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- Evolocumab in high-risk cardiovascular disease affected by primary hypercholesterolemia and mixed dyslipidemia
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Editorial

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Cacao phytochemicals in the prevention of death from cardiovascular disease: commentary on the COSMOS study

Fitoquímicos del cacao en la prevención de muerte por enfermedad cardiovascular: comentario sobre el estudio COSMOS

Nayelli Nájera*

Cacao is a native fruit of America whose seed is the raw material to produce chocolate. Traditionally, pre-Hispanic cultures such as the Olmecs and Mayans cultivated this plant for various purposes. The value that these cultures gave to cacao is reflected in the fact that the drink prepared with the seeds was exclusive to the aristocracy and used in rituals of warriors and priests; in addition, the seeds were used as a form of currency.

More recently, scientific studies have shown the nutritional content of cacao to be high in fiber and proteins and in molecules such as theobromine and caffeine, which give it a slight stimulating effect.

In addition, phytochemicals have been isolated and characterized in the cocoa fruit, such as (-)-epicatechin (EC), a flavanol, which has been the subject of multiple investigations for its beneficial effects in recent years on cardiovascular health. Mexican scientists have been working for years to describe and characterize the molecular mechanisms by which EC exerts its effects, identifying trans-membrane receptors that are selectively activated and trigger specific cellular responses. Multiple in silico (computational systems), *in vitro* (test tube and cell cultures), and preclinical studies have shown EC's effects on modulating mitochondrial function, decreasing oxidative stress, and promoting mitochondrial biogenesis, demonstrating the reduction of myocardial damage induced by ischemia/reperfusion by obstructing the coronary arteries in animals.[1]

As a consequence of all the basic knowledge generated, small-scale clinical studies have been developed to contribute to the improvement of human health, mainly focused on chronic diseases of pandemic magnitude, among which are obesity, type 2 diabetes mellitus, and cardiovascular disease diseases (CVD). These clinical studies have verified the laboratory findings that the EC of cocoa is a molecule with potential pharmacological use for the primary and secondary prevention of CVD. With this arises the need to carry out large-scale studies with hundreds or thousands of patients.[2] However, the negligible economic support for science in Mexico makes it difficult to advance clinical studies for the development of new drugs. Fortunately for science, the sum of efforts among scientists worldwide allows multicenter and multidisciplinary studies to be carried out.

Recently, the COSMOS study: COcoa Supplement and Multivitamin Outcomes Study (COSMOS) was published in the American Journal of Clinical Nutrition (2022) with the results of a randomized, double-blind study, controlled with placebo that included 21,442 participants older than 60 years. The intervention consisted of the consumption of cocoa extract containing 80 mg of (-)-epicatechin/day with a mean follow-up of 3.6 years. The results showed a decrease

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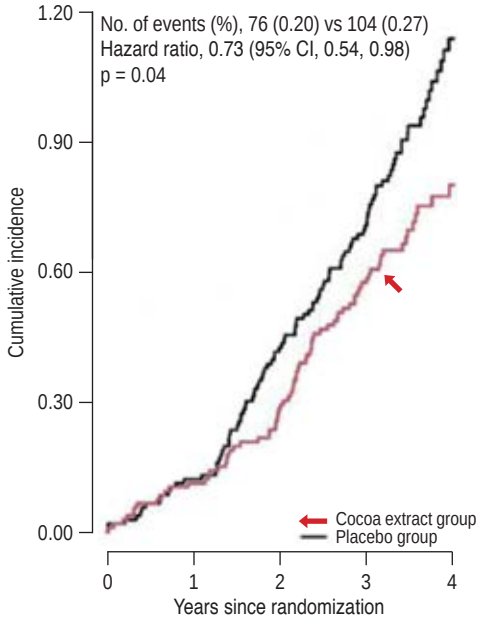
in CVD death (HR: 0.73; 95% CI: 0.54, 0.98) *(Figure 1)* and major cardiovascular events (HR: 0.84; 95% CI 0.71, 0.99).[3]

This means that supplementation with cocoa extracts rich in EC in older adults significantly reduces death from CVD by up to 27%. The significant reduction in death from CVD in the general population represents a phenomenon of great relevance, without precedent, since it is the supplementation with phytochemicals.

The systematic use of this type of supplementation would reduce CVD mortality and the economic impact that this pathology generates.

Finally, other benefits of cocoa phytochemical supplementation are that no adverse effects were found (only 6% reported nausea; HR: 1.06; 95% CI: 1.02, 1.11) and there was also a 5% decrease in symptoms associated with flu (both HRs: 0.95; 95% CI: 0.91, 0.99) and 15% reported a reduction in migraine (HR: 0.85; 95% CI: 0.78, 0.93).



Number at risk

Cocoa extract	10,719	10,569	10,408	9,846	3,462
Placebo	10,723	10,596	10,433	9,872	3,465

Modified from: Sesso HD et al.[3]

Figure 1: Cumulative incidence of death from cardiovascular disease according to the year of follow-up in the group treated with cocoa (arrow) and the placebo group.

This is how a randomized, double-blind, placebo-controlled clinical study with thousands of patients confirms the knowledge reported by basic studies.

It would suffice to say, to conclude, that this is a clear example of the urgent need for both the State and the pharmaceutical industry to invest financial resources into the development of these types of studies. The transferring of the knowledge generated in research laboratories, developed in silico, *in vivo*, or in animals, towards its application in humans will improve, of course, the health of Mexican patients, immersed, as we know, in a tangled skein of multiple risk factors that impact cardiovascular health such as sedentary lifestyle, obesity, diets rich in carbohydrates and fats, diabetes, etcetera.

In conclusion, current therapies based on statins reduce the risk of death from CVD by up to 24%.[4] The results of the COSMOS study report a 27% reduction in mortality from CVD with the use of cocoa phytochemicals; therefore, the combined use of both therapies would synergistically favor the prognosis of patients in primary and secondary prevention.

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Original Research

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Economic evaluation of evolocumab in uncontrolled patients with high-risk cardiovascular disease affected by primary hypercholesterolemia and mixed dyslipidemia

Evaluación económica de evolocumab en pacientes con enfermedad cardiovascular de alto riesgo con hipercolesterolemia primaria y dislipidemia mixta no controlados

Fernando Carlos-Rivera,* Jorge Antonio Guzmán-Caniupan,‡ Adolfo Gabriel Hernández-Garduño,§ Mónica Alva-Esqueda,¶ Luis Miguel Camacho-Cordero,‖ Therese Aubry-de Maraumont**

Keywords:
Economic evaluation, cost-effectiveness, economic impact, evolocumab, cardiovascular disease, hypercholesterolemia.

Palabras clave:
Evaluación económica, costo-efectividad, impacto económico, evolocumab, enfermedad cardiovascular, hipercolesterolemia.

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ABSTRACT

Introduction: Cardiovascular diseases (CVDs) are the leading cause of death worldwide, imposing an enormous clinical and financial burden on healthcare systems. An elevated level of low-density lipoprotein cholesterol (LDL-C) constitutes one of the most important modifiable risk factors for CVDs. **Objectives:** To assess the economic and health outcomes of evolocumab (EVO) added to standard of care (SoC, high-intensity statin with/without ezetimibe) in uncontrolled high-risk adult patients with primary hypercholesterolemia and mixed dyslipidemia (PHMD) in the Mexican Institute of Social Security. **Material and methods:** Using a lifetime Markov model comprising seven health states with annual cycles, we compared the direct medical costs (acquisition of lipid-lowering therapies besides the costs associated with each health state and costs for a transitory event called revascularization), and life-years (LY) expected with EVO+SoC vs SoC alone. The target population was categorized into two groups: PHMD with a history of either myocardial infarction or ischemic stroke and heterozygous familial hypercholesterolemia (HeFH). Both future costs and LY were discounted at a 5% annual rate. **Results:** EVO+SoC had a higher acquisition cost than SoC but was also more effective. The cost per LY additionally gained by using EVO was modeled as $348,629 (MXN) in the first subpopulation and $298,148 (MXN) in patients with HeFH. The model remained robust to plausible changes in the parameters. The probability of EVO+SoC being cost-effective under a willingness to pay threshold of 3 times the gross domestic product per capita estimated for 2020 in Mexico was close to 100% in both subpopulations. **Conclusions:** EVO+SoC may provide a cost-effective intervention.

RESUMEN

Introducción: *Las enfermedades cardiovasculares (ECVs) son la principal causa de mortalidad mundial, imponiendo una enorme carga clínica/financiera a los sistemas de salud. Un nivel elevado de colesterol de lipoproteínas de baja densidad (C-LDL) constituye uno de los factores de riesgo modificables más importantes para ECVs.* ***Objetivos:*** *Evaluar desenlaces económicos y de salud de evolocumab (EVO) agregado al estándar de atención (SoC, estatina de alta intensidad con/sin ezetimiba) en adultos de alto riesgo no controlados, con hipercolesterolemia primaria y dislipidemia mixta (HPDM) en el Instituto Mexicano del Seguro Social.* ***Material y métodos:*** *Usando un modelo Markov de siete estados de salud, de por vida con ciclos anuales, comparamos costos directos (adquisición de terapias hipolipemiantes, costos según estados de salud y del evento transitorio «revascularización») y años de vida (AV) esperados con EVO+SoC vs SoC. La población objetivo se dividió en dos grupos: HPDM con antecedentes de infarto de miocardio o accidente cerebrovascular isquémico; hipercolesterolemia familiar heterocigótica (HFHe). Costos y AV futuros se descontaron 5% anualmente.* ***Resultados:*** *EVO+SoC fue más costoso y más efectivo que SoC. El costo por AV ganado por el uso de EVO fue $348,629 (MXN) en la primera subpoblación y $298,148 (MXN) en pacientes con HFHe. El modelo se mantuvo robusto ante cambios plausibles en los parámetros. La probabilidad de que EVO+SoC sea costo-efectivo para un umbral de aceptabilidad igual a tres veces el producto interno bruto per cápita estimado para 2020 en México fue cercana a 100% en ambas subpoblaciones.* ***Conclusiones:*** *EVO+SoC puede proveer una intervención costo-efectiva.*

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INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, taking an estimated 17.8 million lives (31.8% of all global deaths) in 2017, with coronary heart disease as well as stroke comprising 85% of the total CVD-related deaths.[1] In addition, CVDs constitute the top cause of disability-adjusted life years (DALYs) around the world, with an approximate loss of 366 million DALYs in 2017, which represents 14.64% of the global burden of disease.[2] Since 1990, CVDs have remained the leading grouped cause of death in Mexico.[3] Almost 150,000 people died from CVDs in Mexico in 2018, for a mortality rate of 119 per 100,000 individuals.[4] The crude incidence and prevalence numbers of CVDs in Mexico in 2017 were estimated at 808,600 and 7.2 million, respectively.[5] The financial impact of CVDs is substantial due to the high number of acute episodes in addition to their chronic stages. The annual cost for hypercholesterolemia per patient in Mexico was estimated at $258,761 (MXN), leading to an economic burden of more than $115,000 million (MXN) in 2016.[6]

Statins are the first treatment choice for primary (heterozygous-familial and non-familial) hypercholesterolemia and mixed dyslipidemia (PHMD), as well as for the reduction of low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular (CV) events.[7-10] However, despite the availability of statins and other lipid-lowering therapies such as ezetimibe, used either alone or in combination, many high-risk patients fail to achieve their LDL-C goals.[7,9] Evolocumab, a Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitor, has been evaluated in several clinical trials, showing a significant reduction of LDL-C levels in different groups of patients. Recent results indicate that LDL-C reduction with evolocumab significantly reduces the risk of CV events and is also associated with atherosclerotic plaque regression.[11]

It is important to assess the economic value of evolocumab in Mexico. We used an economic model to evaluate the cost-effectiveness of evolocumab added to the standard of care of high-intensity statin therapy with or without ezetimibe (hereinafter referred to as SoC) in high-risk adult patients with PHMD with uncontrolled LDL-C levels with SoC alone from the perspective of the Mexican Institute of Social Security (IMSS).

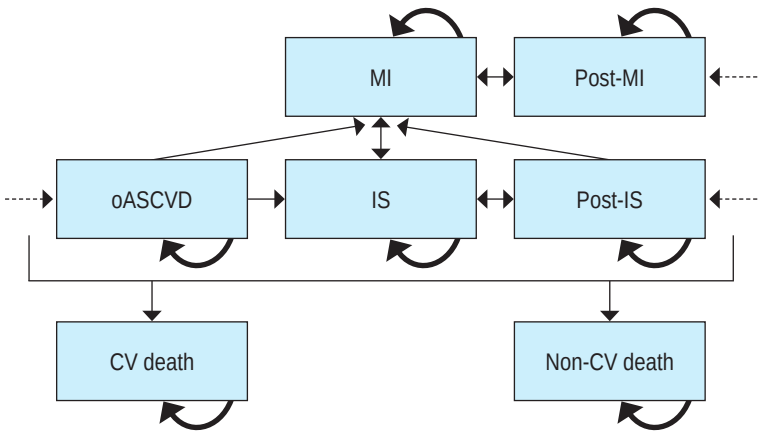

Figure 1: Model structure.
CV = cardiovascular; IS = ischemic stroke; MI = myocardial infarction; oASCVD = other atherosclerotic cardiovascular disease.

