systemic inflammation and endothelial dysfunction, contributing to the development of atherosclerotic disease. To counteract pharyngeal narrowing, negative intrathoracic pressure is generated, which increases mechanical stress on the cardiac chambers. This generates remodeling, with left ventricular hypertrophy and left atrial enlargement. These maladaptive changes may manifest as diastolic failure and AF.

Epidemiology and factors contributing to OSA

Obstructive sleep apnea is a common disorder in adults, and its prevalence has increased with the increasing presence of obesity. It is highly predominant in populations with diabetes, hypertension, heart disease, and stroke. Environmental factors also contribute to the risk of OSA. The epidemiology of OSA depends on the criteria used to diagnose the disease, including how respiratory events are defined, apnea-hypopnea index (AHI) cutoff points, and how diagnostic tests are performed. The criterion of arterial oxygen saturation (SaO_2) drop ≥ 4 % for hypopneas may have greater association with patients who are older, male, obese, and have underlying cardiac disease (e.g., HF, coronary artery disease, AF, or diabetes). The American Academy of Sleep Medicine (AASM) defines hypopneas more broadly (desaturation ≥3 % or awakening) and allows the inclusion of more variable sleep disturbance phenotypes seen in younger, non-obese, and female patients. (2)

A meta-analysis of 17 studies estimated that 936 million adults aged 30-69 years worldwide suffer from mild to severe OSA, with prevalence exceeding 50% in some places. (7) The prevalence of OSA is associated with gender, obesity, and age. It is higher in men (2:1), but rates increase in women after menopause, and become nearly equal in older adults. Prevalence increases with age, particularly in those over 60 years of age.

Obesity is the main modifiable risk factor for OSA. There is an association between OSA and increased waist circumference and neck circumference (with increased prevalence of OSA in those with values >43 and 41 cm in men and women, respectively). (2)

Craniofacial anomalies that narrow the upper airway or increase airway collapsibility may explain the occurrence of severe OSA despite the absence of obesity. Other less well-established risk factors include smoking, family history of OSA, and nocturnal nasal congestion.

The use of substances such as alcohol or benzodiazepines can exacerbate pre-existing OSA. (4)

Clinic

The signs and symptoms of OSAS are summarized in Table 1.

Diagnosis and detection of OSA

Obstructive sleep apnea is usually suspected on the basis of symptoms and confirmed by diagnostic tests, which may be performed by a home sleep apnea study, multichannel polysomnography, or overnight laboratory testing.

Laboratory polysomnography is the gold standard for the diagnosis of OSA, but it can be expensive and difficult to access.

Validated questionnaires can be a quick tool to stratify patient risk.

The diagnosis requires:

1) reported nocturnal breathing disorders (snoring, snorting, gasping, or pauses in breathing during sleep) or symptoms of daytime sleepiness or fatigue that are not explained by other medical conditions.

2) an AHI ≥5 episodes/hour.

OSA can be diagnosed in the absence of symptoms if AHI is ≥15 episodes/hour. Empirical categorization is based on AHI from: 5 to <15 (mild), 15 to 30 (moderate), and >30 (severe). (8)

Recent research has identified hypoxia burden as a predictor of increased CVD risk. (9)

The detection of this pathology is done by questioning the patient, which should include questions about the frequency and severity of snoring, gasping and snorting during sleep, frequent awakenings

or sleep interruptions, and excessive daytime sleepiness. The most commonly used screening questionnaires are the STOP-BANG questionnaire (Table 2), the Berlin questionnaire (Table 3), and the STOP questionnaire. (10) These questionnaires sensitivity is between 77% and 89%, but have lower specificity (32%-34%). The use of the Epworth sleepiness scale is not recommended, as it has higher specificity (67%) but low sensitivity (42%). (10)

On the other hand, given the strong association between OSA and numerous cardiovascular conditions, screening is recommended in patients with:

- Resistant or poorly controlled HTN, pulmonary arterial hypertension (PAH) and recurrent AF.
- NYHA FC II to IV HF, with suspected sleep breathing disorders or excessive daytime sleepiness.
- Tachycardia-bradycardia syndrome, ventricular tachycardia or sudden death survivors and suspected sleep disturbances.
- Angina of nocturnal occurrence, myocardial infarction, arrhythmias or appropriate discharges from implantable cardioverter-defibrillators.
- History of stroke

Cardiovascular consequences

Obstructive sleep apnea is an independent risk factor for CVD. It is also recognized to be associated with metabolic disorders, closely related to cardiovascular diseases. While sleep fragmentation and respiratory stress are contributing factors to OSA-associated pathologies, several clinical studies associate AHI with cardiovascular events. Furthermore, intermittent hypoxia, which mimics the repetition of oxygen saturation-desaturation cycles, has been shown to be the main mechanism responsible for OSA-associated cardiovascular and metabolic complications. (11)

Cardiovascular complications include HTN, AF and other arrhythmias, HF, coronary

artery disease, stroke, PAH, metabolic syndrome, diabetes, and cardiovascular mortality. It is a condi-

Table 1. Clinical manifestations and association with physical examination in obstructive sleep apnea syndrome (OSAS).

Signs and Symptoms	Physical examination
Excessive daytime sleepiness	Obesity
Morning headaches	Increased neck circumference
Memory impairment	Craniofacial abnormalities
Irritability	
Problems with concentration	
Nocturia	
Erectile diffusion and decreased sexual desire	

Table 2. STOP-BANG Questionnaire

Item evaluated	Finding
Snoring	Snoring loudly (more than talking or loud enough to be heard through a closed door).
Tiredeness	Often fatigue or daytime sleepiness
Observed	Observed to stop breathing during sleep
Blood **P**ressure	High blood pressure or current treatment for hypertension
BMI	>35 kg/m^2
Age	>50 years
Neck circumference	>40 cm
Gender	Male

≥ 3 or 4 findings= high risk of OSA
< 3 findings= low risk for OSA
BMI: body mass index; OSA: obstructive sleep apnea

Table 3. Berlin Questionnaire

1) Berlin Questionnaire (BQ)

Name and surname……..……

Weight…….…… Age……..…. BMI…….……

CATEGORY 1

1. Do you snore?

o a. Yes
o b. No
o c. Don't know

If you snore

2. Your snoring is:

o a. A little louder than breathing
o b. As loud as talking
o c. Louder than talking
o d. Very loud (can be heard from another room

3. How frequently do you snore?

o a. Almost every day
o b. 3-4 times per week
o c. 1-2 times per week
o d. 1-2 times per month
o e. Never or almost never

4. Has your snoring bothered other people?

o a. Yes
o b. No
o c. Don´t know

5. Has anyone noticed you stop breathing while sleeping?

o a. Almost every day
o b. 3-4 times per week
o c. 1-2 times per week
o d. 1-2 times per month
o e. Never or almost never

CATEGORY 2

6. How often after sleeping do you feel tired?

o a. Almost every day
o b. 3-4 times per week
o c. 1-2 times per week
o d. 1-2 times per month
o e. Never or almost never

7. Do you feel tired during the day?

o a. Almost every day
o b. 3-4 times per week
o c. 1-2 times per week
o d. 1-2 times per month
o e. Never or almost never

8. Have you ever fallen asleep while driving?

o a.Yes
o b. No

If you answered Yes

9. How often does this happen to you?

o a. Almost every day
o b. 3-4 times per week
o c. 1-2 times per week
o d. 1-2 times per month
o e. Never or almost never

CATEGORY 3

10. Do you have high blood pressure?

o a. Yes
o b. No
o c. Don´t know

Berlin Score
Category 1 (positive ≥ 2 points). -Questions 1-4 = 1 point each. Question 5 = 2 points
Category 2 (positive ≥ 2 points)- -Questions 6-8 = 1 point each.
Category 3 (positive if BMI is > 30Kg/m² or there is HTN
High risk = 2 positive categories (positive Berlin)
Low risk = ≤ 1 positive category (negative Berlin)
BMI: body mass index; HTN: hypertension

tion with negative feedback potential, exacerbating disorders that in turn may worsen OSA.

The relationship between OSA and **hypertension** has been extensively investigated and there is convincing evidence that there is a dose-effect relationship between the severity of OSA and the degree of blood pressure (BP) elevation. (12)

The pathophysiological mechanisms by which OSA contributes to BP elevation are multifactorial. On the one hand, OSA-induced hypoxemia causes systemic inflammation and oxidative stress, resulting in increased endothelin-1 generation and decreased nitric oxide production in endothelial cells, increased arterial peripheral resistance, and elevated BP. On the other hand, periodic hypoxemia, frequent awakenings and lack of sleep cause activation of the sympathetic nervous system, which leads to increased cardiac output and peripheral vasoconstriction, and thus promotes BP elevation. Patients with OSA have a higher prevalence of isolated diastolic HTN and the underlying mechanism could be due to tachycardia and shortening of diastole. Compared with subjects without OSA, subjects with OSA also have greater activation of the renin angiotensin system. Taken together, these ef-

fects lead to an elevation of BP due to vasoconstriction and sodium and water retention. In addition, primary hyperaldosteronism is very prevalent in subjects with OSA, highlighting the importance of screening them for primary hyperaldosteronism. These patients are more likely to develop drug-resistant HTN. Finally, sleep deprivation due to OSA has been shown to be associated with endothelial dysfunction and arterial stiffness. (13)

Adherence to continuous positive airway pressure (CPAP) is associated with greater reductions in nocturnal BP.

OSA and **atrial fibrillation** share many risk factors and comorbidities (male sex, HTN, congestive HF, coronary artery disease). The presence of OSA has been shown to predict pre-discharge AF after coronary revascularization surgery. In addition, untreated OSA doubles the risk of AF recurrence in patients after electrical cardioversion, and treatment of OSA with CPAP attenuates that risk. (14,15)

Multiple possible mechanisms can trigger AF in patients with OSA, but underlying to hypoxia and hypercapnia. Altered intrathoracic pressure generates increased sympathetic tone and autonomic dysregulation. This may lead to structural and functional atrial remodeling and cause electrophysiological alterations. (16)

Treatment of AF is more difficult in these patients. In the ORBIT-AF trial, patients with OSA had significantly worse symptoms, even though they were under rhythm control therapy. People with OSA had more episodes of recurrent AF, even after catheter ablation. Treatment of OSA is indispensable for the proper management of AF and maintenance of sinus rhythm. The cohort of patients treated with CPAP in the ORBIT-AF trial were less likely to progress to persistent AF compared with those who did not receive such treatment. Moreover, other trials have demonstrated less AF after catheter ablation in patients with OSA treated with CPAP compared with a risk of up to 57% AF recurrence in those not treated with CPAP. (17,18)

Although it seems reasonable to optimize sleep quality to avoid complications such as AF, to date there is no evidence to support the use of CPAP to prevent AF. The SAVE study failed to demonstrate significant differences in patients treated with CPAP vs. control. (19,20)

In addition to AF, OSA is associated with other cardiac rhythm disturbances and sudden cardiac death. These include sinus pauses, ventricular tachycardia and first-degree atrioventricular block. Nocturnal hypoxemia is independently a strong predictor of sudden death. In general, patients experience a reduction in cardiac arrhythmias when treated with CPAP. (21)

Obstructive sleep apnea and **heart failure** share numerous risk factors and pathophysiological mechanisms, which together may contribute to HF progression or refractoriness to treatment. Obstructive sleep apnea has a high prevalence and is associated with adverse outcomes in patients with HF, related to hospitalization and mortality. There is also an increased risk of central sleep apnea in these patients.

Obstructive sleep apnea is more frequent in HF patients with reduced left ventricular ejection fraction (LVEF), with an estimated prevalence ranging between 12% and 53%.

Although confirmatory studies are lacking, it is postulated that OSA may adversely affect HF patients through several mechanisms. Heart failure is a state of sympathetic overactivity in addition to the autonomic imbalance associated with OSA in response to hypoxemia, which may generate concomitant physiological stress. Moreover, the rise in intrathoracic pressure due to inspiratory effort exerts an increase in transmural pressure in the heart and great vessels, leading to increased afterload, reduced stroke volume, and higher myocardial oxygen consumption. (22)

Considering these pathophysiological mechanisms, CPAP therapy would be expected to have benefits in patients with HF. In addition to improving airway obstruction in OSA and reducing inspiratory effort, CPAP decreases venous return (preload) and may attenuate sympathetic activity. However, these physiological benefits have not yet translated into improved clinical outcomes in patients with OSA and HF. (23, 24)

In patients with HF and central sleep apnea, continuous positive airway pressure is associated with improved sleep quality and nocturnal oxygenation but has not been shown to affect survival. (25)

Regarding **coronary artery disease**, the prevalence of OSA in patients presenting with acute coronary syndromes (ACS) is up to 69%. In addition, OSA has been associated with an increased risk of adverse events after ACS. (6)

Intermittent hypoxia and concomitant increased sympathetic activity, inflammation, endothelial dysfunction, and elevated blood pressure are associated with higher risk of cardiovascular morbidity and mortality. Obstructive sleep apnea has been associated with coronary artery calcification, plaque instability, and vulnerability. During obstructive apneas, increased adrenergic tone and hypoxemia may increase the risk of myocardial ischemia. (2)

Patients with suspected OSA who present with ACS are more likely to be male and have conventional risk factors. On admission, these patients have higher levels of BP, C-reactive protein, and B-type natriuretic peptide (BNP), all of which are long-term predictors of CV morbidity and mortality. (6) Obstructive sleep apnea has also been associated with an increased risk of adverse events after percutaneous coronary intervention (PCI) for ACS. One study followed-up 89 consecutive patients after PCI for ACS for a mean of 227 days. The incidence of major adverse events (cardiac death, reinfarction, and revascularization of the treated vessel) was significantly higher in patients with OSA (23.5% vs. 5.3%). (26)

Whether CPAP therapy reduces the risk of myocardial infarction is still debated, and the timing of

starting treatment in the acute setting is a point of discussion.

Obstructive sleep apnea is highly prevalent (55%) among hemorrhagic **stroke** patients and significantly increases the risk of ischemic stroke. (27)

It also increases the risk of stroke through a variety of factors that lead to vascular damage in the brain. Repeated hypoxia can cause damage to the endothelium and release of proinflammatory factors, such as plasma cytokines, tumor necrosis factor-alpha, and interleukin-6. This may ultimately cause vascular dysfunction by increasing endothelin, neurovascular oxidative stress, and susceptibility to injury. (2)

Untreated OSA in stroke patients can cause cognitive impairment, decreased concentration, and excessive daytime sleepiness, which may prolong hospital stay and hinder rehabilitation. (28)

Trials with CPAP in post-stroke patients, despite their difficult follow-up, have shown promise for stroke recovery and secondary prevention. (29)

The prevalence of OSA is as high as 70% to 80% among patients with **pulmonary arterial hypertension** diagnosed by right heart catheterization. (30)

Obstructive sleep apnea should always be ruled out because of 3 conditions: it is associated with higher mortality; it requires adjustment of the appropriate treatment; and due to the possibility of coexistence with other PAH etiologies that might require different treatment strategies.

Although the mechanism behind PAH associated with OSA is not fully understood, it is postulated to be due to a combination of factors including pulmonary arteriolar remodeling, susceptibility to hypoxia, and underlying left heart disease. (31)

A study of WHO group I PAH patients showed that there was no significant difference in mortality between patients with and without OSA; however, mortality was significantly higher in patients with nocturnal hypoxemia, suggesting that the duration and severity of oxygen desaturation, characteristic of OSA, is an important risk factor for the development of PAH. (32)

Although data on the effect of CPAP on hemodynamic variables have been inconsistent, some reviews conclude that CPAP therapy is associated with a reduction in mean pulmonary artery pressure (mPAP) in patients with OSA and PAH. (33,34)

Although CPAP appears to improve hemodynamic variables including mPAP and systolic PAP in patients with OSA and PAH, the mechanisms are still unclear.

As we know, in the context of **metabolic syndrome and type 2 diabetes**, the severity of insulin resistance is directly related to nocturnal hypoxia in non-obese patients with OSA.

Alterations in lipid metabolism are also observed in patients with OSA.

The desaturation index, another indicator of the severity of nocturnal hypoxia, has been identified as an independent contributor to hypercholesterolemia and hypertriglyceridemia. (35)

In patients with metabolic syndrome, the prevalence of moderate to severe OSA is very high, around 60%. In this population, OSA is independently associated with increased glucose and triglyceride levels, as well as markers of inflammation, arterial stiffness and atherosclerosis. (36, 37) Although CPAP has been shown to reduce blood pressure and markers of sympathetic activation, it has not been shown to affect lipid levels, glycemic control, or rates of metabolic syndrome or diabetes. (1)

Prognosis

Moderate and severe OSAS are associated with an increased risk of vascular complications and all-cause mortality. This relationship may differ between genders. (38) Observational studies have shown a significant reduction in mortality with positive airway pressure, with greater risk reduction observed among patients with HF. However, large randomized controlled trials have not yet demonstrated an effect of positive airway pressure, including CPAP, on survival. (24) In an analysis of the Sleep Heart Healthy Study, CPAP prescription was associated with 42% lower mortality among patients with severe OSAS, but this risk reduction was not observed until 6 to 7 years of follow-up. (39)

Treatment

There are numerous treatment options for OSA. (5) Lifestyle intervention and weight loss of 10% reduces AHI by 26%.

Continuous PAP treatment during sleep is indicated with AHI ≥15, or ≥5 with symptoms (daytime sleepiness, cognitive impairment, mood disorders or insomnia), or comorbidities (hypertension, ischemic heart disease or history of stroke).

The objective is to avoid airway collapse with constant positive inspiratory and expiratory pressure. It requires a nocturnal laboratory titration study and an adherence of 40-80 % (4 hs or more per night) during 70 % of the period of use is defined.