MATERIAL AND METHODS

A lifetime Markov cohort state-transition model, adapted from previous publications,[12-15] was built in Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA). The model comprises seven health states *(Figure 1)*: myocardial infarction (MI); ischemic stroke (IS); other atherosclerotic CVD (oASCVD) that captures less severe CV events, namely peripheral artery disease, angina, transient ischemic attack, and carotid stenosis; post-MI; post-IS; CV death; and non-CV death. Only post-MI, post-IS, and oASCVD were considered as initial states. The states for MI and IS cover the first year period after the event, while post-event health states cover the subsequent years. Revascularization (RV), either urgent or elective, is included as a procedure (i.e., cost) and not as a separate health state because the baseline rates already incorporate the impact of RV on subsequent event rates. The model considers annual cycles and half-cycle correction. The effectiveness is reported in terms of life-years (LY).

Target population

The target population comprises adult patients with PHMD and high CV risk who have

not met their LDL-C goals despite receiving SoC. The patients were categorized into two distinct subpopulations: (i) individuals with PHMD plus a history of either MI or IS and (ii) individuals with heterozygous familial hypercholesterolemia (HeFH).

Model inputs

Baseline characteristics: main baseline characteristics for individuals with PHMD plus a history of either MI or IS were defined according to the data available in the FOURIER trial *(Table 1)*.[16] Baseline LDL-C in this subpopulation (175 mg/dL) corresponds to the midpoint of the range (160 to 190 mg/dL) considered as «high» in the CARMELA study.[17] Likewise, the main baseline characteristics for individuals with HeFH *(Table 2)* were defined according to data from the RUTHERFORD-2 trial.[18] Distribution among initial health states for individuals with HeFH (35.56% post-MI, 3.33% post-IS, 61.11% oASCVD) is also based on the RUTHERFORD-2 trial,[18] with specific values derived from Borissov et al.[15] Baseline LDL-C in this subpopulation (217.8 mg/dL) was estimated as the weighted average for patients with definite/probable HeFH diagnosis off and on treatment, as reported by Benn et al.[19]

Baseline risks: the baseline CV event rates represent the rates for patients treated with SoC. The rates are adjusted by age and LDL-C level to reflect the risk in the target population, using the formula:

$$r_a = r_0 \times HR(\Delta age/age) \times RR^{(\Delta LDL)}$$

where r_a is the adjusted baseline rate; r_0 is the baseline rate at mean age (see below); HR_{age} is the hazard ratio (HR) for age, taking a value of 1.03 from the model developed by Wilson et al.;[20] Δage is the age difference between cycle age and the mean age of the cohort from which the baseline rate was obtained; RR is the rate ratio (RR) per 1 mmol/L of LDL-C reduction (equal to 0.78, which is the RR for any major vascular event in the CTTC trial),[21] and ΔLDLc is the LDL-C difference in mmol/L after subtracting the mean LDL-C of the population being evaluated from the cohort LDL-C from which the baseline rate was obtained. The cohort baseline annual CV event rate for a mean age of 67 years and mean LDL-C level of 103.2 mg/dL for the PHMD with a history of

Table 1: Main model inputs in the primary hypercholesterolemia and mixed dyslipidemia plus history of either myocardial infarction or ischemic stroke subpopulation.

Description	Base-case value	Source
Baseline characteristics		
Mean age (years)	62.5	FOURIER trial[16]
Proportion of females (%)	24.6	FOURIER trial[16]
Mean LDL-C (mg/dL)	175.0	CARMELA study[17]
Concomitant use of ezetimibe (%)	5.2	FOURIER trial[16]
Distribution among initial health state		
Post-MI (%)	80.7	Based on the proportions of patients with a history of MI (81.1%) or of previous stroke (19.4%) in the FOURIER trial[16]
Post-IS (%)	19.3	
oASCVD (%)	0.0	
Baseline annual CV event rate*	10.0	Toth et al.[13]
Relative reduction of LDL-C with evolocumab (%)	59.0	FOURIER trial[16]

LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; IS = ischemic stroke; oASCVD = other atherosclerotic cardiovascular disease; CV = cardiovascular.
* Represents the rate per 100 patient-years under standard of care, calculated for a mean age of 67 years and mean LDL-C level of 103.2 mg/dL.

Table 2: Main model inputs in the heterozygous familial hypercholesterolemia subpopulation.

Description	Base-case value	Source
Baseline characteristics		
Mean age (years)	51.0	RUTHERFORD-2 trial[18]
Proportion of females (%)	42.2	RUTHERFORD-2 trial[18]
Mean LDL-C (mg/dL)	217.8	Benn et al. 2012[19]
Concomitant use of ezetimibe (%)	62.0	RUTHERFORD-2 trial[18]
Distribution among initial health state		
Post-MI (%)	35.56	Derived from Borissov et al.[15] which used data collected in the RUTHERFORD-2 trial[18]
Post-IS (%)	3.33	
oASCVD (%)	61.11	
Baseline annual CV event rate*	7.99	Derived from Borissov et al.[15]
Relative reduction of LDL-C with evolocumab (%)	59.2	RUTHERFORD-2 trial[18]

LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; IS = ischemic stroke; oASCVD = other atherosclerotic cardiovascular disease; CV = cardiovascular.
* Represents the rate per 100 patient-years under standard of care, calculated as -LN (1 - 0.55) / 10; where LN is natural logarithm and 0.55 is the predicted 10-year risk for mean age of 51.16 years and mean LDL-C level of 155.46 mg/dL.

either MI or IS subpopulation is 10.0 per 100 patient-years *(Table 1)*. These three parameters were obtained from an observational study conducted in the United Kingdom[13] that applied inclusion criteria similar to those used in the FOURIER trial.[16] The parameters for the cohort used as a reference in the HeFH subpopulation are shown in *Table 2*. The baseline CV event rates are further adjusted in the model once patients experience additional CV events based on the study by Wilson et al., where HRs due to two and three vascular beds involved (vs only one) were 1.35 and 1.83, respectively, and a CV event in the previous year increased the rate by 46%.[20] All rates were converted to risks assuming a constant rate over time (exponential survival function).[14]

Non-CV mortality: mortality from non-CVD causes was assumed to be the same as that of the IMSS adult beneficiary population. The age- and sex-specific non-CV mortality rates were estimated as the difference between the corresponding rates for all-cause and CV mortality, both calculated from the number of deaths (classified by cause) that occurred in individuals aged ≥ 18 years affiliated to IMSS in 2018 according to the National Institute of Statistics and Geography (INEGI)[22] and the IMSS adult beneficiary population in the middle of 2018, based on the Mexican population projections elaborated by the National Population Council (CONAPO)[23] and the IMSS coverage of social security data found in the National Survey of Employment and Social Security (ENESS) 2017.[24]

Treatment effect: The predicted effectiveness of evolocumab on reducing CV event rates in each subpopulation is based on the relative LDL-C reduction observed with evolocumab in the FOURIER[16] and RUTHERFORD-2[18] trials. In particular, the model draws on the treatment differences between the mean percentage reduction of LDL-C levels with evolocumab administered subcutaneously once every two weeks and placebo (both on top of SoC): at week 48 in the FOURIER trial (59.0%,[16] applied to PHMD plus a history of either MI or IS) and at week 12 in the RUTHERFORD-2 trial (59.2%,[18] applied to HeFH). The absolute reductions in LDL-C levels with evolocumab were calculated as the product of the corresponding baseline LDL-C level and the relative reduction in LDL-C. Further, the absolute reductions were converted from mg/dL to mmol/L by dividing them by 38.67.[12] For SoC, the relative

reduction in LDL-C was set to zero because patients were assumed to be treated with SoC at baseline.[14]

Absolute LDL-C reductions from baseline were converted into reductions in CV events based on the relationship between LDL-C level and occurrence of CV events reported in the FOURIER trial. Specifically, the model employs the RRs per 1 mmol/L of LDL-C reduction estimated from the HRs for the key secondary endpoint, which consists of CV death, MI, or IS: 0.84 (95% confidence interval, 0.74-0.96) in the first year and 0.75 (0.66-0.85) for subsequent years.[16] The RR of CV events per 1 mmol/L of LDL-C reduction was defined as:

$$RR = HR^{(1/\Delta LDLc)}$$

where HR as it was previously referred, while ΔLDLc indicates the mean LDL-C reduction in the FOURIER trial[16] after the imputation for missing values (1.38 mmol/L, equal to 53.4 mg/dL).[25] Hence, the adjusted rate of CV events for patients treated with evolocumab (r_{a_EVO}) is given by the following formula:[14,15]

$$r_{a\_EVO} = r_a * RR^{\Delta LDLc}$$

where r_a is the baseline CV rate adjusted by age and LDL-C level, calculated for SoC (see above).

It is important to note that the benefits of evolocumab regarding the reduction of LDL-C and CV events observed in the FOURIER trial[16] were largely consistent across major predefined subgroups related to demographic and disease characteristics, including baseline LDL-C level and baseline risk factors (e.g., previous CV events or presence of familial hypercholesterolemia). The benefits of evolocumab were also consistent across levels of intensity of statin therapy, regardless of ezetimibe use.[16] Therefore, the treatment effect observed in the overall trial population of FOURIER was applied across all modeled target subpopulations.

Resource use and costs: The model considers the direct medical costs consisting of the acquisition of hypolipemiant therapies plus the management associated with health states and RV procedures. All costs are expressed in Mexican pesos (MXN) at values as of August 2020. The list price of a 140-mg prefilled syringe of evolocumab ($2,983.00 [MXN]) was provided by Amgen Mexico. The acquisition cost for high-intensity statins was calculated as a simple average of atorvastatin 40 and 80 mg/day,[7] using a price of $11.20 (MXN) per 10-tablet pack of atorvastatin 20 mg.[26] The daily dose of ezetimibe was a 10 mg tablet,[7] with an acquisition cost (if applied) being calculated from a price of $126.00 (MXN) per pack (each pack containing 28 tablets).[27] *Table 3* presents the estimates of costs associated

Table 3: Costs for cardiovascular events and revascularization procedures.

Item	DRG code	Cost
Myocardial infarction, acute care	281	$157,844.05
Ischemic stroke, acute care	064	$61,661.16
Non-fatal CV event, follow-up	Not applicable	$30,343.28*
oASCVD, annual cost	Not applicable	$30,343.28‡
Cardiovascular death	284	$173,484.63
Revascularization	248 and 233§	$230,395.20

DRG = diagnosis related groups at the Mexican Institute of Social Security (2018 version);[28] CV = cardiovascular; oASCVD = other atherosclerotic cardiovascular disease.
* From Hunt et al.[29] This value was also used as annual cost for both the post-MI and post-IS health states.
‡ Assumed to be equal to the follow-up cost of a non-fatal CV event.
§ Weighted average. See description in text. Notes: (1) Costs based on DRG are expressed in operative-substantive level values.[28] (2) All costs were updated by inflation to 2020 and are expressed in Mexican pesos.

Table 4: Predicted cardiovascular event rates, life years, and discounted costs.

	PHMD plus history of either MI or IS			HeFH		
Outcomes	EVO+SoC	SoC	Difference	EVO+SoC	SoC	Difference
MACE*	**1.35**	**1.71**	**-0.36**	**1.73**	**2.28**	**-0.55**
MI	0.58	0.76	-0.18	0.82	1.14	-0.31
IS	0.14	0.18	-0.05	0.20	0.29	-0.09
CV death	0.63	0.77	-0.14	0.71	0.85	-0.15
Life years						
Undiscounted	12.50	9.35	3.15	18.31	12.73	5.58
Discounted	8.28	6.69	1.59	10.71	8.42	2.29
Discounted costs ($)	**1,180,405**	**625,845**	**554,560**	**1,415,406**	**731,747**	**683,660**
LLT	564,395	8,772	555,623	738,120	18,893	719,227
Acute care	140,074	193,841	-53,767	149,003	228,601	-79,597
Follow-up	237,408	183,550	53,858	308,295	229,128	79,167
Revascularization	238,529	239,683	-1,154	219,988	255,125	-35,137

PHMD = primary hypercholesterolemia and mixed dyslipidemia; HeFH = heterozygous familial hypercholesterolemia; EVO = evolocumab; SoC = standard of care; MACE = major adverse cardiovascular event; MI = myocardial infarction; IS = ischemic stroke; CV = cardiovascular; LLT = lipid-lowering therapies.
* Expressed as per patient rate. **Note:** Costs are expressed in Mexican pesos.

with diverse CV events and RV procedures. They were computed from the 2018 Diagnosis Related Groups (DRG) costs at the operative-substantive level in IMSS[28] and Hunt *et al*.[29] The annual cost for the health states denominated MI and IS was calculated as the sum of their corresponding acute care and follow-up costs. The cost of the transitory event named RV corresponds to the weighted average of percutaneous coronary intervention (PCI, DRG code 248) and coronary artery bypass graft surgery (CABG, DRG code 233), considering that most (88.3%) of the RV procedures correspond to PCI. This percentage was derived from the proportional distribution between ST-elevation myocardial infarction (STEMI; 73.2%) and non-ST-elevation myocardial infarction or unstable angina (NSTEMI/UA; 26.8%) reported in the RENASCA-IMSS study,[30] and the probabilities of PCI conditional to STEMI (91.8%) and NSTEMI/UA (87.0%) estimated from the RENASICA III study.[31] Conservatively, the cost for non-CV death was set to zero.