Continuous PAP treatment showed improvement in somnolence, blood pressure and quality of life. Sometimes there is intolerance to the treatment due to problems of adaptation to the mask, claustrophobia, nasal congestion, or dry mouth or nose.

In patients intolerant to CPAP therapy or requiring additional ventilatory support, bi-level positive airway pressure (BiPAP) therapy is a treatment alternative since it allows the use of different inspiratory and expiratory pressures and is useful in patients who cannot tolerate high expiratory pressures. Adherence is similar to that of CPAP (40-80 %). (40)

Adaptive servoventilation (ASV) may be an option for OSA, especially in cases where apnea persists or is complicated by central apnea in the absence of HF (LVEF <45 %). (41)

Positional therapy is indicated in cases of isolated

events, or predominantly in supine position (AHI is twice as high in the supine position than that in the lateral decubitus position). In selected patients it has a similar efficacy to CPAP. Long-term adherence is low (10%) due to discomfort.

Oral appliances are an alternative to CPAP for mild to moderate obstructive apneas. Adherence is generally higher than for CPAP, and as with CPAP, there is improvement in sleepiness, ambulatory blood pressure and markers of inflammation. They should be prescribed by a physician and adjusted by a qualified dentist.

Upper airway surgery is an acceptable alternative on occasions when there are multiple levels of obstruction and collapse.

Finally, bariatric surgery in patients with body mass index ≥35 kg/m2, may improve OSA in addition to its multiple metabolic benefits. (42)

CONCLUSIONS

Obstructive sleep apnea is a growing health problem affecting nearly one billion people worldwide, and is an independent cardiovascular risk factor.

The cardiovascular and metabolic comorbidities associated with this entity are a major concern, due to the worsening prognosis and the complexity of integrated treatment.

Intermittent hypoxia, a characteristic factor of OSA, is the key intermediary mechanism underlying metabolic and cardiovascular complications.

Understanding the molecular pathways involved in the metabolic and cardiovascular consequences of OSA is a priority for new pharmacological tools, in combination with, or as an alternative to continuous positive pressure.

Continuous positive airway pressure, first-line therapy for the treatment of OSA, is very effective in improving symptoms and quality of life, but has limited effect on comorbidities. Lifestyle changes and weight loss should be part of the treatment whenever indicated.

The current literature clearly points to OSA as an emerging risk factor for modulating the cardiometabolic consequences of cardiovascular disease. However, OSA is commonly underdiagnosed.

There are several challenges. We need to do more screening for OSA in patients with both cardiovascular disease and traditional risk factors. There is need to provide a cost-effective way to perform adequate screening and diagnosis of OSA in millions of patients with other manifestations. Portable monitoring and new technologies for OSA diagnosis are promising options in high-risk groups, as full polysomnography may not be readily available

Conflicts of interest

None declared.

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

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OPINION ARTICLE

Is Endomyocardial Biopsy Essential for Heart Transplant Follow-Up? "The essential may be invisible to the microscope."

¿Es indispensable la biopsia endomiocárdica para el seguimiento del trasplante cardíaco?

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ABSTRACT

Endomyocardial biopsy is considered the gold standard for diagnosing and monitoring acute heart transplant rejection. However, due to its invasiveness and limitations, alternative diagnostic methods have emerged. The most developed include gene expression profiling and determination of donor-derived cell-free DNA (liquid biopsy).
Both methods enable surveillance of rejection beyond early months post-transplantation. They have shown promising results when used individually as well as when combined. Their main strength lies in their high negative predictive value to rule out acute rejection.
Nevertheless, further work is needed to establish standardized cut-off points, validate these methods in unselected populations and at earlier stages post-transplantation, improve access to these techniques, and conduct larger studies using clinically relevant endpoints.

Key words: Liquid biopsy - Gene expression profiling - Acute rejection - Heart transplantation - Endomyocardial biopsy

RESUMEN

Se acepta a la biopsia endomiocárdica como el patrón de oro para el diagnóstico y la vigilancia del rechazo agudo del trasplante cardíaco. Pero debido a su invasividad y limitaciones, han surgido otros métodos diagnósticos que permiten detectar rechazo del injerto. Los más desarrollados son el perfil de expresión génica y la determinación de ADN libre circulante del donante (biopsia líquida).
Ambos métodos permiten realizar vigilancia del rechazo más allá de los primeros meses del trasplante. Su uso en forma aislada y especialmente su combinación ha mostrado muy buenos resultados. Su principal mérito es la posibilidad de descartar rechazo debido a su alto valor predictivo negativo.
Aún queda pendiente establecer los puntos de corte, probarlos en poblaciones no seleccionadas y en etapas más precoces del trasplante, mejorar la accesibilidad a estas técnicas y disponer de estudios de mayores dimensiones que usen puntos finales de importancia clínica.

Palabras clave: Biopsia líquida - Perfil de expresión génica - Rechazo agudo - Trasplante cardíaco - Biopsia endomiocárdica

INTRODUCTION

Heart transplantation is recognized as the optimal therapeutic option for patients with end-stage heart disease.

Transplant rejection and infections are the most frequent complications during the first year post-transplantation. Since rejection may result in graft loss, early detection is crucial to initiate timely and appropriate treatment. (1)

In 2021, an observational and retrospective study conducted in our country reported findings consistent with international data, showing that acute rejection was the leading cause of hospitalization during the first year post-transplantation, being cellular rejection the most predominant. (2)

Acute rejection encompasses a broad spectrum of presentations, ranging from hemodynamic deterioration to genetic alterations, each with different possible diagnosis. (3) (Figure 1)

Hemodynamic deterioration, most commonly presenting as heart failure, can be diagnosed through a thorough medical history and physical examination,

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as well as through basic diagnostic tests, such as laboratory analysis and chest X-ray.

Imaging studies can identify structural and/or functional alterations. Echocardiography and magnetic resonance imaging (MRI) can detect increased myocardial thickness, diastolic dysfunction, ventricular dilatation and systolic dysfunction, which may be suggestive of rejection, but, unfortunately, at a more advanced stage than desired, since the objective is to anticipate structural organ damage and initiate early treatment. (4-9)

For this reason, endomyocardial biopsy (EMB) has become a routine diagnostic procedure. Endomyocardial biopsy reveals microscopically different degrees of cellular infiltrate, necrosis, and/or hemorrhage, which are indicators of rejection. Moreover, it allows for grading the severity of rejection and guiding appropriate treatment.

At the molecular level, the release of graft-derived deoxyribonucleic acid (DNA) can be determined by quantifying the percentage of donor-derived cell-free DNA (dd-cfDNA), representing a diagnostic alternative for identifying rejection.

Finally, at the genetic level, specific variants associated with rejection have been identified. Gene expression profiling (GEP) allows for the identification of patients at higher risk of rejection.

Within the clinical-genetic spectrum, the closer we get to the molecular level, the earlier we can detect the event. (10-12)

PROBLEM STATEMENT

The most widely used and cost-effective technique for diagnosing and monitoring transplant rejection is the EMB. Although it has adequate sensitivity and specificity for detecting cellular rejection, it has certain limitations, including its invasiveness, potential complications, inconsistency in grading intermediate levels of cellular rejection and challenges in interpreting antibody-mediated rejection.

Among the complications of EMB, cardiac tamponade—although rare (<0.5%)—and the potential to induce tricuspid regurgitation must be mentioned. (13,14)

A key factor to consider is that current immunosuppressive therapy has significantly reduced the incidence of acute rejection. Additionally, most routine EMB procedures are performed in asymptomatic patients with a low probability of rejection, which further reduces the diagnostic performance of this technique. (15)

Over the last few decades, a reduction in the incidence of rejection has been observed across all intervals post-transplantation. A comparative observational study of two groups of transplant recipients—those transplanted between 1990 and 2000, and those transplanted between 2000 and 2010, found that although the latter group had more risk factors for developing rejection, the incidence was lower in this group at all intervals post-transplantation (0-6 months: 60.2% vs. 21.5%, p<0.001; 6-12 months: 26.8% vs. 1.8%,

Fig. 1. Diagnostic methods for acute transplant rejection according to the spectrum of presentation

Hemodynamic deterioration	Functional/ structural alterations	Alteraciones celulares	Molecular alterations	Genetic alterations
Heart failure	Systolic dysfunction Ventricular dilatation Increased wall thickness	Infiltrados Linfocitarios Necrosis Hemorragia	Graft-derived cell-free DNA	Variants associated with cellular rejection
Clinical signs Chest X-ray Laboratory alterations	Transthoracic echocardiography Magnetic resonance imaging	Biopsia endomiocárdica	dd-cfDNA	Gene expression profiling

dd-cfDNA, donor-derived cell-free DNA.

p<0.001; 12-36 months: 32.3% vs. 10.5%, p=0,006). (16)

The decline in the rejection incidence, particularly after the sixth month, markedly reduces the probability of its detection by EMB in asymptomatic patients.