Discount rates: In the base-case, both costs and LY were discounted at a 5% annual rate, according to Mexican guidelines.[32]

Sensitivity analyses: Both deterministic and probabilistic sensitivity analyses were conducted to assess uncertainty surrounding the incremental cost-effectiveness ratio (ICER). Deterministic sensitivity analysis comprised the evaluation of five scenarios regarding the price of evolocumab (5% change up/down), discount rates (high/low according to Mexican guidelines[32]), and use of CTTC[21] RRs instead of those derived from the FOURIER trial,[16] in addition to the univariate analysis over the costs of CV events and other parameters involved in the risk estimations. Probabilistic sensitivity analysis consisted of 1000 second-order Monte Carlo simulations for each subpopulation, using the distributions recommended by Briggs et al:[33] gamma (with assumed standard errors equal to 10% of the mean values) for costs, normal for LDL-C reductions and mortality, and log-normal for the RRs of CV events per 1 mmol/L of LDL-C reduction and the HRs from Wilson et al.[20] The 95% confidence intervals were used to define the lower and upper bounds and to parameterize the probability distributions. Results of the scenario analyses are presented in a table, whereas those for the

univariate and probabilistic sensitivity analyses are summarized graphically through tornado diagrams and cost-effectiveness acceptability curves (CEAC).

RESULTS

Base case analyses

Table 4 shows the predicted CV event rates per patient, LY (both undiscounted and discounted), and discounted costs disaggregated by item with each intervention for the two subpopulations analyzed. Evolocumab added to SoC decreased the lifetime rate of any major adverse CV event (MACE) by 21 and 24.1% in patients with PHMD plus a history of either MI or IS and in patients with HeFH, respectively. The highest absolute risk reductions were observed for MI, followed by CV death, while the relative reductions in risk varied from 17.5% (CV mortality in HeFH) to 30% (IS in HeFH). The benefit of adding evolocumab is reflected in a higher life expectancy, leading to gains of 3.15 LY for the first subpopulation and 5.58 LY for the second. These values represent relative improvements of 33.7% and 43.8%, respectively. The main cost driver in patients receiving evolocumab and SoC was the acquisition of hypolipemiant therapy, accounting for around half of the total costs in both subpopulations. In the groups of SoC alone, costs owing to RV procedures contributed the most. Overall discounted costs in patients receiving evolocumab as add-on treatment nearly doubled those of the SoC alone, mainly driven by the differences in the acquisition cost of lipid-lowering therapies.

Since the addition of evolocumab to SoC was associated with both more costs and more effectiveness in comparison with SoC alone, incremental analyses were warranted *(Table 5)*. The cost per LY gained with evolocumab added to SoC over SoC alone for patients with PHMD plus a history of either MI or IS was $348,629 (MXN). The ICER was lower (i.e., more cost-effective) for the HeFH subpopulation, yielding a value of $298,148 (MXN) per LY gained.

Scenario analyses

Table 5 shows the incremental values of cost and LY, as well as the ICERs, calculated for the five scenarios evaluated as part of the deterministic sensitivity analysis. All values can be compared to those obtained during the base case analyses. A relative variation of ± 5% in the price of evolocumab resulted in equivalent changes in ICER estimates. When the annual discount rate of 7% for both costs and LY was

Table 5: Incremental cost-effectiveness analyses: evolocumab added to SoC vs SoC alone.

	PHMD plus history of MI or IS			HeFH		
Scenarios	**Δ Cost**	**Δ LY**	ICER	**Δ Cost**	**Δ LY**	ICER
Base-case	**$554,560**	**1.59**	**$348,629**	**$683,660**	**2.29**	**$298,148**
5% increase in EVO price	$582,237	1.59	$366,029	$719,364	2.29	$313,719
5% decrease in EVO price	$526,883	1.59	$331,230	$647,956	2.29	$282,578
High discount rates*	$474,304	1.26	$376,837	$560,506	1.70	$329,364
Low discount rates‡	$661,415	3.15	$209,861	$860,832	5.58	$154,371
Use of CTTC rate ratios§	$474,681	1.23	$384,626	$567,491	1.83	$310,261

SoC = standard of care; PHMD = primary hypercholesterolemia and mixed dyslipidemia; HeFH = heterozygous familial hypercholesterolemia; LY = life years; ICER = incremental cost-effectiveness ratio; EVO = evolocumab. The symbol Δ denotes incremental.
* An annual rate of 7% for both costs and LY.[32]
‡ Annual rates of 3% and 0% (i.e., undiscounted) for costs and LY,[32] respectively.
§ 0.73 (myocardial infarction), 0.79 (ischemic stroke), and 0.86 (cardiovascular death) per 1 mmol/L of low-density lipoprotein cholesterol reduction.[21]
Note: All costs and ICER values are expressed in Mexican pesos.

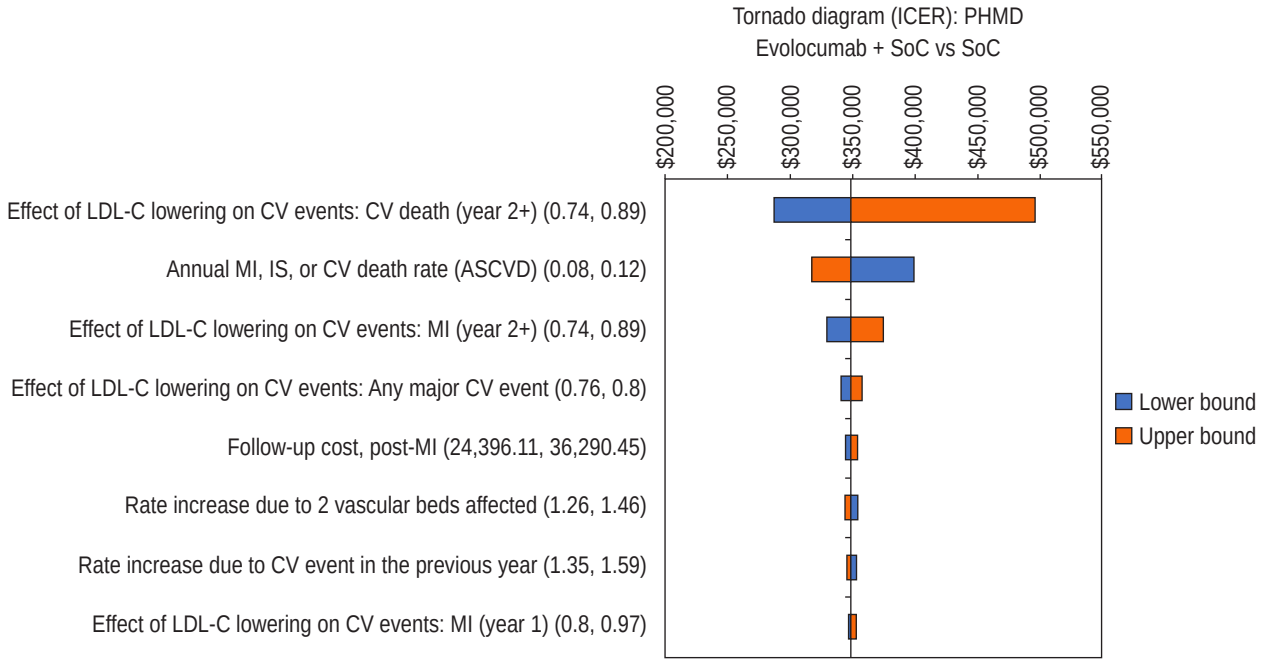

Figure 2: Univariate sensitivity analyses: PHMD. Values in parentheses at the end are 95% confidence intervals. ICER values are expressed in Mexican pesos.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; ICER = incremental cost-effectiveness ratio; IS = ischemic stroke; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PHMD = primary hypercholesterolemia and mixed dyslipidemia (with a history of either MI or IS); SoC = standard of care.

applied, the ICERs increased moderately (by 8 and 10% in PHMD plus a history of either MI or IS and HeFH subpopulations, respectively). In contrast, low annual discount rates (3% for costs and 0% for LY) led to considerable improvements in ICERs, dropping their values by 40% for the PHMD with a history of either MI or IS subpopulation and 48% for the HeFH subpopulation. Using the CTTC[21] RRs of CV events per 1 mmol/L of LDL-C reduction instead of those derived from the FOURIER trial[16] produced slightly higher ICERs compared with the ones from the base case.

Univariate sensitivity analyses

Figures 2 and 3 present the tornado diagram containing the parameters that have an impact of > 1% on the ICER for the corresponding subpopulations. In both cases, the ICER is mainly sensitive to changes in the RRs of CV events per 1 mmol/L of LDL-C reduction for CV death and MI in year two onwards and to the baseline annual MACE rate.

Probabilistic sensitivity analyses

Figure 4 displays the CEAC with add-on evolocumab therapy for each subpopulation. The probability of evolocumab added to SoC being cost-effective compared with SoC alone under a willingness to pay threshold of $521,435 (MXN) –which is equivalent to three times the gross domestic product (GDP) per capita for 2020 in Mexico estimated by the authors with data from the International Monetary Fund[34,35] available at the time the analyses were done– was 97.7% and 99.3% for PHMD plus a history of either MI or IS and HeFH subpopulations, respectively.

DISCUSSION

To our knowledge, this is the first economic evaluation of evolocumab in Mexico. The present study found evolocumab added to SoC had ICERs of $298,148 (MXN) in patients with HeFH and $348,629 (MXN) in patients with PHMD plus a history of either MI or IS.

These values are equal to 1.72 and 2.00 times, respectively, our estimate of GDP per capita for 2020 in Mexico, meeting international criteria for cost-effectiveness acceptability thresholds.[36] Thus, despite significantly higher acquisition cost, the use of evolocumab is cost-effective due to its clinical benefit, characterized by a high potency combined with a simple dosage schedule allowing to achieve a predictable effect in LDL-C reduction, which in turn leads to a considerable decrease in risk of suffering fatal and disabling CV events. It is noteworthy that the model predicted meaningful improvements in survival for patients who received evolocumab added to SoC, yielding gains of 3.15 and 5.58 years in life expectancy over those treated with SoC alone in patients with PHMD plus a history of either MI or IS, and in patients with HeFH, respectively. Sensitivity analyses confirmed the robustness of the cost-effectiveness results.

Because of some methodological differences (e.g., health states considered, characteristics of the target population, type of prevention, sources of clinical information, cost vectors, discount rates), it is difficult to compare the results of our study with those in other published studies. However, there is congruence in several aspects. For example, as other authors have previously reported,[12-15,37-39] we found that evolocumab added to SoC may provide a cost-effective intervention when administered to a certain high-risk population, such as in secondary prevention of individuals with PHMD and those with HeFH. In addition, the lower (i.e., better) ICER with HeFH predicted by our model is consistent with that in previous studies.[12,14]

There are several limitations to this study. First, the relative reduction in LDL-C with evolocumab applied in the model to the HeFH subpopulation is based on a short-term clinical trial.[18] Interestingly, the mean percentage reduction in LDL-C levels after 12 weeks of treatment in the RUTHERFORD-2 trial[18] (59.2%) is almost identical to the corresponding value in the FOURIER trial[16] (59.0%), where the

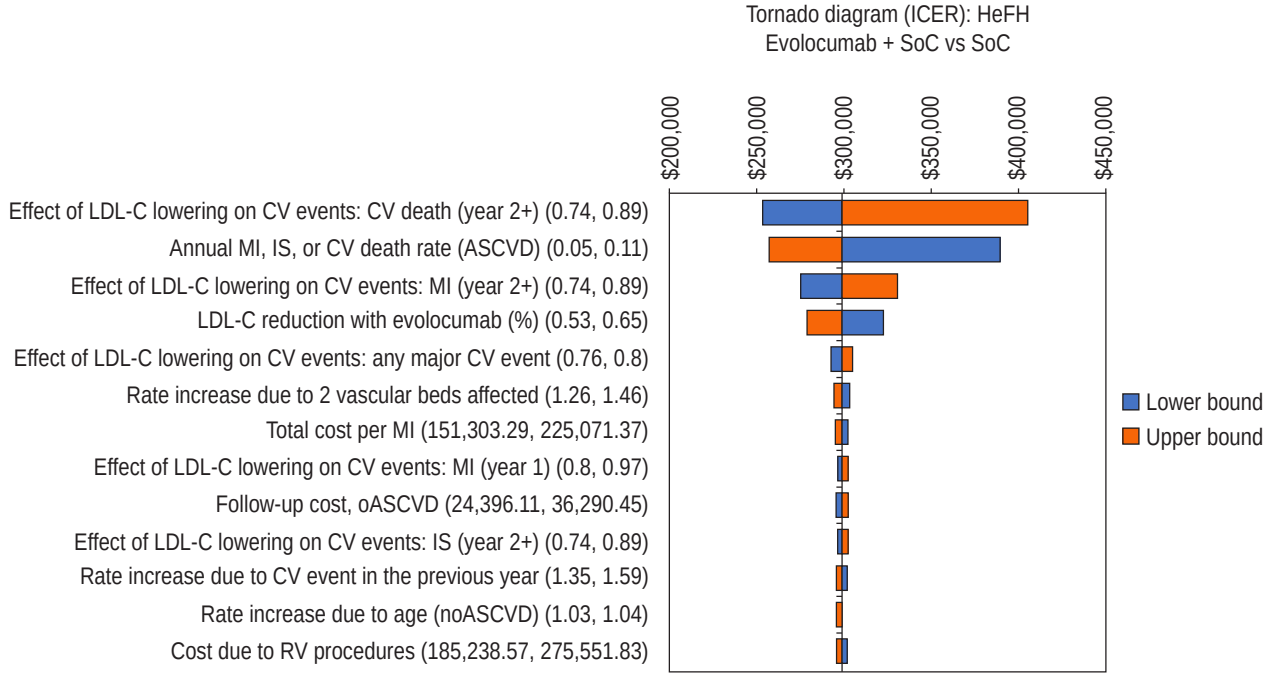

Figure 3: Univariate sensitivity analyses: HeFH. Values in parentheses at the end are 95% confidence intervals. ICER values are expressed in Mexican pesos.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; ICER = incremental cost-effectiveness ratio; IS = ischemic stroke; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; noASCVD = without ASCVD; oASCVD = other ASCVD; RV = revascularization; SoC = standard of care.

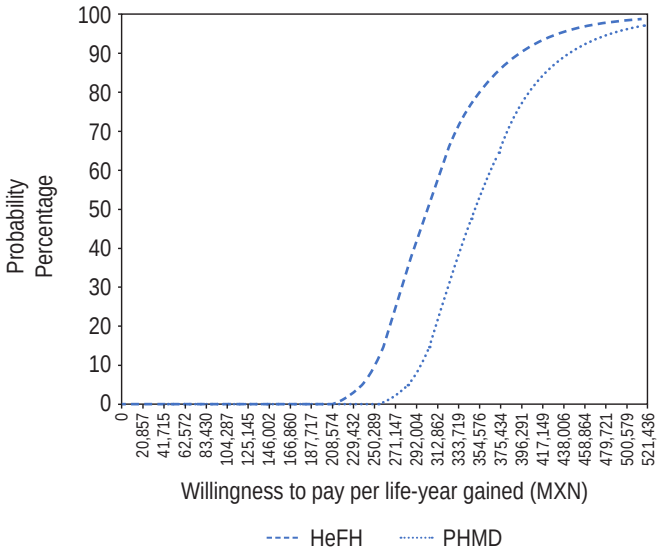

Figure 4: Cost-effectiveness acceptability curves with add-on evolocumab therapy. HeFH = heterozygous familial hypercholesterolemia; IS = ischemic stroke; MI = myocardial infarction; MXN = Mexican pesos; PHMD = primary hypercholesterolemia and mixed dyslipidemia (with a history of either MI or IS).

median duration of follow-up was 2.2 years. Second, since the model had a lifetime horizon, the effect of LDL-C lowering on CV events from year two onwards is constant, and it was based on the results of the FOURIER trial.[16] Although the limited follow-up time in the FOURIER trial[16] may have some uncertainty about the long-term effects of evolocumab. It is worth mentioning that there is evidence of sustained hypolipemiant effect with evolocumab for up to five years.[40] In addition, given that the process of atherosclerotic plaque accumulation and its eventual outcome in terms of CV events requires some time, it is possible to hypothesize that the therapeutic benefit of evolocumab from year three onwards will be greater in magnitude than that observed in year 2. It is also worth noting that the ICERs under the scenario considering the RRs of CV events per 1 mmol/L of LDL-C reduction found in the CTTC trial,[21] which had a median follow-up of 5.1 years, were similar to those obtained during the base case analyses. A third limitation is that the cost analyses were focused on certain direct medical costs. Incorporation of other sources of costs associated with CV events, such as payment of disability leave and pensions, funeral expenses, and other end-of-life costs, would have led to more favorable results for evolocumab. Regarding this agent, its price was maintained fixed during the whole horizon but if a price erosion eventually occurred, the cost-effectiveness results would improve. Another limitation consisted of the exclusion of supplementary effectiveness measures such as the quality-adjusted life years (QALYs) or DALYs, which presumably would also lead to improved ICERs.

Finally, it is important to keep in mind that the results of these analyses are only applicable to the subpopulations evaluated, including their specific risk profiles. In the same way, the results are only generalizable to Mexican healthcare institutions with cost vectors like those of the IMSS.

CONCLUSIONS

Results from this modeling study found that the addition of evolocumab to SoC may provide a cost-effective intervention for high-risk adult patients with PHMD plus history of either MI or IS as well as for those with HeFH when SoC alone is insufficient to meet their LDL-C goals. The cost-effectiveness of the evolocumab treatment strategy will impact longer survival and fewer complications in this type of patient at high risk of complicated CVDs.

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Usefulness of echocardiography in athletes: experience of a Portuguese center

Utilidad de la ecocardiografía en deportistas: experiencia de un centro portugués

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Keywords:
Electrocardiogram, echocardiography, athlete, pre-participation screening, sudden cardiac death.

Palabras clave:
Electrocardiograma, ecocardiografía, atleta, evaluación pre-participación, muerte súbita cardiaca.

ABSTRACT

Introduction: Pre-participation screening aimed at the detection of disorders associated with sudden cardiac death is universally supported by major medical societies. However, the best method for screening remains controversial. The aim of this study was to evaluate the prevalence of structural cardiac lesions identified by echocardiography in apparently healthy athletes referred for pre-participation screening. **Material and methods:** We conducted an observational retrospective study (January 2017-December 2019) performed in a single center. We evaluated echocardiograms of athletes under 35 years of age, performed in the first evaluation for pre-participation screening. **Results:** A total of 1,981 different athletes' echocardiograms were included; 36 exams (1.8%) reported structural cardiac lesions. The most common cardiac lesions found were mitral valve prolapse (n = 5), atrial septal aneurysm (n = 5) and atrial septal defect (n = 4). The bicuspid aortic valve and left ventricular hypertrophy were each present in 3 athletes (n = 3); ventricular septal defects, left ventricular noncompaction, aortic dilatation and dilated cardiomyopathy were each found in 2 athletes (n = 2). Less frequent lesions were present in only one athlete, such as hypertrophic cardiomyopathy, surgically-corrected transposition of the great arteries, and pulmonary valve stenosis. Notably, among 36 patients with structural abnormalities in echocardiography, only 6 (16.7%) had positive standard pre-participation screening (combining personal and family history, physical examination and electrocardiogram). **Conclusions:** Echocardiography plays an important role in detecting cardiac structural abnormalities that would otherwise escape standard screening protocols and could be left unnoticed. This study suggests a potential benefit of including echocardiography in the first evaluation for pre-participation screening of competitive athletes.

RESUMEN

Introducción: *Las principales sociedades médicas respaldan universalmente el cribado previo a la participación destinado a la detección de trastornos asociados con la muerte súbita cardiaca. Sin embargo, el mejor método para la detección sigue siendo controvertido. El objetivo de este estudio fue evaluar la prevalencia de lesiones cardiacas estructurales identificadas por ecocardiografía en atletas aparentemente sanos, referidos para tamizaje pre-participación.* ***Material y métodos:*** *Realizamos un estudio observacional retrospectivo (enero 2017-diciembre 2019) de un único centro. Se evaluaron ecocardiogramas de atletas menores de 35 años, realizados en la primera evaluación para tamizaje pre-participación.* ***Resultados:*** *Se incluyeron en total 1,981 ecocardiogramas de atletas diferentes; 36 exámenes (1.8%) reportaron lesiones cardiacas estructurales. Las lesiones cardiacas más frecuentes encontradas fueron prolapso de la válvula mitral (n = 5), aneurisma del tabique interauricular (n = 5) y comunicación interauricular (n = 4). La válvula aórtica bicúspide y la hipertrofia ventricular izquierda estuvieron presentes cada una en tres atletas (n = 3); defectos del tabique ventricular, miocardiopatía por ventrículo izquierdo no compacto, dilatación aórtica y miocardiopatía dilatada se encontraron cada uno en dos atletas (n = 2). Las lesiones menos frecuentes se presentaron en un solo atleta, e incluyeron miocardiopatía hipertrófica, transposición de grandes arterias corregida quirúrgicamente, estenosis de válvula pulmonar, entre otras. En particular, entre 36 pacientes con anomalías estructurales en la ecocardiografía, sólo 6 (16.7%) tuvieron un examen estándar previo a la participación positivo (combinando antecedentes personales y familiares, examen físico y electrocardiograma).* ***Conclusiones:*** *La ecocardiografía transtorácica juega un papel importante en la detección de anomalías estructurales cardiacas que de otro modo escaparían a los protocolos de detección estándar y podrían pasar desapercibidas. Este estudio sugiere un beneficio potencial de incluir la ecocardiografía en la primera evaluación para la detección previa a la participación de atletas competitivos.*

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INTRODUCTION

Regular physical activity and exercise are widely recommended by the scientific community since it is associated with a decrease in cardiovascular and all cause-mortality.[1,2] On the other hand, in susceptible individuals, the practice of intense exercise may paradoxically increase the risk of cardiac events and sudden cardiac death (SCD).[1,3]

Estimates on the incidence of SCD in competitive athletes are widely inconsistent, varying from 1 in a million to 1 in 5,000 athletes per year, mainly due to heterogeneous populations and unstandardized study designs.[1,4] In most cases, the mechanism of SCD is a sudden ventricular arrhythmia that occurs as a consequence of a previously silent culprit disease.[3,5] As a result, screening subjects for cardiovascular (CV) diseases potentially associated with SCD as part of a pre-participation screening (PPS) is widely supported by major medical societies.[1,6] However, the best method for CV screening remains controversial and is still under debate.[1,7] Along with medical history and physical examination, different countries apply different regulations regarding complementary exams to be used in PPS in competitive athletes.[3,7] These exams may include electrocardiogram (ECG), exercise testing or compulsory echocardiography.[3] Although echocardiography may be able to identify additional structural disorders, there is still insufficient evidence to recommend routine echocardiographic screening.[8,9]

In Portugal, in recent years, there has been a growing trend in the registration of competitive athletes in sports federations. In 2020 there were around 587,812 registered athletes, about 57 per 1,000 inhabitants.[10] These are significant numbers that make it important to establish a cost-effective PPS methodology prior to the initiation of exercise that is capable of detecting potentially life-threatening CV disease and preventing sudden death events.

The aim of this study was to evaluate the prevalence of structural cardiac lesions identified by echocardiography in apparently healthy athletes referred for pre-participation screening.

MATERIAL AND METHODS

In the Sports Medicine Center of Guimarães (SMCG), all athletes undergo a CV evaluation consisting of family and personal medical history, physical examination and ECG. In the first evaluation, by local protocol, every athlete undergoes an echocardiogram regardless of age, sex, degree of activity or sport's modality. The European Society of Echocardiography recommends complete two-dimensional and color Doppler echocardiogram with standard transthoracic echocardiographic views performed by experienced cardiologists and pediatric cardiologists.[11]

In this study, we retrospectively evaluated consecutive echocardiograms of athletes under 35 years of age that were performed in the first evaluation for PPS between the years 2017 and 2019.

RESULTS

A total of 1,981 different athletes were included. Structural cardiac lesions were found in 36 (1.8%) individuals. In this subgroup, the median age was 18.5 (IQR = 16) years, the vast majority of athletes were male (91.7%; n = 33), of the white race (94.4%; n = 34), and the most represented sport was football (66.7%; n = 24). Demographic characteristics discriminated by sports modality are described in *Table 1*.

Cardiac lesions found in athletes' echocardiograms are described in *Table 2*. The most frequent lesions were mitral valve prolapse (MVP, n = 5) and atrial septal aneurysm (ASA, n = 5). Four athletes presented with *ostium secundum* atrial septal defect (ASD); bicuspid aortic valve (BAV) and left ventricular hypertrophy (LVH) were each present in 3 athletes. Ventricular septal defects (VSD), left ventricular noncompaction (LVNC), aortic dilatation and dilated cardiomyopathy (DCM) were each present in 2 patients.