It can be concluded that during early post-transplant stages, rejection remains the leading cause of hospitalization and mortality, and that the current diagnostic method is invasive, involves complications, and its diagnostic performance decreases after six months post-transplantation in asymptomatic patients, who represent the majority. These factors underscore the need for new strategies to enhance this scenario.

The methods discussed in this article focus on detecting molecular and genetic alterations, beyond the scope of the microscope.

MOLECULAR AND GENETIC DIAGNOSTIC TECHNIQUES

Donor-derived cell-free DNA (dd-cfDNA)

Under normal conditions, the continuous turnover of cells in various tissues results in the presence of circulating cell-free DNA in the bloodstream. The principle underlying the dd-cfDNA technique is the release of donor genetic material into the recipient's blood. Consequently, the detection and quantification of this material may raise alerts during the patient follow-up. It is well established that rejection induces the release of greater amounts of the donor DNA, leading to elevated levels in the recipient's blood. Donor-derived cell-free DNA is expressed as the percentage of the donor DNA relative to the total cell-free DNA in the analyzed sample. The term liquid biopsy has become widely accepted to describe this technique.

A comparative study of dd-cfDNA and EMB showed the normal value of dd-cfDNA and its correlation with the histological grade of rejection. This study also demonstrated that an increase in the dd-cfDNA percentage precedes to histological evidence of rejection. (17)

In 2018, the Donor-Derived Cell-Free DNA-Outcomes AlloMap Registry (D-OAR) research group found that dd-cfDNA had a higher negative predictive value (NPV) than EMB after 55 days post-transplantation. (18)

In an observational study, the Genomic Research Alliance for Transplantation (GRAfT) included 171 transplanted recipients monitored by EMB and dd-cfDNA. It was found that 80% of patients with dd-cfDNA levels suggestive of rejection (value >0.25%), had not been identified by EMB, and the vast majority of these patients subsequently developed clinically evident rejection during follow-up. (19,20)

The DEDUCE study demonstrated that, after the second year of follow-up, dd-cfDNA levels progressively increased and were associated with the development of graft vasculopathy, reducing the sensitive of acute rejection diagnosis. (21)

Patients with higher grade of cellular rejection exhibit a greater percentage of cell-free DNA. Antibody-mediated rejection is also associated with elevated levels of cell-free DNA as the rejection grade increases. These levels are typically higher than those observed in cellular rejection and are characterized by a distinct amino acid composition.

A consistent finding across all studies is that this technique has a high NPV, approximately 97-99%, and has led to a reduction in the number of EMB procedures. EMBs were performed only when dd-cfDNA levels were markedly elevated, to confirm rejection and categorize its severity.

In conclusion, this technique may be used after the early post-transplant stage, from the second or third month after transplantation. Its high NPV primarily facilitates the exclusion of both cellular and antibody-mediated rejection, even earlier than EMB, and is associated with a decreased frequency of routine EMB procedures. (22-26)

Gene expression profiling (GEP)

The way in which our genes are expressed determines the functional phenotype of all cells, including immune function.

The expression of certain lymphocyte genes has been associated with an increased response and a higher likelihood of cellular rejection.

The most widely used commercial tests detect the presence of 11 genes associated with rejection, establishing a risk score based on their activation profile.

Some of the genes involved include CD3E (lymphocyte activation) and NKG7 (cytotoxicity), among others. (27)

A prospective study by the International Society for Heart and Lung Transplantation (ISHLT) showed that more than 55 days post-transplantation, heart transplant recipients with a low gene expression profiling (GEP) score did not experience rejection with hemodynamic compromise, death or retransplantation. This validated the use of GEP in populations at low immune risk.

This technique has demonstrated a high NPV (around 98%), but a low positive predictive value (PPV), although not inferior to that of routine EMB procedure.

As with the dd-cfDNA technique, fewer EMB procedures were performed in patients monitored by GEP. (28)

The cut-off point at which the GEP score is considered elevated varies, depending on the baseline immune risk (e.g. sensitized patients) and time post-transplantation. It must be determined serially, since it may vary over time. (29-31)

Regarding the limitations of GEP, it does not allow determining whether damage is occurring at the time of assessment, nor is it useful for diagnosing antibody-mediated rejection, as it identifies genetic variants in the lymphocytes, which are responsible for cellular rejection. (32,33)

Fig. 2. Combined use of dd-cfDNA and genetic expression profiling

Gene expression profiling	dd-cfDNA	Interpretation
Negative	Negative	Rejection is unlikely
Positive	Negative	Other causes of immune activation
Negative	Positive	Rejection is ruled out
Positive	Positive	Rejection is highly probable

Combination of diagnostic tests

According to the evidence analyzed to date on molecular and genetic tests, each technique has been used individually, but they can be used in combination.

The ISHLT published a prospective, observational, multicenter study that included 2077 patients who underwent both tests (GEP and dd-cfDNA) between 2018 and 2021. It is important to note that this study only refers to cellular rejection.

The results were classified as follows:

- Double negative
- Positive GEP / negative dd-cfDNA
- Negative GEP / positive dd-cfDNA
- Double positive

The incidence of cellular rejection was very low in the double-negative group, 1.5%, compared to 22% in the double-positive group, with intermediate values observed in the other groups.

Using this strategy, the number of EMB procedures decreased significantly (8.8% in the double-negative group) compared to previous levels, and the 2-year survival rate was 94.9%. Only 2.7% of patients experienced graft dysfunction.

The author's interpretation of the results is shown in Figure 2. If both tests are negative, rejection is considered unlikely, whereas if both tests are positive, rejection is considered highly probable. When GEP is positive and dd-cfDNA is negative, other causes of immune activation, such as infections, should be considered. When only dd-cfDNA is positive, cellular or antibody-mediated rejection must be ruled out. (31,32)

Clinical applicability and areas of uncertainty

Is EMB the gold standard for diagnosing acute heart transplant rejection?

According to the references analyzed, it could be said that EMB is the complementary study with the greatest sensitivity and specificity during the first months post-transplantation. Beyond the disadvantages due to its invasiveness and potential complications, it can be said that after 3 months and even more after 6 months post- transplantation, EMB loses sensitivity, leaving its complications as the main concern.

Another aspect to highlight is that the assessment of the myocardium is partial, as we only examine small samples, and although the inflammation caused by rejection is systemic, it starts in patches. Therefore, in response to the first question, it can be accepted that during the first 3 months post-transplantation, EMB continues to be the gold standard. After this period, GEP and dd-cfDNA techniques have shown excellent NPV for ruling out rejection, thus reducing the need for invasive diagnostic tests.

Regarding the ability to detect rejection, dd-cfDNA technique has shown, in some registries, better sensitivity and specificity than GEP, and also the ability to detect both cellular and antibody-mediated rejection.

Gene expression profiling indicates whether there is activation of the immune system, but it does not provide information about tissue injury. Therefore, it would be a good complement to dd-cfDNA technique. Both techniques have been shown to reduce the number of biopsies per person-year during follow-up.

It is important to note that most studies included patients at low immune risk; they were not recent transplant recipients nor were they sensitized. Consequently, the incidence of rejection in these studies was very low, which means that we do not know the sensitivity and specificity in a general population of transplant recipients.

There are no studies that assess their performance beyond 5 years post-transplantation. However, this is not a clinical concern. From 6 months to 5 years post-transplantation, the analyzed studies showed good results, and rejection can be detected even earlier than with EMB.

The IMAGE study assessed, through a questionnaire, how the different diagnostic tests impacted patients' quality of life, showing markedly favorable results for the less invasive techniques.

Considering the analyzed information, a surveillance scheme can be proposed combining the different diagnostic techniques, adjusting each one to its best diagnostic profile at different stages of follow-up.

Thus, from the immediate postoperative period up to 2-3 months post-transplantation, EMB has been shown to be the best method to detect rejection, since all new trials were conducted in patients at least 55 days post-transplantation.

After this period, a scheme using the new surveillance techniques would allow for earlier detection of rejection and a reduction in the number of EMB.

This scheme has been validated only in patients at low immune risk and asymptomatic. In cases of symp-

toms or imaging suggestive of rejection, EMB should be performed.

Theoretically, GEP and dd-cfDNA determination could allow titration of immunosuppressants. Evidence is still lacking, but some ongoing studies, such as MOSAIC, are exploring this objective. (34)

Both dd-cfDNA and GEP are being used in many transplantation centers, but not yet in Argentina, where economic limitations exist.

In most of these studies, these techniques were compared with EMB as the gold standard. Conducting larger studies with clinical endpoints, such as mortality or retransplantation, is still a pending issue.

Undoubtedly, these techniques provide valuable information, but several aspects remain to be clarified:

1. Cut off point for dd-cfDNA.
2. Cut-off point for GEP.
3. Value at an earlier post-transplant stage.
4. Value in sensitized population.
5. Should a positive dd-cfDNA be treated as rejection?
6. Is it possible to adjust the immunosuppressants dosing based on the values of these techniques?
7. General access to these tests.
8. Availability of study results including clinical endpoints.