Less frequent lesions were present in only one athlete, such as subaortic membrane, patent ductus arteriosus, hypertrophic cardiomyopathy (HCM), surgically corrected transposition of the great arteries (TGA), persistent left superior vena cava with coronary sinus dilatation, dysplastic pulmonary valve

Table 1: Demographic characteristics discriminated by type of sport.

Type of sport	N (%)	Median age	Male sex, N (%)	White race, N (%)
Football	24 (66.7)	15.5	23 (95.8)	22 (91.7)
Referees	3 (8.3)	25.0	3 (100.0)	3 (100.0)
Combat sports	2 (5.6)	32.5	1 (50.0)	2 (100.0)
Rugby	2 (5.6)	22.5	2 (100.0)	2 (100.0)
Basketball	1 (2.8)	14.0	1 (100.0)	1 (100.0)
Boxing	1 (2.8)	23.0	0 (0.0)	1 (100.0)
Cycling	1 (2.8)	20.0	1 (100.0)	1 (100.0)
Handball	1 (2.8)	10.0	1 (100.0)	1 (100.0)
Volleyball	1 (2.8)	30.0	1 (100.0)	1 (100.0)
Total	36 (100.0)	18.5 (IQR = 16)	33 (91.7)	34 (94.4)

stenosis, right ventricle dilatation and coronary fistula between the left coronary artery and pulmonary trunk. Among the two black athletes with documented cardiac lesions on echocardiograms, one presented with HCM and the other with DCM. Among female athletes, two had ASA and one ASD.

Only three of the athletes with echocardiographic lesions had an abnormal ECG tracing (8.3%), namely an athlete with ventricular pre-excitation (MVP), another with negative T waves from V4 to V6 leads (VSD) and a black athlete with Q waves and negative T waves in the inferior leads and deep, negative/biphasic T waves in V2-V6 leads (HCM). Only one athlete (DCM) reported a family history of sudden cardiac death, and the other (corrected TGA) reported previous cardiac surgery. Two athletes presented with systolic murmurs in physical examination (one with corrected TGA and the other with dysplastic pulmonary valve stenosis). Overall, only 6 of the 36 athletes (16.7%) with cardiac lesions on echocardiogram presented positive findings when combining personal and family background, physical examination and ECG *(Table 2)*.

DISCUSSION

This study reports a cardiac lesion incidence of 1.8%, overlapping what is described in the literature.[7,8] Football is the most common sport practiced in this region, explaining the greatest number of abnormalities associated with this modality. Highly dynamic sports, like football, are known to pose a higher risk for SCD.[4]

Most European institutions (including Portugal) follow a specific workup based on European Society of Cardiology recommendations. The first-line evaluation protocol consists of personal and family history and physical examination, with the inclusion of a 12 lead ECG.[12] Additional investigation is required only if the first evaluation returned any positive findings.[12] On the other hand, in the United States of America (US), the latest guidelines from the US Preventive Services Task Force recommends against screening with resting or exercise ECG in asymptomatic adults with low risk of CV events.[13]

Institutions that use echocardiography as a first line in PPS are rare since the evidence supporting the use of echocardiography in routine screening is still scarce.[1,8]

However, some cardiac structural abnormalities that can easily be recognized with echocardiography can be missed on physical examination and ECG.[14]

In our study, only 16.7% of patients with documented cardiac lesions had a positive non-echocardiographic PPS, which would leave the remaining 83.3% unnoticed and unaddressed prior to sports participation. Not all cardiac lesions pose an increased risk of SCD, but many are associated with an increased risk of non-lethal CV events and thus require intervention or surveillance.[8]

In concordance with some studies, our findings suggest that the use of echocardiography in at least the first PPS of competitive athletes may improve the effectiveness of programs in detecting cardiac lesions and, possibly, help prevent SCD in athletes.[8,14]

Studies analyzing the cost-effectiveness of adding routine echocardiography to PPS protocols report increased sensitivity in detecting cardiac lesions otherwise not detected by standard screening, but with an estimated 20 to 30% increase in cost.[8,15]

Study limitations. Echocardiograms were performed in different laboratories and reported by different cardiologists without a standardized revision process.

We did not study clinical outcomes nor evaluate the costs of echocardiography inclusion in PPS. Therefore, we cannot objectively infer the prognostic significance or the cost-effectiveness of these findings.

The single-center nature further limits the generalizability of our findings.

CONCLUSIONS

To our knowledge, this report is the first published with a Portuguese sample that studies the impact of the inclusion of echocardiography in PPS for competitive athletes. Echocardiography plays a unique role in detecting cardiac structural abnormalities that would otherwise escape standard screening protocols based on medical history, physical examination and ECG alone.

In this study, we report that 83.3% of the cardiac lesions that were found by echocardiography in this population would not be detected by the standard screening protocol. This finding emphasizes the importance of echocardiography in structural heart disease detection and suggests a potential benefit of echocardiography in the first evaluation for PPS of competitive athletes. Nevertheless, larger studies with cost-effective analysis will be necessary to objectively support a recommendation

Table 2: Cardiac lesions prevalence in echocardiogram and abnormalities detection by standard non-echocardiographic pre-participation screening.

Type of lesion	Prevalence N (% within lesions; % overall)	Abnormal standard PPS N (% within type of lesion)
Atrial septal aneurysm	5 (13.9; 0.25)	0 (0)
Mitral valve prolapse	5 (13.9; 0.25)	1 (20)
Atrial septal defect	4 (11.1; 0.20)	0 (0)
Bicuspid aortic valve	3 (8.4; 0.15)	0 (0)
Left ventricular hypertrophy	3 (8.4; 0.15)	0 (0)
Ascending aortic dilation	2 (5.6; 0.10)	0 (0)
Dilated cardiomyopathy	2 (5.6; 0.10)	1 (50)
Left ventricle noncompaction	2 (5.6; 0.10)	0 (0)
Ventricular septal defect	2 (5.6; 0.10)	1 (50)
Coronary fistula (LCA-PT)	1 (2.8; 0.05)	0 (0)
Corrected great arteries transposition	1 (2.8; 0.05)	1 (100)
Dysplastic pulmonary valve stenosis	1 (2.8; 0.05)	1 (100)
Hypertrophic cardiomyopathy	1 (2.8; 0.05)	1 (100)
Patent ductus arteriosus	1 (2.8; 0.05)	0 (0)
Persistent left superior vena cava	1 (2.8; 0.05)	0 (0)
Right ventricle dilatation	1 (2.8; 0.05)	0 (0)
Sub-aortic membrane	1 (2.8; 0.05)	0 (0)

LCA = left coronary artery; PPS = preparticipation screening; PT = pulmonary trunk.

on the inclusion of echocardiograms in PPS protocols.

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Clinical case

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Case report: COVID-19 mRNA vaccine association with acute myocarditis

Reporte de caso: asociación de vacuna COVID-19 mRNA con cuadro de miocarditis aguda

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Keywords:
Acute myocarditis, COVID-19, mRNA vaccine, ESAVI.

Palabras clave:
Miocarditis aguda, COVID-19, vacunas mRNA, ESAVI.

ABSTRACT

A 50-year-old woman presented to the Emergency Department with chest pain, the elevation of cardiac enzymes, and no electrocardiographic alterations. Coronary angiography was performed in which no obstructive lesions were found. A cardiac magnetic resonance study reported an image consistent with acute myocarditis without evidence of myocardial ischemia. The patient received the first dose of Pfizer-BioNTech vaccine two days before the onset of symptoms. In most cases of myocarditis, its clinical manifestations lie in a wide spectrum, and the etiological diagnosis is indeterminate. In recent months, the probable association between cases of myocarditis with COVID-19 mRNA vaccines has been established. The use of the COVID-19 mRNA vaccine has demonstrated significant benefits in reducing morbidity and mortality related to SARS-CoV-2 virus infection. This event may be a transitory process that does not represent a contraindication for the application of the vaccine.

RESUMEN

Se presenta el caso de una mujer de 50 años atendida en el Servicio de Urgencias por dolor torácico y elevación de enzimas cardiacas; no tuvo alteraciones electrocardiográficas. Se realizó coronariografía en la que no se encontraron lesiones obstructivas. Un estudio de resonancia magnética cardiaca reportó imagen compatible con miocarditis aguda sin evidencia de isquemia miocárdica. La paciente había recibido una primera dosis de vacuna Pfizer-BioNTech dos días antes de la aparición de los síntomas. En la mayoría de los casos de miocarditis, el diagnóstico etiológico se encuentra indeterminado y sus manifestaciones clínicas tienen un amplio espectro. En los últimos meses, se ha establecido la asociación probable entre casos de miocarditis con vacunas COVID-19 mRNA. El uso de vacunas COVID-19 mRNA ha demostrado el beneficio significativo en la reducción de morbilidad y mortalidad relacionadas a la infección por el virus SARS-COV-2. Este puede ser un proceso transitorio que no representa una contraindicación para la aplicación de la vacuna.

INTRODUCTION

Myocarditis is an inflammatory disease of the myocardium, defined according to the World Health Organization (WHO) by histological, immunological, and histopathological criteria.[1] Although the etiological diagnosis of a myocarditis picture is mostly indeterminate, a wide variety of infectious agents (especially viral infections), systemic diseases, drugs and toxins can cause the disease with a broad spectrum of manifestations. The clinical manifestations range from subclinical disease to chest pain similar to the one caused by acute coronary syndrome or pericarditis. Myocarditis can even be complicated by the development of cardiogenic shock or sudden death from lethal arrhythmias.[2] In recent months, the probable association between cases of myocarditis with COVID-19 mRNA vaccines has been established. The use of the COVID-19 mRNA vaccine has demonstrated significant benefit in reducing morbidity and mortality related

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to SARS-CoV-2 virus infection. Multiple manifestations of side reactions to the vaccine have been described, such as the development of myocardial inflammation seen in this case.

CASE PRESENTATION

A 50-year-old female patient with a history of systemic high blood pressure and smoking was treated in the Emergency Department. She presented oppressive chest pain of sudden onset unrelated to physical exertion, with irradiation to the lower jaw and left arm (intensity 10/10 visual analogue scale) accompanied by nausea and vomiting of gastric content.

In the initial evaluation, hours after the onset of symptoms, the patient was unchanged on physical examination, and the 12-lead electrocardiogram was normal *(Figure 1)*. Initial laboratory tests highlighted elevation of troponins (high-sensitivity troponin 281 pg/mL) with a significant marker increase at two hours (hsTropT 441 pg/mL). With the clinical picture of angina and the increase in cardiac enzymes, the initial diagnosis was established of non-ST-segment elevation myocardial infarction (NSTEMI). The patient had received the first dose of COVID-19 Pfizer-BioNTech vaccine two days before the onset of symptoms.

The antithrombotic treatment was initiated (aspirin, clopidogrel and anticoagulation with enoxaparin), atorvastatin, metoprolol and enalapril as part of the protocol established by NSTEMI management guidelines. Diagnostic coronary angiography *(Figure 2)* was performed, in which no significant angiographic lesions were found in epicardial arteries. Once the existence of obstructive coronary lesions as the cause of the myocardial injury had been ruled out, cardiac magnetic resonance imaging was performed *(Figure 3)*. The process of acute myocarditis was observed, and a preserved biventricular function; myocardial ischemia was discarded.

With this information, the diagnosis of acute myocarditis was integrated; a treatment previously indicated for the management of NSTEMI was discontinued. The subsequent evolution was towards clinical improvement; the patient not develops heart failure and was discharged home with a diagnosis of acute myocarditis.

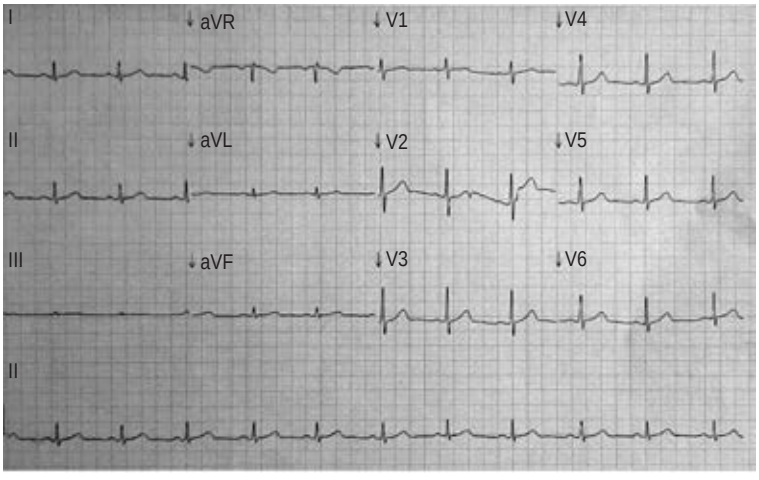

Figure 1: Initial electrocariogram (ECG). Normal ECG, without signs of myocardial ischemia.