Considering the available information on heart transplant rejection, it can be said, paraphrasing Antoine de Saint-Exupéry, that "what is essential may be invisible to the microscope."

Conflicts of interest

None declared.

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

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SCIENTIFIC LETTER

Endo-Epicardial Catheter Ablation of Ventricular Tachycardia in Arrhythmogenic Right Ventricular Cardiomyopathy

Ablación endo-epicárdica de taquicardia ventricular en miocardiopatía arritmogénica del ventrículo derecho

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic, structural heart disease characterized by the progressive atrophy of the ventricular myocardium and replacement by fibro-fatty tissue. It has been widely described that ARVC typically progresses from the epicardium to the endocardium; therefore, the results of ablation via the endocardial approach are limited. Some studies involving a small number of patients suggest that a combined endo-epicardial approach yields better results. We present the case of a 38-year-old male patient with ARVC who was referred to our center due to an electrical storm and was treated using the endo-epicardial approach.

The patient was diagnosed with ARVC at age 18, when cardiac magnetic resonance imaging revealed inferolateral gadolinium enhancement in the right ventricle (RV). An implantable cardioverter-defibrillator (ICD) was implanted in 2014 for secondary prevention of sudden death. He was referred to our department due to multiple episodes of ventricular tachycardia (VT) with appropriate ICD shocks (3 episodes within the last 24 hours). Doppler echocardiography showed RV dilatation with preserved systolic function; the RV diameter was 45 mm in the 4-chamber view. Tricuspid annulus plane systolic excursion (TAPSE) was 24 mm and peak systolic velocity at the lateral tricuspid annulus by pulsed wave tissue Doppler imaging (S-wave TDI) was 0.08 m/s. Right ventricular fractional shortening was 38%. We decided to perform endo-epicardial catheter ablation.

Under general anesthesia, programmed ventricular stimulation was performed from the RV apex (S1S1-S2: 600-320 ms) inducing sustained VT with complete left bundle branch block morphology, inferior axis and R wave transition in V4, and absence of hemodynamic instability. The procedure continued with activation mapping during VT and scar mapping of the RV outflow tract, with the area of the greatest interest in the anterior region of the RV (precocity of 25 ms), topo-stimulation: 94%. The next step was the epicardial approach.

The procedure began with the instillation of lidocaine, followed by the needle-in-needle technique to access the pericardium. A 18G external needle was inserted below the xiphoid process. After inserting the 18 needle, a 21 micropuncture needle was introduced and advanced until the heartbeat was felt, indicating entry into the pericardial space. Radio-opaque contrast was injected to confirm optimal positioning. Then, a 0.018-inch guidewire was advanced through the micropuncture needle. After verifying the correct positioning of the needle within the pericardial sac, the needle was removed. A flexible introducer was advanced and the 0.018-inch guidewire was exchanged for a 0.032-inch guidewire. A standard 8F introducer was advanced over this guidewire.

The Pentaray mapping catheter and the contact force sensing ablation catheter were advanced through the 8 Fr introducer. A non-fluoroscopic-based three-dimensional navigation system was used for epicardial anatomical reconstruction and to create an activation map of VT with evidence of its entire circuit and of mesodiastolic potentials in the anterior region of the RV. This resulted in the cessation of VT.

Voltage map and isochronal late activation mapping (ILAM) with deceleration zones were created during sinus rhythm. There was evidence of greater scar extension in this area, as well as late potentials in

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Fig. 1. A. Endocardial right ventricular (RV) activation mapping. **B.** Ventricular tachycardia. **C.** Voltage map. **D.** Epicardial approach with guidewire placed in the pericardium, ablation catheter in the right ventricular outflow tract (RVOT) and intracardiac ultrasound probe in the right atrium. **E.** ECG showing sinus rhythm with inverted T-waves in the right precordial leads. **F.** Catheter in the pericardium for mapping points in high-density mapping, ablation catheter in the RVOT, ultrasound probe. **G.** Applications of radiofrequency energy from the endocardial surface of the RV.

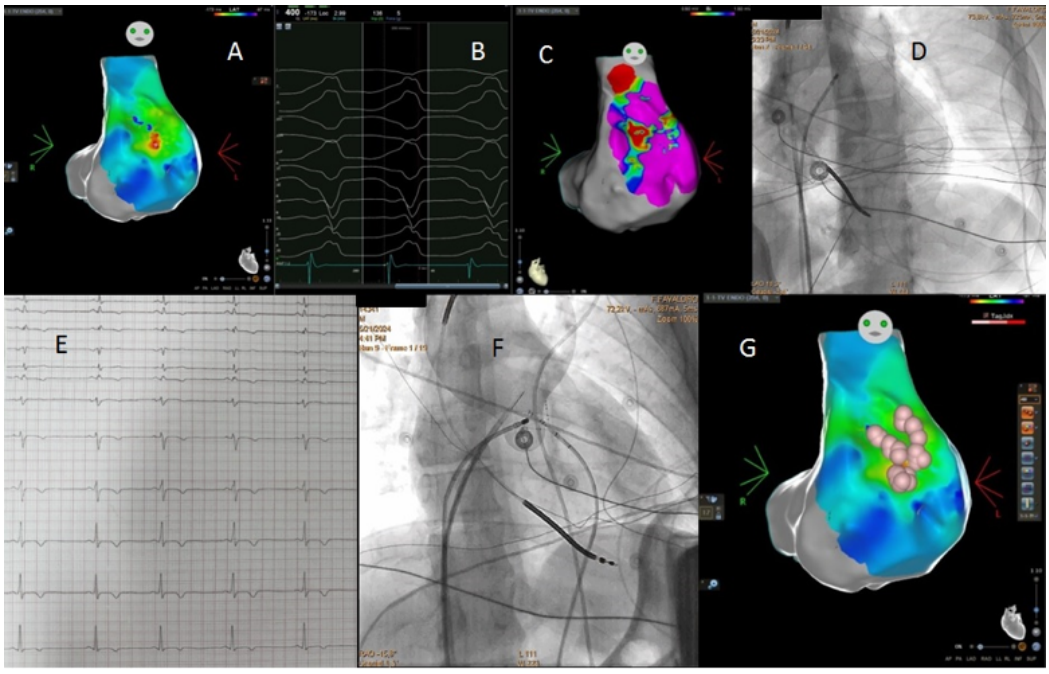
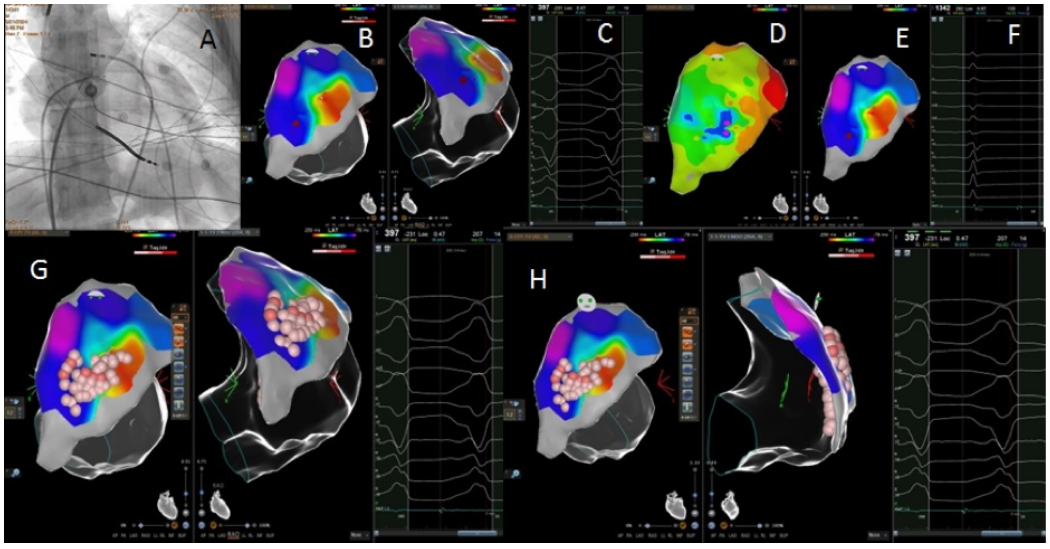


Fig. 2. A. Fluoroscopy showing contact force sensing catheter in the pericardium. **B.** Activation map from the pericardium. **C.** Ventricular tachycardia. **D** and **E.** Isochronal late activation mapping (ILAM) with deceleration zones in coincidence with the activation map during tachycardia. **F.** Sinus rhythm with late potentials. **G.** Applications of radiofrequency (RF) energy from the epicardium. **H.** G. Applications of RF energy from the endocardium and epicardium.



the anterior region of the RV, in coincidence with the activation map. Topo-stimulation was performed with 98% agreement in the same area. A total of 35 applications of radiofrequency energy (25 W) were delivered using an external contact force sensing catheter with an irrigated tip until the diastolic potentials disap-

peared during sinus rhythm. Endocardial applications were complemented from the anterior region of the RV (35 W). At the end of the procedure, programmed ventricular stimulation was performed (S1-S1-S2: 500-280-280 ms) up to the ventricular refractory period, without inducing VT. A pericardial drain was left in place for 48 hours, and no complications developed. After a 10-month follow-up period, the patient remained free of arrhythmias.

The patient's progress indicates that voltage and deceleration maps in sinus rhythm are a useful tool that correlates with the activation map during tachycardia, and that VT ablation with a first-line endo-epicardial approach provides promising results in patients with ARVC.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

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SCIENTIFIC LETTER

Acute Pericarditis Associated with Graves-Basedow Disease: A Case Report

Pericarditis aguda asociada a enfermedad de Graves-Basedow: a propósito de un caso

AINHOA ECHENIQUE CLERIGUÉ[1], UXUE MILLET OYARZABAL[1], ALAÍN GARCÍA OLEA[1], JAVIER GREGORIO REKONDO OLAETXEA[1]

Acute pericarditis is a frequent reason for consultation in clinical practice and the viral etiology is the most common in our setting. Among non-infectious causes, autoimmune and inflammatory diseases stand out, accounting for 5-15% of cases of acute or recurrent pericarditis. (1) Regarding endocrine-metabolic etiologies, the relationship between pericardial disease and hypothyroidism is well known, (2) but its possible association with hyperthyroidism has only been described in isolated cases such as the present one. (3)

The patient is a 72-year-old woman with hypertension and colon adenocarcinoma in remission since 2009 as the only relevant medical history, who presented to the emergency department with progressive exertional dyspnea, orthopnea, and lower extremity edema of three- week evolution. She also reported weight loss, nervousness, and tremors for the past four months, coinciding with a period of increased stress. Physical examination revealed absent vesicular murmur in the lung bases and pretibial pitting edema. On arrival, laboratory tests showed B-type natriuretic propeptide (NT-proBNP) value of 9452 pg/mL as the only finding of interest. An electrocardiogram (ECG) presented sinus rhythm with negative T waves in the right precordial leads and no other abnormalities. The transthoracic echocardiogram exhibited preserved biventricular function with moderate mitral and tricuspid regurgitation, and minimal pericardial effusion (Figure 1A). During her stay in the emergency department, she presented with palpitations, and de novo atrial fibrillation at 120 bpm, so frequency control treatment (bisoprolol 2.5 mg/24 h) and anticoagulation were initiated (Figure 1B).

After the first few days of admission, she showed good improvement in congestive signs, with resolution of symptoms and spontaneous return to sinus rhythm. An endocrinology evaluation was requested due to TSH <0.01 mU/L, for a normal value (NV) of 0.27 - 4.2 mU/L, with elevated free thiroxine and thyroid peroxidase antibodies of 5.44 ng/dL (NV 0.8 - 1.8 ng/dL) and 513 IU/ml (NV <34 IU/ml), respectively.

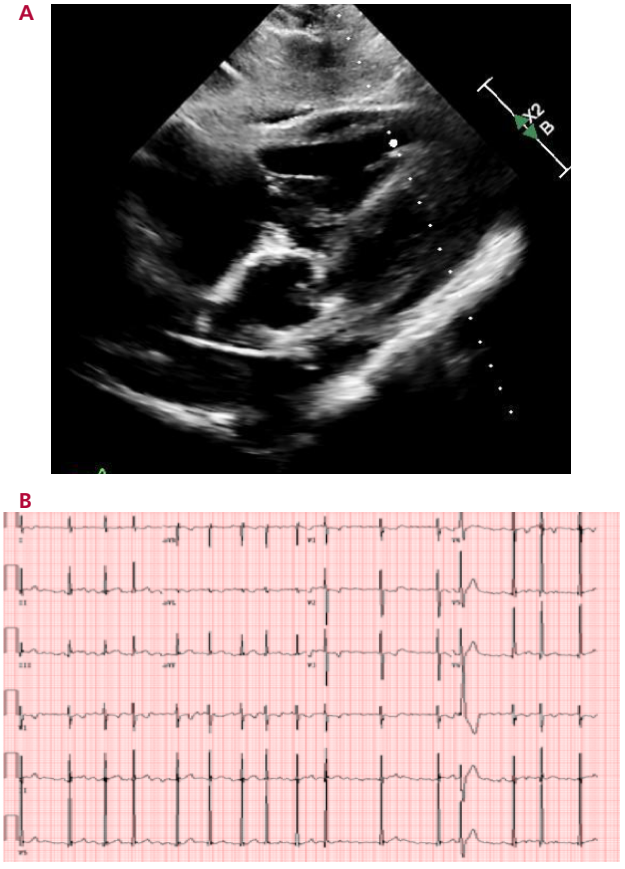

Fig. 1. A. Echocardiogram with minimal pericardial effusion. **B.** ECG showing atrial fibrillation with controlled ventricular response.

Further testing with thyroid-stimulating immunoglobulin antibodies, which revealed elevated levels (31.7 IU/L for a NV<1.75 IU/L), as well as scintigraphy (Figure 2A) and thyroid ultrasound, showed findings consistent with Graves-Basedow disease. The condition was interpreted as the first decompensation of heart failure in the context of hyperthyroidism, and

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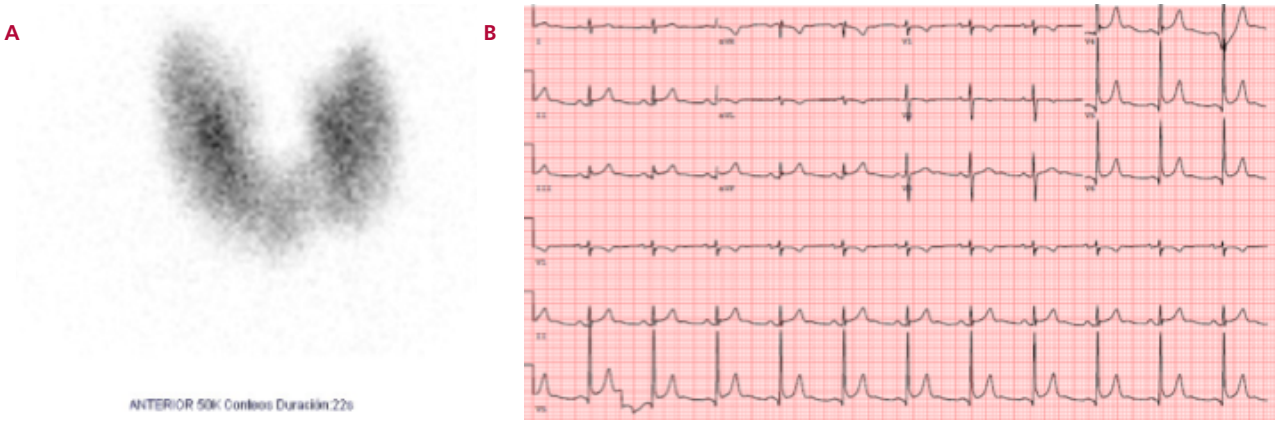

Fig. 1. A. Thyroid scintigraphy showing a thyroid gland of normal morphology, diffusely enlarged, with increased uptake and homogeneous distribution of the radiotracer, consistent with diffuse hyperfunctioning goiter. **B.** ECG in sinus rhythm at 70 bpm. Note the diffuse PR segment depression with inferolateral ST-segment elevation with a concave morphology, not present on previous ECGs.

treatment was started with oral methimazole, 10 mg every 8 hours.

Seventy-two hours after starting antithyroid treatment, the patient presented a fever peak of 38°C and chest pain consistent with pericarditis, with pericardial friction on auscultation and ECG (Figure 2B) compatible with acute pericarditis, and no pericardial effusion on a new echocardiogram. Anti-inflammatory treatment was started with ibuprofen 600 mg every 8 hours and colchicine 0.5 mg daily, with rapid resolution of symptoms. In serial blood tests, inflammatory markers remained low: C-reactive protein 4 mg/L, negative PCT with normal leukocytes and negative cultures.

The patient was discharged in a state of euvolemia, with diuretic, antithyroid, and anti-inflammatory treatment initiated during hospitalization.

Graves' disease is an autoimmune thyroid disorder and the leading cause of hyperthyroidism. Its most common cardiovascular manifestations are atrial fibrillation, tachycardia, and heart failure. (1) Its relationship with acute pericarditis has been previously published by multiple authors, with cases progressing to cardiac tamponade (2) or recurrent pericarditis. (3). Although the underlying pathophysiology is unknown, some authors have proposed as a mechanism the interaction of autoantibodies with pericardial receptors, similar to what occurs in cases of ophthalmopathy and dermopathy associated with this disease. (4) Other hypotheses are based on the relationship between both entities and viral infections such as the Epstein-Barr virus, or the direct toxicity of thyrotoxicosis on the fat metabolism of the pericardium. (2) Finally, published cases of acute pericarditis after initiation of antithyroid treatment could suggest a possible direct relationship with these drugs. In our case, the temporal relationship of only 72 hours after the initiation of antithyroid treatment does not seem to point to a direct association, given that in previously published cases, the onset of symptoms is significantly later, occurring from two weeks (4) to several years later. (5)

Acute pericarditis is a common condition and is usually harmless, although in some cases it can lead to high morbidity and mortality in the absence of treatment. Graves-Basedow disease is one of the few conditions associated with pericarditis that could benefit from targeted treatment. Although the causality between the two has not yet been established, it is important to recall their association for the proper management of patients with symptoms compatible with both conditions.