DISCUSSION

Myocarditis affects individuals of all ages with a predominance of young people.[3] In all cases of this inflammation, it is necessary to exclude coronary artery disease or other cardiovascular diseases that could explain the clinical manifestations. Electrocardiographic manifestations are nonspecific and may include concave elevation of the ST segment, atrioventricular block, increased duration of the QRS complex, alterations (if any) of repolarization. The elevation of troponins is also frequent because it causes acute myocardial damage.[2] Based on the clinical picture, electrocardiographic alterations, and the elevation of troponins, it is not uncommon for myocarditis to be initially classified as an acute coronary syndrome.

Although the gold standard for the diagnosis and definition of myocarditis requires an endomyocardial biopsy for histopathological study, it is only recommended in some cases. A significant percentage of patients with myocarditis are diagnosed with non-invasive imaging studies in conjunction with the clinical picture and laboratory studies. Cardiac magnetic resonance imaging is a valuable tool in the diagnosis of this pathology because it detects of inflammation, edema, necrosis, and fibrosis in myocardial tissue.[4]

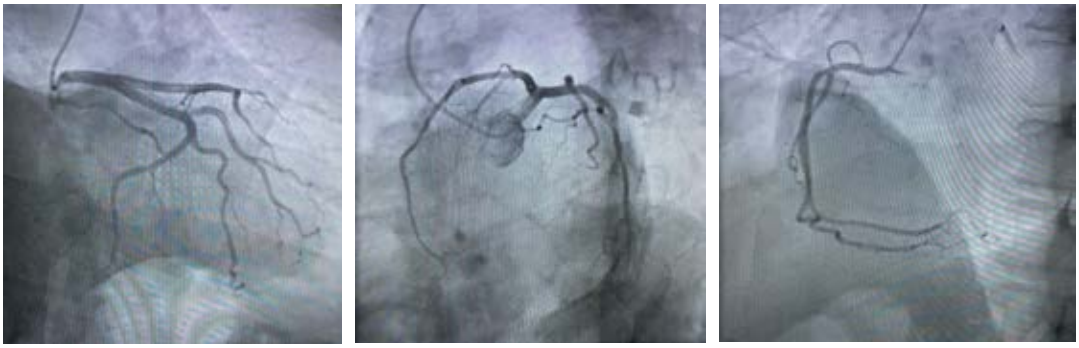

Figure 2: Coronary angiography. Coronary arteries without significant stenosis, thrombolysis in myocardial infarction (TIMI) 3 flow.

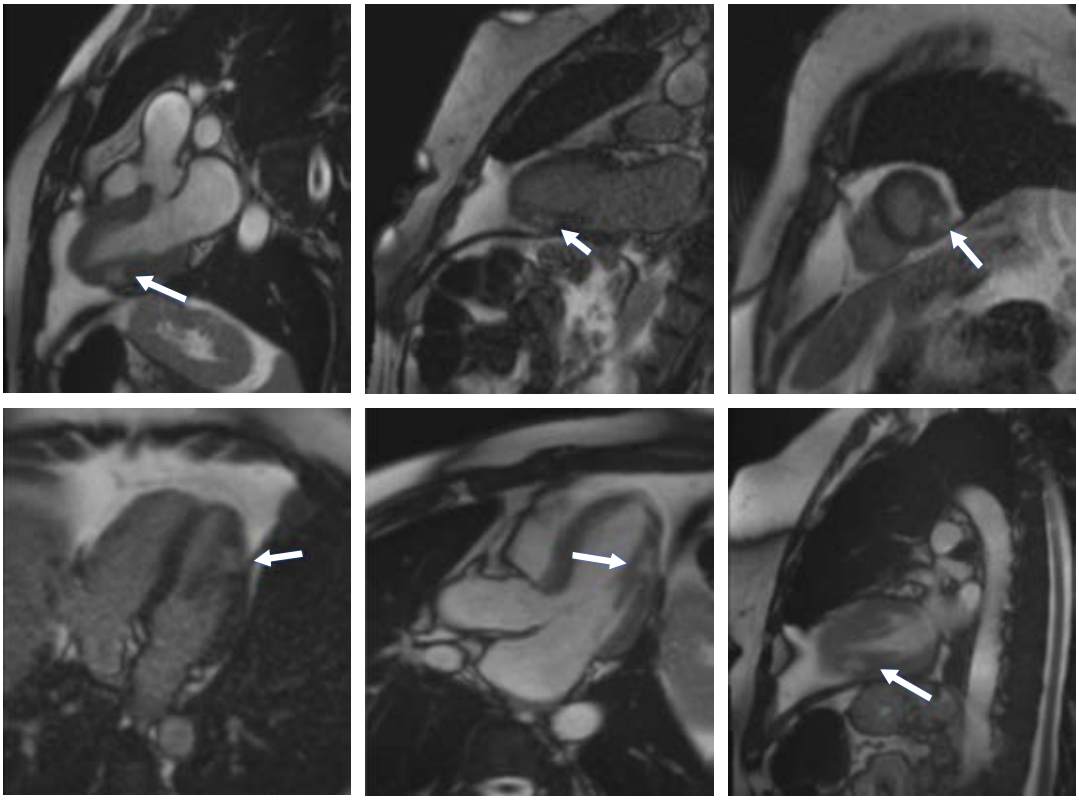

Figure 3: Cardiac magnetic resonance imaging. Zone of focal late gadolinium enhancement compatible with acute myocarditis (arrows).

Because of the absence of a clear etiology, the antecedent of having received the Pfizer-BioNTech vaccine two days before the onset of symptoms was considered the causative agent of the myocarditis in this case. Although a significant percentage of the acute myocarditis cases do not demonstrate a definite etiology, it is important to emphasize that, recently, an association has been suggested between cases of myocarditis and COVID-19 mRNA vaccines, including the Pfizer-BioNTech vaccine.[5]

Case events reported in the literature have usually appeared after the application of the second dose of COVID-19 mRNA vaccine;

the clinical manifestations include chest pain two to three days after the vaccine is applied. Most patients described in these publications were young men who required hospitalization for myocarditis; none of them had a history of other illnesses or a COVID-19 infection. All the patients presented an elevation of cardiac enzymes. The cardiac magnetic resonance study results were compatible with myocarditis. It is important to emphasize in the very low incidence of myocarditis associated with mRNA vaccines. In the larger series, after approximately 300 million COVID-19 mRNA vaccine doses were administered, there were 1,226 reports of probable myocarditis/pericarditis, 67% of which followed the second dose, making it a rare adverse event.[6]

The Institutional Center for Pharmacovigilance was informed of the case, which was evaluated as an event allegedly attributable to vaccination or immunization. The case was considered as serious and with a causality association consistent with the a vaccine-related event, according to the Manual of Standardized Procedures for epidemiological Surveillance of Events Allegedly Attributable to Vaccination or Immunization (ESAVI), version 2021.[7] The case was reported to the corresponding health authority in the national ESAVIs reporting system.

CONCLUSIONS

The case of a diagnosed patient with acute myocarditis and a history of COVID-19 vaccination close to the onset of symptoms is reported. A causal relationship between vaccination and myocarditis can be attributed here because there is a temporal relationship between vaccine administration and the appearance of ESAVI with no other underlying cause. Of note, there is consistency with similar reports in the literature. It is important to continue monitoring future cases closely and reporting similar ESAVIs in a timely manner to establish whether a pharmacovigilance signal exists.

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Difficult diagnosis infective endocarditis in a pediatric patient: case report

Endocarditis infecciosa de difícil diagnóstico en la edad pediátrica: reporte de caso

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Keywords:
Infective endocarditis, pediatric assistant, endocarditis, cardiology, echocardiogram.

Palabras clave:
Endocarditis infecciosa, pediatría, endocarditis, cardiología, ecocardiograma.

ABSTRACT

Infective endocarditis (IE) remains a diagnostic challenge because its clinical manifestations are nonspecific and mimic other entities. IE has been extensively studied and documented in adults but less so in children. Here we describe a clinical case of IE that is difficult to diagnose. This is a thirteen-year-old male patient who came to the emergency department of the Hospital Infantil Universitario de San José due to fever for one year, predominantly in the afternoon. The patient has a history of corrected myelomeningocele, Arnold Chiari malformation type 1, neurogenic bladder and hydrocephalus and is a user of the ventriculoatrial shunt. On admission, a urinary tract infection by a multidrug-resistant germ was documented, which was initially considered the cause of his fever. Multiple echocardiograms were performed, all without evidence of IE. However, in addition to fever and ventriculoatrial shunt, *Streptococcus mitis* bacteremia and positive rheumatoid factor were documented, establishing a definitive diagnosis of IE according to modified Duke criteria. This case illustrates the importance of maintaining a high suspicion of IE, even in patients with an atypical clinical presentation without specific findings for IE and directing additional studies based on the Duke criteria. This requires knowledge of the typical etiologic microorganisms as well as the findings that constitute the vascular and immunologic phenomena contemplated in the modified Duke criteria.

RESUMEN

La endocarditis infecciosa (EI) continúa siendo un desafío diagnóstico debido a que sus manifestaciones clínicas son inespecíficas y simula otras entidades. La EI ha sido ampliamente estudiada y documentada en adultos, pero no tanto en niños. Aquí se describe un caso clínico de EI de difícil diagnóstico. Se trata de un paciente masculino de 13 años, quien acudió al Servicio de Urgencias del Hospital Infantil Universitario de San José por fiebre durante un año de predominio vespertino. Cuenta con antecedentes de mielomeningocele corregido, malformación de Arnold Chiari tipo 1, vejiga neurogénica e hidrocefalia y es usuario de derivación ventriculoatrial. Al ingreso, se documentó una infección de vías urinarias por un germen multirresistente, la cual inicialmente se consideró la causa de su fiebre. Se realizaron múltiples ecocardiogramas, todos sin evidencia de EI. Sin embargo, además de fiebre y la derivación ventriculoatrial, se documentó bacteriemia por Streptococcus mitis *y factor reumatoide positivo, estableciendo un diagnóstico definitivo de EI según los criterios de Duke modificados. Este caso ilustra la importancia de mantener una alta sospecha de EI, aun en pacientes con una presentación clínica atípica sin hallazgos específicos para EI y dirigir los estudios adicionales con base en los criterios de Duke. Para ello, es necesario conocer cuáles son los microorganismos etiológicos típicos, así como los hallazgos que constituyen los fenómenos vasculares e inmunológicos contemplados en los criterios de Duke modificados.*

INTRODUCTION

Infective endocarditis (IE) is defined as the microbial infection of the endocardium, whether in previously healthy hearts or in susceptible ones with risk factors, like instrumentalization.[1] Nowadays, IE mainly affects patients with congenital cardiopathies, whereas it was previously more common in those with rheumatic cardiomyopathy.[2]

IE is an important disease in the paediatric population, despite having a considerably lower incidence and mortality than adults.[3] The incidence among children with congenital heart disease has been reported to be between 40 and 60 cases per 100,000 such children.[4] Its mortality rates are still significant (5-10% in

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children) despite the progress in the diagnosis and treatment.[5] Here, the case of a male 13-year-old patient with fever is present, multiple comorbidities, positive urine and blood cultures, but no evidence of vegetations on echocardiograms, which led to a delay in the diagnosis.

CASE PRESENTATION

The case involves a 13-year old male patient who presented to the emergency department of the Hospital Infantil Universitario de San José redirected from the neurosurgery outpatient consult due to longstanding fever, predominantly in the evening, of 39-40 ºC, which began after a ventriculoatrial shunt which had been performed year earlier. Relevant medical history includes a correction of myelomeningocele in 2007, type 1 Arnold Chiari malformation, neurogenic bladder for which he receives prophylaxis with trimethoprim-sulfamethoxazole, chronic constipation, flaccid paraparesis and hydrocephalus initially treated with a ventriculoperitoneal shunt, which was subsequently changed to a ventriculoatrial shunt.

On admission, the patient presented no other additional symptoms. On physical examination, he was found to be tachycardic and febrile. A working diagnosis of systemic inflammatory response syndrome of unknown origin was established, for which he was admitted for observation. Initial laboratory testing showed leukocytosis, highly C reactive protein, urine analysis with pyuria, bacteriuria, positive leukocyte esterase and microscopic haematuria. An abdominal echography showed splenomegaly and enlarged kidneys. Because of his medical background, a urinary tract infection (UTI) was diagnosed, and a measurement of procalcitonin was ordered, which came back positive. Urine cultures isolate *E. coli* with an AmpC (serin-betalactamasas) resistance profile, which prompted treatment with ceftriaxone.

The patient had already had a transthoracic echocardiogram (TTE) performed on an outpatient basis, which showed no anomaly. Nevertheless, the study was repeated, documenting free pericardial fluid of 2 mm, with no vegetations or other findings. However, pediatric infectiology considered that regardless of the absence of vegetations infective endocarditis must be suspected and requested additional studies.