Conflicts of interest

None declared.

(See conflicts of interest forms on the website).

Ethical considerations

Not applicable

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The importance of understanding the reality of heart failure in our community

La importancia de conocer la realidad de la insuficiencia cardíaca en nuestro medio

CRISTHIAN EMMANUEL SCATULARO[1, MTSAC,]

Heart failure (HF) is a clinical syndrome caused by structural and/or functional impairment of the heart, characterized by objective evidence of congestion or insufficient tissue perfusion, associated with elevated natriuretic peptides (1-3). It has an increasing incidence and prevalence, related to increased life expectancy and the expansion of cardiovascular risk factors in the global population, generating high direct and indirect costs in health systems as a result of progressive hospitalizations due to decompensation of the disease. (1-3)

In this regard, it is essential to describe the main clinical, demographic, and socioeconomic characteristics of patients with HF, the available diagnostic tools, and the treatments used, in order to improve the management of this condition in our daily practice. Knowing our patients with HF is imperative from a healthcare perspective.

The registry SEPE-HF (*Santa Cruz epidemiology and research on heart failure*) has attempted to describe epidemiological aspects and the medical management of patients hospitalized for HF in different hospitals in the city of Santa Cruz de la Sierra (Bolivia), one of the most important cities in the country and therefore with a large volume of patients under follow-up. (4)

Firstly, it should be noted that most of the characteristics described in relation to risk factors, clinical management, and mortality are similar to other registries in the region, highlighting the increasing prevalence of HF with preserved ejection fraction and the high burden of diabetes mellitus and atrial fibrillation. (5)

In this cohort, Chagas cardiomyopathy is one of the main etiologies in patients with HF over 50 years of age, surpassing ischemic and valvular causes. This is clearly related to its geographical distribution, the chronicity of the disease, and the high rate of infestation in the population in previous years. These patients are frequently hospitalized for congestion or arrhythmic complications and have a poorer prognosis, highlighting the need for studies to evaluate the behavior of HF in patients with Chagas disease. (3)

It should also be noted that echocardiograms were performed on only 75% of hospitalized patients, which could be related to the unavailability of this resource in some centers. We must therefore continue to deepen our understanding of the difficulties faced by health systems in our region and how to create possible solutions.

With regard to the therapeutic approach, this registry highlights the opportunity that hospitalizations represent to optimize the entire spectrum of outpatient treatment, including specific drugs for HF, hygienic-dietary measures, and vaccination, in order to prevent further decompensations. (1-3)

Heart failure registries, such as ARGEN-IC and SEPE-HF, are a real stimulus for new population studies to understand how this disease behaves in our region. (4,5)

Ethical considerations

Not applicable.

Conflicts of interest

None declared.

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

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AUTHORS' REPLY

Dear Scatularo, Cristhian Emmanuel

We appreciate your interest in our work recently published in the journal of the Argentine Society of Cardiology. Your valuable comments on the clinical characterization of heart failure in our SEPE-HF registry representing the city of Santa Cruz de la Sierra, Bolivia, are greatly appreciated. The detailed description of epidemiological aspects, limitations in diagnostic access, and therapeutic opportunities provides a clear perspective on the challenges in managing HF in resource-limited settings. In this context, we are conducting a subanalysis of the SEPE-HF registry, which complements the study's overview by identifying associations between etiologies, comorbidities, and precipitating factors of decompensation. This detailed analysis allows us to identify mixed clinical patterns that could correspond to specific HF phenotypes with different prognostic and therapeutic implications. This approach favors the development of more personalized and effective strategies based on the local epidemiological reality.

It undoubtedly enriches the scientific discussion and encourages us to continue generating local evidence on HF.

Sincerely,

Roberto Cristódulo
On behalf of the authors
Interventional Cardiologist National Health Fund, Obrero No. 3, Santa Cruz, Bolivia.
dr.robertocristodulo@gmail.com

Extreme Adaptation of the Cardiovascular System: A Look from Antarctica

Adaptación extrema del sistema cardiovascular: una mirada desde la Antártida

BRUNELLA BERTAZZO[1]

The extreme living conditions in Antarctica represent a unique natural setting for studying human physiology. Recent work by Puigdomenech et al., carried out at the Belgrano II Antarctic Base, analyzes how prolonged confinement, photoperiod alteration, and extreme isolation affect cardiovascular function in a group of healthy military personnel over a 12-month period. (1)

The study shows a significant decrease in heart rate and blood pressure, both at rest and during exercise, accompanied by an increase in heart rate variability. This pattern, consistent with a predominance of vagal tone, suggests a positive neurovegetative adaptation, with no differences between the months of continuous light and darkness. The absence of atmospheric pollution may have favored this behavior.

These findings are consistent with previous studies conducted in similar contexts. Arendt et al. described how changes in light exposure at Antarctic bases affect circadian rhythms and autonomic functioning. (2) Mairesse et al. after a prolonged stay in Antarctica, also observed neurobehavioral and sleep adaptations reflecting a favorable physiological reorganization. (3)

Garrett-Bakelman et al., as part of the NASA Twins Study, reported a decrease in heart rate and blood pressure during prolonged space flights, findings that reinforce the analogy between Antarctic conditions and space missions. (4)

In addition, Rajagopalan et al. highlighted the direct link between exposure to environmental pollution and cardiovascular dysfunction, emphasizing the importance of the environment in regulating autonomic tone. (5) In this sense, Antarctica's clean air is positioned as a relevant modulating factor.

The article by Puigdomenech et al. not only provides original data, but also invites us to consider Antarctica as a valuable experimental model for research in extreme and space medicine. The implications of

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these results range from occupational medicine in remote conditions to the preparation of extra-planetary missions. Understanding how the cardiovascular system adapts in these contexts is key to addressing new challenges in science and global health.

Ethical considerations
Not applicable.

Conflicts of interest
None declared.

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

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AUTHORS' REPLY

Dear Dr. Brunella Bertazzo

We would like to thank you for your opinion about our work.

We agree with your opinions and the comparisons with other experiences in extreme living conditions.

We observed an increase in autonomic nervous system activity over cardiac function, which suggests an increased neurovegetative pattern, predominantly vagal.

This hibernation state resembles that of another mammal, the bear. In the boreal winter, it initiates a state of lethargy that allows it to conserve energy and survive the scarcity of food and the low temperatures typical of this season. Hibernation is not a constant deep sleep, but rather a significant reduction in metabolism, heart rate and body temperature.

Physiologically, its heart rate drops from 40-50 to about 10 beats per minute, respiratory rate drops by half, and temperature is reduced by 4 to 5 degrees Celsius.

Future research will provide us with additional information on biochemical parameters (acetylcholine, melatonin, cortisol, noradrenaline, etc.) that will explain more clearly the mechanisms involved in this physiological adaptability to these extreme conditions.

Ricardo Iglesias

Beyond the Image: In Memory and Legacy of Dr. Roberto Lang

Más allá de la imagen, memoria y legado del Dr. Roberto Lang

On June 10, 2025, Dr. Roberto Lang—an internationally renowned leader in the field of echocardiography—passed away after a short illness. His accomplishments and contributions have left a lasting mark on cardiac care worldwide. His death is an irreparable loss for his family, his numerous friends he made over the course of his 73 years, and the entire cardiology community, which regards him as a true master. He was always willing to support those in need, and his absence is deeply felt by all of us who had the privilege of knowing and respecting him.

Dr. Roberto Lang's contributions to science are immeasurable. He served as Director of the Noninvasive Cardiac Imaging Laboratories and as Professor of Medicine and Radiology at the University of Chicago. Throughout his extensive career, he published over 720 articles on cardiac imaging and physiology, authored more than 120 book chapters, and edited 12 books. He was also on the editorial boards of the world's leading cardiology journals.

Many of us shared unforgettable moments with him: we fondly recall his participation in Miguel Ángel García Fernández's congresses, particularly the *Echo Wars*, where he brought humor and fearlessness by donning the most unexpected costumes.

I must also mention the intimate interview during Martín Lombardero's course at La Rosa Negra in 2017, where he shared tales from his student days at the University of Buenos Aires and his sudden departure to Israel in 1977.

As president of the American Society of Echocardiography (ASE) in 2010, he played a key role in having Buenos Aires selected as the inaugural host city of the World Summit of Societies—an event that was a resounding success in 2011.

Over the last eight years, together with Dr. Salvador Spina, we had the opportunity to share with him the examination boards of the National Board of Echocardiography (NBE) and the Sociedad Interamericana de Imágenes Cardiovasculares (SISIAC). He will be greatly missed.

He did not like to be called Bobby, Robbie, or Robert—he was Roberto, an Argentinian at heart, with a four-dimensional soul. He often ended his lectures in Latin America with a resounding "¡Viva Argentina!" (a phrase that reflected his deep love for his country).

Roberto Lang was a one-of-a-kind innovator and a trailblazer in the field of ultrasound. He introduced real-time 3D transesophageal echocardiography, a technique that delivers exceptionally high-quality images. In 2006, he conducted the world's first study using this technique, which revolutionized the evaluation of cardiac structures. His ongoing research in this field has changed the approach to echocardiography forever.

He was a visionary ahead of his time: his presentations on holographic imaging, virtual reality, and artificial intelligence not only predicted the future, but also helped to shape it.

Recognized around the world for his deep commitment to education, he participated in every course, congress, roundtable, symposium, and workshop to which he was invited. He never missed a single event—except for the births of his two grandchildren.

He lived in the same city, Chicago, for 40 years, where—together with his wife Lily, whom he met in Buenos Aires—he raised their children: Dr. Gabriel Lang, a gastroenterologist, and Daniella Lang, a psychologist.

He was not only an exceptional scientist but was even more remarkable for his humanity. He always found time to share his knowledge and passion for imaging in a way that showed a generosity rarely seen among great scientists.

In the professional realm, he left an immense legacy in the field of echocardiography. But on a personal

level, his impact was even greater. He was a man who inspired, loved, and guided his family, made others laugh and remained humble despite being recognized as one of the greatest figures in contemporary cardiology.

He was an exceptional person. Those of us who had the privilege of spending time with Roberto will miss his kindness, brilliant intellect, generosity, deep respect for others and humanistic view of medicine, which was never overshadowed by the advanced technology he mastered.

Throughout his life, he witnessed and participated in the entire evolution of echocardiography, from the early days of M-mode to automated 4D imaging, virtual reality, and the application of artificial intelligence to ultrasound. He was a passionate about the most sophisticated advancements in new technologies and AI in daily medical practice.

He often said that nothing would be the same after artificial intelligence arrived in medicine, and that future generations of students would require a completely different kind of education. He predicted that those who failed to adopt AI in the coming years would be considered dinosaurs. Nevertheless, he never ceased to raise the ethical and moral issues surrounding its misuse.

We will remember him as a beacon that lit the way for everyone who came into contact with him. His absence leaves an enormous void; we have lost a brilliant scientist, a friend, a brother and an extraordinary human being, someone who was truly set apart from the rest.

Dear Roberto, may your smile continue to light our path, since we owe the best in us to you.

Roberto Lang has become a legend, and I am convinced that his legacy will live on forever in the thousands of hearts he touched.

Jorge Lowenstein[MTSAC]

SAC and its Commitment to Medical Residencies and Continuing Education

La SAC y su compromiso con las residencias médicas y la formación continua

The founders of the Argentine Society of Cardiology (SAC), who came from renowned national universities (such as those of Buenos Aires, Córdoba, and Rosario) as well as from prestigious public hospitals, had a strong commitment with the quality of medical education and clinical research. The intellectual heritage of the SAC is closely linked to Bernardo Houssay and is evident in its founders and presidents, including Braun Menéndez, Oscar Orias, and Alberto Taquini. These leaders demonstrated that the essence of our institution lies in education and research. (1,2)

As part of this founding commitment, the Teaching Department, which is now part of the Institute of Continuing Education, is proud to offer a biannual course generated from SAC´s headquarters and a three-year course in the district of Córdoba. Between both, they have provided theoretical training to more than 550 residents throughout the country for over 30 years.

Doctors Trongé and Iglesias led the first medical education consensus in cardiology published in the Argentine Journal of Cardiology, where they established the objectives and procedures for training cardiology residents. (3)

From 2012 to 2015, the SAC developed the Medical Residencies Manual, a painstaking effort involving several members of our society, including Hugo Grancelli, Amanda Galli, Héctor Roiter, Alberto Alves de Lima, Jorge Thierer, and Ricardo Migliore, among others. This document served as the basis for the publication of the Reference Framework for Medical Residencies Training: Cardiology Specialty, published by the National Ministry of Health in 2015, which accurately describes the objectives of a residency and the competency profile for the training of medical human resources in cardiology. (4)

In light of the recent conflict with medical residents in national hospitals, the SAC addressed the medical community through the Medical Societies Forum, which represents a broad spectrum of specialties in adults. We communicated our position on the conflict, which we consider a symptom of the serious situation of the health system, which has suffered progressive deterioration over time. It is imperative to discuss how the residency system is financed, including the teaching structure and the time devoted to teaching and research. This irreplaceable training system must be reevaluated, encouraging it as a path to medical specialties and ensuring the necessary tools for its sustainability and that of residents in their life projects.

For the SAC and the Medical Societies Forum, residency is, above all, an intensive learning stage that must be carried out under adequate supervision, with opportunities for reflection, training, and teaching support. Although healthcare is part of the training process, it cannot displace the main goal of the residency: the comprehensive training of resident physicians and, above all, the patient´s safety.

Several public and private institutions, together with their medical professionals, are making a significant effort to sustain residency programs in order to ensure quality training. These programs, in addition to benefiting professional training, produce committed and well-trained specialists, adding value to the community.

The discussion in recent weeks about medical residencies should not be limited to the form of a salary or scholarship payment; it should include a reconsideration of the health system that values this training tool not only for its technical quality, but also as a means of transmitting values and academic rigor. It should consider the economic sustainability of the institutions that offer training systems, as well as the encouragement and recognition of teachers and mentors.

In light of the current worrying situation, characterized by a lack of coverage of vacancies in various specialties and an increase in dropouts during residencies, we must not lose sight of our priorities.

In this regard, the SAC is focused on the promotion of the "University Institute". Together with Drs. Héctor Deschle, Ricardo Iglesias, Marcelo Trivi, Alejandro Hita, Marisa Pagés, and others, and with the expert support of Amanda Galli, our objective is to develop a general profile of the physician, and based on this premise, to establish objectives for the design of a training system and the topics to be covered.

General Profile of the Physician We Need

"To accomplish the role of transformative leadership in health realities and of representative agent of

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individuals and social groups before the health care system, in order to become defenders of the HEALTH CARE SYSTEM."

The cardiologist must accomplish the following:

1. Medical Knowledge
   Sound scientific and technical training in the corresponding field of health sciences, supported by knowledge and understanding of basic sciences and relevant social sciences. The candidate will possess the skills to recognize situations and problems that affect the health of individuals and social groups, promoting the preservation, maintenance, and development of these individuals, community groups, and general society health.
2. Communication
   Development of broad communication and management skills to implement changes in the health system, and interact in multi-professional teams to provide comprehensive health care to both individuals and the community. The cardiologist must also be able to work cooperatively in interdisciplinary teams and perform effectively anywhere in the country, possessing the necessary knowledge to plan and evaluate health services and resources.
3. Management
   Optimization in the use of new technologies, taking into account ethical and financial issues, and, especially, the patient´s benefit.
4. Health Promotion
   Promotion training in healthy lifestyles through communication skills to guide individuals and groups in their health protection, and improve the quality of care by responding to all the patient´s health needs through promotion, protection, and recovery services. Acknowledge the health needs of each individual and the community, achieving a balance between the patient´s expectations and those of society at large, both in the short and long term.
5. Research
   Adequate training to contribute to research and knowledge management related to health, to share and disseminate this knowledge, as well as to recognize its limitations and the need for ongoing updating of skills inherent to their professional practice.
6. Professionalism and Ethics
   Have a broad humanistic education and a clear vision of responsibility and social justice, as well as ethical and deontological training to possess a clear awareness that the honor and dignity of the profession constitute a paradigm of high performance and prestige in society. The cardiologist must strengthen behavioral sciences knowledge to establish an appropriate doctor-patient relationship, understanding the psychological, social, and cultural dimensions of health and disease processes, and practice the profession respecting professional ethics in the context of different delivery modalities (public, private, social security).
7. Primary care training strengthening.
   Strong primary care can contribute to strengthening the overall performance of the health system by providing affordable and accessible care; coordinating patient care so that they receive the most appropriate services in the appropriate setting; reducing avoidable hospital admissions.

Cardiologists who promote the SAC must be competent professionals in the care of patients with cardiovascular conditions, respecting the cultural, humanistic, and ethical values of patients and their families, and acting within the framework of medical ethics.

The SAC's commitment to its mission of improving the country´s cardiovascular health and its vision of being a leader in cardiovascular health training and information in our country and the region are the reasons for our existence and what we have been working for as a team on a strategic plan in line with the times we live in.

In memory of Dr. Houssay, I leave you with one of his quotes: "Science is not expensive; ignorance is expensive."

Pablo Stutzbach MTSAC,
President of the Argentine Society of Cardiology

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