On the fifth day of hospitalization, blood cultures isolated *Streptococcus mitis* penicilin sensitive. Additionally, bone scintigraphy that had been performed on an outpatient basis showed nonspecific hyperuptake. Paediatric rheumatology was therefore consulted, who ordered a rheumatoid factor (RF) that was reported positive on day six of hospitalization. With these last findings, and although no vegetations were documented on TTE, the patient was considered to have confirmed infective endocarditis on account of meeting one major criteria (*S. mitis* bacteremia) and three minor criteria (fever > 38 ºC, predisposing heart condition and positive RF) of the modified Duke criteria. Therefore, it was decided to finish seven days of ceftriaxone for the UTI and then initiate antibiotics for the EI with crystalline penicillin for six weeks. As suggested by the pediatric infectious disease consultant since the culprit organism was sensitive to this treatment. The patient response to treatment was favorable with no new febrile peaks, so during the second week of targeted antibiotic therapy the patient was transferred home to complete the remainder of the treatment under a hospitalization-at-home model in charge of healthcare professionals designated by his health insurance company. He subsequently continued to be followed for his multiple comorbidities on an outpatient basis without evidence of recurrence of the IE.

DISCUSSION

In the present clinical case, the diagnosis of IE was made with the modified Duke criteria. According to the literature, it is not frequent to have a patient with all the clinical findings; for instance, Osler nodes and Janeway lesions are found only in 2.7% and 1.6% of patients with IE, respectively.[1] This case was a diagnostic challenge due to the multiple medical comorbidities, which led to the treating physicians towards erroneous diagnoses, like urinary tract infection and renal abscess. A case report was found of a patient with a history of hydrocephalus corrected with VA shunt (ventriculotrial shunt), Arnold

Chiari type 2 malformation, myelomeningocele and glomerulonephritis that after 14 years of the placement of the valve developed IE, which guides to confirm the relevance of such record in this case.[6]

It is crucial to consider IE in the presence of fever of unknown origin, which is found in 90% of all cases associated with risk factors. However, in this instance, despite the fact that pediatric infectology suggested this diagnosis,

Table 1: Modified Duke Infective Endocarditis Criteria.[7]

Mayor criteria	Minor criteria
Blood culture positive for IE A. Typical microorganisms consistent with IE from 2 separate blood cultures: • *Viridans streptococci*, *Streptococcus bovis*, HACEK *group, Staphylococcus aureus*; or • Community-acquired enterococci, in the absence of a primary focus; or B. Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: • At least 2 positive cultures of blood samples drawn 12 h apart; or • All of 3 or a majority of > 4 separate cultures of blood (with first and last sample drawn at least 1 h apart) • Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer > 1: 800 **Evidence of endocardial involvement** A. Echocardiogram positive for IE, defined as follows: • Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or • Abscess; or • New partial dehiscence of prosthetic valve B. New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)	• Predisposition, predisposing heart condition or injection drug use • Fever, temperature 38º C • Vascular phenomena — Major arterial emboli — Septic pulmonary infarcts, — Mycotic aneurysm — Intracranial hemorrhage — Conjunctival hemorrhages — Janeway's lesions • Immunologic phenomena — Glomerulonephritis — OSLER'S nodes — ROTH'S spots — Rheumatoid factor • Microbiological evidence: — Positive blood culture but does not meet a major criterion as noted above — Serological evidence of active infection with organism consistent with IE
Definite infective endocarditis • 2 major criteria or • 1 major criterion and 3 minor criteria or • 5 minor criteria **Possible infective endocarditis** • 1 major criterion and 1 minor criterion or • 3 minor criteria **Rejected** 1. Firm alternate diagnosis explaining evidence of infective endocarditis; or 2. Resolution of infective endocarditis syndrome with antibiotic therapy for ≤ 4 days 3. No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤ 4 days 4. Does not meet criteria for possible infective endocarditis, as above	

IE = infective endocarditis; HACEK = Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella; IgG = immunoglobulin G.

cardiology did not consider it due to the absence of vegetations on cardiac image and by distractors that suggested other sources of infection. The placement of the AVD a year ago and the subsequent onset of fever was not taken into proper consideration. These findings pointed to IE from the beginning and should not have been disregarded despite a negative echocardiogram.

According to the reviewed literature, echocardiograms should always be interpreted in the light of clinical findings and blood cultures. Therefore, the presence of a normal image does not rule out the existence of IE, as sensitivity is 75% and specificity is 90%.[8] It is recommended that if clinical suspicion is high normal TTE should be followed up with a transesophageal echocardiogram (TEE), which has a sensitivity of 90%. Despite, in childhood TEE is rarely needed, it can help in cases such as: aortic root abscess, prosthetic valves, chest wall deformity and obesity. Unfortunately, this test was not performed because the patient's health insurance did not authorize it. In the absence of images showing myocardial compromise, the presence of other findings that suggest heart disease, such as clinical signs or symptoms of heart failure or elevations in pro-BNP levels, should increase the index of suspicion. The patient in this case did not present such clinical findings and the pro-BNP (brain natriuretic peptide) was not documented because this lab test was authorized by his health insurance. However, not all patients with IE develop heart failure or may do so only late in the disease course. Therefore, the absence of such findings does not rule out IE. Nevertheless, in the absence of direct evidence of myocardial involvement, as in this case, it is necessary to differentiate simple bacteremia from IE. The modified Duke criteria are an invaluable tool in this sense as they allow us to make this difficult differential diagnosis. Bacteremia with a typical organism meets a major criteria, but is not by itself sufficient to establish a diagnosis of definitive IE. Instead, at least one other major or three minor criteria must also be met. (The modified Duke criteria even indicate that definitive IE should be diagnosed if five minor criteria are present, even in the absence of any major criteria.) As described above, this patient met one major criteria and three minor criteria, so a diagnosis of definitive IE rather than simple bacteremia is justified according to the modified Duke criteria *(Table 1)*.

Regarding treatment, IE, like many diseases in pediatrics, there is insufficient evidence to allow adequate comparison between alternative therapies. Treatment regimens are therefore chosen on the basis of regimens used for the adult population, with the first line of empirical treatment being ampicillin/sulbactam and aminoglycosides according to American Heart Association (AHA) guidelines.[4] Comparing AHA 2015 guidelines and European Society of Cardiology (ESC) guidelines, it can be seen that both of them recommend the use of bactericides over bacteriostatics.[3,9] Regarding treatment, AHA recommends IV medication for a treatment period of four-eight weeks.[10] As for the case, the change of antibiotic was made due to the resolution of the UTI and the sensitivity shown by the cultures.

CONCLUSIONS

A normal echocardiogram does not exclude the diagnosis of endocarditis, and a repeat echocardiogram may be indicated.

In the clinical scenario, there may be multiple antecedents together with non-specific clinical manifestations that may lead to other etiologies and to an erroneous diagnosis, leading to a delay in the appropriate treatment, so management should always be multidisciplinary.

Transesophageal echocardiography is a very useful diagnostic tool in this type of case in which we have negative transthoracic echocardiograms.

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Infective endocarditis following transcatheter aortic valve replacement with SAPIEN 3 prosthetic valve

Endocarditis infecciosa temprana posterior a reemplazo valvular aórtico transcatéter con válvula protésica SAPIEN 3

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Keywords:
EI-TAVR, *Streptococcus mitis*, transesophageal echocardiogram, SAPIEN 3 prosthetic valve.

Palabras clave:
EI-RVAT, Streptococcus mitis, *ecocardiograma transesofágico, válvula protésica SAPIEN 3.*

ABSTRACT

Infective endocarditis in native valves or in surgically replaced valves has been widely reported in the literature; however, it is still in a continuous process of investigation regarding infective endocarditis in transcatheter bioprosthetic valves. We present the case of a 66-year-old female patient with the diagnosis of early infective endocarditis (IE) of percutaneous prosthetic aortic valve SAPIEN 3 who had a favorable clinical evolution and outcome with conservative treatment with antibiotics despite that in-hospital mortality incidence due to IE-TAVR, represents > 40%. The report of new cases with their different characteristics, various treatments and results obtained, is considered of great importance to support the diagnosis and medical care for future patients.

RESUMEN

La endocarditis infecciosa en válvulas nativas o en válvulas reemplazadas quirúrgicamente ha sido ampliamente descrita en la literatura; sin embargo, respecto a la endocarditis infecciosa en válvulas bioprotésicas transcatéter, aún se encuentra en un proceso continuo de investigación. Presentamos el caso de una paciente de 66 años con diagnóstico de endocarditis infecciosa temprana de válvula protésica aórtica percutánea SAPIEN 3, quien tuvo una evolución clínica y desenlace favorable con tratamiento médico conservador basado en antibióticos, a pesar de que la incidencia de mortalidad intrahospitalaria a causa de EI-TAVR, representa más de 40%. Reportar nuevos casos clínicos con sus diferentes características, sus tratamientos y resultados obtenidos, se considera de suma importancia para apoyar a un mejor diagnóstico y tratamiento médico en futuros pacientes.

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INTRODUCTION

Infective endocarditis in native valves or in surgically replaced valves has been widely reported in the literature; however, it is still in a continuous process of investigation regarding infective endocarditis in transcatheter bioprosthetic valves since these have relatively little time to be approved for international use. The echocardiogram is currently the main diagnostic tool for endocarditis; however, identifying endocarditis in biological prosthetic valves is complicated —even in expert hands— due to the characteristics that it has, such as metal struts, which prevent adequate visualization of its leaflets.[1]

CASE PRESENTATION

We present the case of a 66-year-old female patient with a diagnosis of early infective endocarditis (IE) of percutaneous prosthetic aortic valve SAPIEN 3, who began with an ischemic cerebral vascular event, corroborated by studies of cabinet and laboratory. Her medical history of relevance included six months with the diagnosis of diabetes mellitus, arterial hypertension that was diagnosed a

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year before, frailty and partial dependency as a geriatric syndrome, also with the diagnosis of chronic systolic heart failure with mildly reduced ejection fraction (44%) and severe aortic valve stenosis. Her echocardiogram reported AVA (aortic valve area) 1 cm^2, a peak velocity of 4.39 m/s and a mean gradient of 65 mmHg. The patient was attended by replacement with a biological aortic prosthetic SAPIEN type transcatheter, with no incidents during the procedure.

Her condition began nine months later, with clinical data of neurological deficit characterized by hemiparesis and sensitive loss of the left part of the body, together with dyslalia and dysarthria, with loss of sphincter control, so she decided to visit medical emergencies for an evaluation. During the admission, the patient presented the same neurological alterations, and physical examination identifies a mid-systolic expulsive of grade II in aortic focus without irradiation to neck vessels, hemodynamically stable, no breathing difficulty and fever of 39 ºC. Within the diagnostic protocol performed on the patient —blood cultures and echocardiogram— magnetic resonance imaging (MRI) revealed hyperintensity zone in T2 Flair *(Figure 1)* and four positive blood cultures with *Streptococcus mitis* (predominant microorganism in endocarditis after transcatheter aortic valve replacement (TAVR) isolation.[2,3]

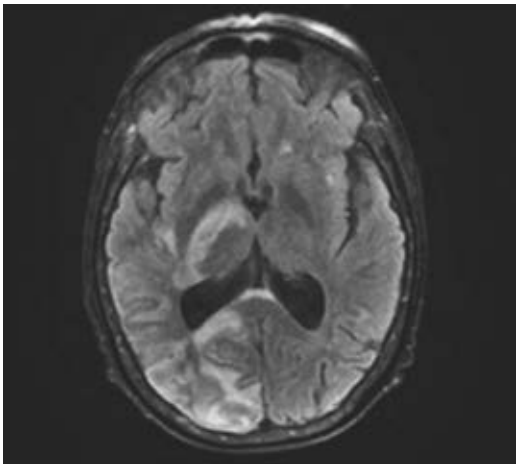

Figure 1: Zone of hyperintensity in T2 Flair, magnetic resonance.

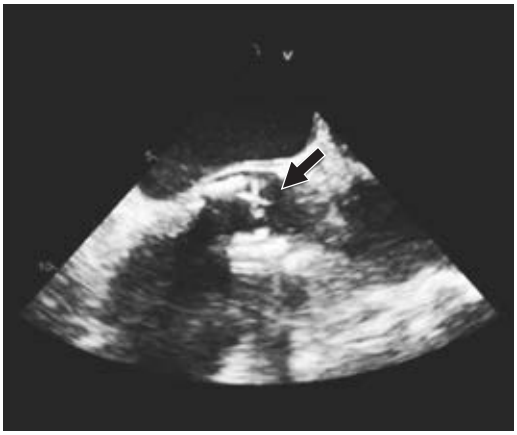

Figure 2: View of the prosthetic aortic valve in transesophageal echocardiography.

The transesophageal echocardiogram in mode 2D and 3D showed three little masses suggestive of vegetations in the aortic prosthetic valve. In the image *(Figure 2)*, a small and mobile mass is observed (black arrow) about 2 × 2 mm on the ventricular side of the prosthetic aortic valve, at the level of prosthetic discs that are not commonly seen clearly, due to interposition of the valve stent/struts.[1]

The third and fourth images of the 3D transesophageal echocardiogram seen at 130 degrees *(Figure 3)* show other pedunculated and mobile masses on the arterial side of the aortic prosthetic, suggestive of vegetations (black arrow) of 3 × 2 and 5 × 3 mm (area 0.2 cm^2).

Before the procedure, the protocol for the eradication of septic foci was followed (dental evaluation, negative nasal and otic cultures) without identifying sites of active infection. During three weeks, antibiotic treatment —vancomycin and ceftriaxone— was given, coursing a favorable clinic evolution, with no fever, negative blood cultures at the ten days of treatment, without new episodes or data of neurologic or cardiac fail. It was decided that the patient left the hospital to continue with the same intravenous treatment for three weeks, with a follow-up of external consultation.

DISCUSSION

The incidence of infective endocarditis after TAVR continues to be low, with ranges of 0.5 to

3% within the first year[4,5] and up to 5.8% at five years of follow-up,[6] being more frequent the in-hospital post-TAVR infective endocarditis, with 0.3%.[2] However, in-hospital mortality due to IE-TAVR represents a high incidence of > 40%[2-4] developing as main complications fever, heart failure and systemic embolism[4] and, as reported in the present case, *Streptococcus mitis* as one of the main causative microorganisms.[7]

The mobility, size, number of masses and adherence —specifically to the prosthesis leaflets— are characteristics that may imply a high risk of detachment and development of septic embolism as a complication. These characteristics are frequently described in the Edwards SAPIEN valve.[1]

In-hospital mortality and all-cause mortality from IE-TAVR occurred in 46% of patients in the analyzes of the partner studies. Although the rates of endocarditis after TAVR remain low, the infectious consequences are catastrophic, with high numbers in mortality after diagnosis.[3] Despite the fact that the mortality rate of infective endocarditis in TAVR is high (> 40%),[2,4] this case did not have a fatal end, with the established conservative measures, having a favorable clinical evolution different from that described in the literature where it is reported that mortality is higher with medical treatment versus surgical treatment.[8,9]

The use of third-generation cephalosporin associated with a glycopeptide showed excellent results. *Streptococcus mitis* has demonstrated in vitro susceptibility to this combination, and by allowing shorter treatment regimens, bacterial resistance and adverse effects such as nephrotoxicity are reduced.[7]

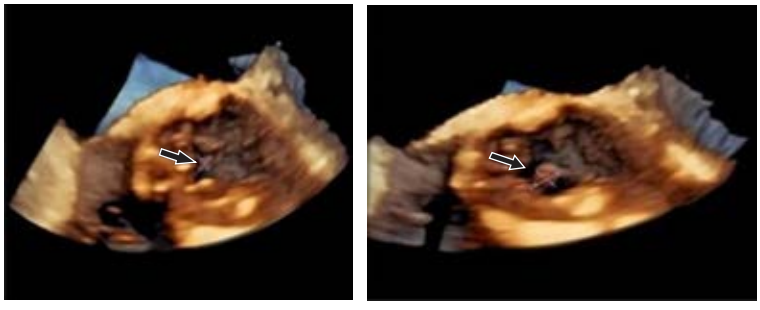

Figure 3: View showing a suggestive image of vegetation in 3D transesophageal echocardiogram.

Although various risk factors associated with prosthetic valve endocarditis such as cirrhosis, pulmonary disease or chronic kidney disease have been described.[4] The range of factors that influence early and/or late complications of TAVR are still to be studied, especially of the infectious type (such as the isolation of different germs and their effective treatment), the previous techniques, during the intervention and/or post-surgery care. For this reason, the exploration and reporting of cases with their different characteristics, various treatments and results obtained, is considered of great importance to support the diagnosis and medical care for future patients.

CONCLUSIONS

In the short time since one of the best treatments for valve replacement has been implemented, the factors that influence early or late complications of TAVR have yet to be described; mainly, of the infectious type such as the isolation of different germs, previous techniques and their treatment during the intervention or post-surgery care.

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Hidroclorotiazida

Información para prescribir (versión reducida)

1. Denominación distintiva: ROFUCAL®

2. Denominación genérica: Hidroclorotiazida

3. Forma farmacéutica y formulación: Tabletas

Cada tableta contiene:

Hidroclorotiazida ..... 12.5 mg o 25 mg

Excipiente cbp. ..... 1 tableta

4. Indicaciones terapéuticas: ROFUCAL® es un diurético de la familia de las tiazidas que está indicado en: Hipertensión arterial. Como monoterapia o combinado, para incrementar el efecto de otros antihipertensivos cuando se trata de formas más severas de hipertensión. En Edema, cuando está asociado a insuficiencia cardiaca congestiva, cirrosis hepática y en terapia con corticoesteroides y estrógenos. ROFUCAL® es útil también en el tratamiento de edemas relacionados con disfunción renal, como el síndrome nefrótico, la glomerulonefritis y la insuficiencia renal crónica. **5. Contraindicaciones:** el uso de ROFUCAL® está contraindicado en pacientes con anuria e hipersensibles al principio activo o componentes de la formulación, así como a otros fármacos derivados de las sulfonamidas. **6. Precauciones generales:** en pacientes que reciben tratamiento con dosis mayores de tiazidas, se pueden presentar casos de hiperuricemia o franca gota. Una diabetes latente puede hacerse manifiesta con el tratamiento a base de tiazidas. Los diuréticos pueden en dosis mayores precipitar una azoemia en pacientes con insuficiencia renal. **7. Restricciones de uso durante el embarazo y la lactancia:** no se recomienda su uso en embarazadas sanas o con edema pues se expone a la madre y al feto a un riesgo innecesario. Los diuréticos no previenen el desarrollo de toxemias del embarazo y no hay evidencia concluyente de que sean útiles en su tratamiento. Las tiazidas cruzan la barrera placentaria y aparecen en la sangre del cordón umbilical existiendo un riesgo de ictericia neonatal, trombocitopenia y otros posibles efectos adversos. **8. Reacciones secundarias y adversas:** Sistema gastrointestinal: Anorexia, irritación gástrica, náuseas, vómito, diarrea y muy ocasionalmente pancreatitis y sialoadenitis. Sistema Nervioso Central: Mareos, vértigo, parestesias y cefaleas. Hematológicos: Leucopenia, neutropenia/agranulocitosis, trombocitopenia, anemia aplásica y anemia hemolítica. Cardiovasculares: Hipotensión ortostática, vasculitis. Hipersensibilidad: Púrpura, fotosensibilidad, erupción cutánea, urticaria, fiebre y reacciones anafilácticas. Renales y urinarias: Disfunción renal y nefritis intersticial. Otros: Hiperglucemia, glucosuria, hiperuricemia, espasmo muscular, debilidad, inquietud, visión borrosa transitoria, calambres. **9. Interacciones medicamentosas y de otro género:** cuando se administran en forma conjunta otros fármacos puede ocurrir interacción con diuréticos tiazídicos como ROFUCAL®. **Alcohol, barbitúricos o narcóticos:** Puede haber aumento de la presión ortostática. **Aminas presoras:** Puede disminuir la respuesta a las aminas presoras, pero no lo suficiente como para no utilizarlas. **Anfotericina B, corticoesteroides o corticotropina:** Pueden intensificar el desequilibrio hidroelectrolítico, hipocalemia especialmente. **Anticoagulantes orales:** Pueden disminuir los efectos anticoagulantes. **Agentes antiinflamatorios no esteroideos:** Éstos pueden disminuir el efecto diurético. **Colestiramina y colestipol:** Retardan la absorción de ROFUCAL®. **Glucósidos digitálicos:** La hipopotasemia o la hipomagnesemia inducida por tiazidas favorece la aparición de arritmias cardiacas inducidas por digital. **Hipoglucemiantes orales e insulina:** Puede requerirse ajuste de la dosis de antidiabéticos. **Litio:** Los diuréticos disminuyen la depuración renal de litio y aumentan el riesgo de toxicidad. **Medicamentos para la gota:** La hidroclorotiazida puede aumentar el nivel de ácido úrico sérico. **Otros antihipertensivos:** Efecto aditivo o potencializante de sus efectos. **Sales de calcio:** Los diuréticos tiazídicos pueden incrementar los niveles séricos de calcio debido a la reducción de la excreción. **Probenecid o sulfinpirazona:** Se recomienda aumentar su dosis ya que la hidroclorotiazida puede tener efectos hiperuricémicos. **Relajantes no despolarizantes del músculo esquelético (ej. tubocurarina):** la hidroclorotiazida puede potenciar el efecto. **Ciclofosfamida, metotrexato:** Las tiazidas pueden reducir la excreción renal de los fármacos citotóxicos y potenciar su efecto mielosupresor. **10. Precauciones en relación con efectos de carcinogénesis, mutagénesis, teratogénesis y sobre la fertilidad:** estudios conducidos en animales no reportaron efectos carcinogénicos, mutagénicos así como tampoco alteraciones sobre la fertilidad a dosis terapéuticas. **11. Dosis y vía de administración:** ROFUCAL® se administra por vía oral. La dosis aplicada debe ser individual y acorde a la respuesta del paciente. ESQUEMA POSOLÓGICO DE ROFUCAL®. **Pacientes adultos con hipertensión arterial:** Inicio: 25 mg/día dosis única o repartida en varias tomas.*Ajustar la dosis según las cifras de tensión arterial. Máx: 50 mg diarios. **Pacientes adultos con edema:** 25 a 100 mg/día en una o dos tomas. Máx: 100 mg diarios.**

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*Algunos pacientes responden con una dosis inicial de 12.5 mg/día sola o combinada con otros antihipertensivos.

**Algunos pacientes responden al tratamiento intermitente (en días alternos o de tres a cinco días/semana).

Pacientes pediátricos con hipertensión arterial: Dosis pediátrica usual: 2.5 mg/kg/día en dos tomas. Lactantes <6 meses: hasta 3.5 mg/kg/día en dos tomas. Niños hasta 2 años: 12.5-37.5 mg/día en dos tomas. Niños 2-12 años: 37.5-100 mg/día en dos tomas. Muy pocos pacientes requieren de dosis altas sostenidas. **12. Manifestaciones y manejo de la sobredosificación o ingesta accidental:** además de la diuresis esperada, la sobredosis de ROFUCAL® puede producir grados variables de letargia, la cual puede progresar al coma en pocas horas con mínima depresión de las funciones respiratorias y cardiovasculares y sin evidencia de cambios en los electrolitos séricos o deshidratación. Además del lavado gástrico y del tratamiento de apoyo para el estupor o coma, puede ser necesario tratamiento de los efectos gastrointestinales. No se ha establecido claramente el grado en que la hidroclorotiazida es eliminada por hemodiálisis. Se debe mantener la hidratación y el equilibrio hidroelectrolítico, la respiración, las funciones cardiovascular y renal. **13. Presentaciones:** Caja de cartón con 15, 30 o 60 tabletas de 12.5 mg en envase de burbuja. Caja de cartón con 20 o 30 tabletas de 25 mg en envase de burbuja. **14. Leyendas de protección:** su venta requiere receta médica. No se deje al alcance de los niños. No se use durante el embarazo ni en mujeres en periodo de lactancia. Literatura exclusiva para médicos. Reporte las sospechas de reacción adversas al correo: farmacovigilancia@cofepris.gob.mx Para mayor información del producto o para reportar eventos adversos comuníquese al teléfono en la ciudad de México 4040-7671 0 LADA nacional sin costo al 01800-200-0170 o correo electrónico: farmacovigilancia@probiomed.com.mx **15. Nombre y domicilio del laboratorio:** PROBIOMED S.A. DE C.V. Yácatas No 307, Colonia Narvarte, Delegación Benito Juárez 03020 México, D.F. **16. Número de registro del medicamento ante la secretaría:** Reg. No. 74276 SSA IV.

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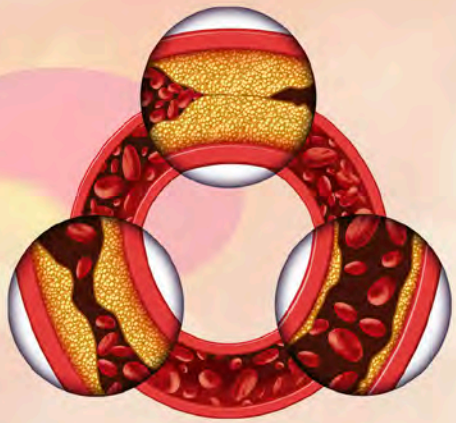

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Edema: 25 a 100 mg/día en una o dos tomas. **Dosis máxima:** 100 mg diarios.

*HTA: Hipertensión Arterial.

Referencias: 1. Bell K, *et al.* Hypertension: the silent killer: Updated JNC-8 Guideline Recommendations (2015). Alabama Pharmacy Association; 1:1-8. **2.** Información para prescribir amplia. Rofucal®. **3.** Uchiwa, H., Kai, H., Iwamoto, Y., Anegawa, T., Kajimoto, H., ... Fukuda, K. (2017). Losartan/hydrochlorothiazide combination is safe and effective for morning hypertension in Very-Elderly patients. Clinical and Experimental Hypertension, 40(3), 267–273.

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