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Editorial

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Message from the president of ANCAM

Mensaje del presidente de la ANCAM

Arturo Guerra-López*

Prevention is our goal, and medical education is our mission.
Arturo Guerra López, MD

To the motto of our Association, «Prevention is our goal», a second mandate could be added: «Medical education is our mission.» Both duties are parallel and complementary to the extent that the prevention path is paved by information and awareness. With the technological and scientific wealth on which modern cardiology is founded, and above the fine art of diagnosing and healing cardiovascular diseases (one of the scourges of contemporary humanity), prevention is the hallmark of today's medicine and tomorrow.

We are witnessing a renaissance of the old art of disease prevention, in our times solidly based on experimental basic and applied science, molecular biology, general and cellular physiology, pharmacology, and other disciplines. The technological and scientific spiral has, however, costly consequences. Rapid technological progress condemns many expensive machines to obsolescence quickly, impacting the health economy, mainly in poor or medium-developed countries like ours. On the other hand, the fast development of scientific knowledge demands a continuous reshaping of the diaphanous understanding of diseases and our clinical and therapeutic abilities. Therefore, all of us, the specialists and scientists positioned at the highest point of the professional pyramid, up to the base of it, made up of our esteemed colleagues, the family, and general and community physicians, must every day be depositories of continuous medical education.

Consequently, reinforcing our educational activities at all levels will be one of the primary purposes of the present presidency, through every known teaching strategy like thematic courses and conferences, workshops, symposia, web seminars, and educational materials aimed at raising and improving the knowledge and diagnostic, preventive, and curative skills of all levels of the cardiovascular care pyramid. The above, without letting aside a vast support and encouragement plan for clinical research based on the scientific method and the learning of those fundamental tools, biostatistics, and the fine art of writing a scientific article. Our *Casa del Corazón* (the Heart House) should be a valuable space to fulfill this ambitious plan. The sober but elegant and modern facilities, its location with easy access, and the capacity of its main auditorium make our *Casa del Corazón* the ideal place to organize, most of the year, all these cardiovascular and scientific education efforts. Of course, our regional meetings and the national congress will continue to be, as they are now, the forums for the timely review of the most critical issues in cardiology, as well as the form of personal bonding and the strengthening of the friendship that unites us.

I fraternally summon to those who accompany me on the Directive Board, to the colleagues' members of the Advisory Council and the Editorial Committee of our Journal, and to everyone in our Association to help to carry out this educational effort.

ANCAM has always been a democratic institution that is apolitical but open to all ideas, inclusive and humanist, punctually nationalist, but at the same time (and not paradoxically)

* President of ANCAM. Mexico.

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universal. In this context, we fraternally extend our hand to all other institutions and cardiovascular organizations so that with absolute equality, we form a single front that will help the Mexican State to confront decisively and head-on the cardiovascular and cardiometabolic flagella, the principal cause of death and disability in our country.

We can put in the intelligence, wisdom, will, enthusiasm, and time to carry out the preventive and educational tasks required by cardiovascular and cardiometabolic epidemics. Nevertheless, the three State branches (Executive, Judiciary, and Legislative), and the three levels of the Executive branch (federal, state, and municipal), must develop and execute the appropriate public policies to halt or ameliorate, at least, the epidemic impact of these terrible diseases. Only in this way will we lighten the disease burden of these maladies, one of whose etiopathogenic roots are unhealthy lifestyle habits.

Our Association, proudly, in an abridged length of time, has established itself as one of our nation's most comprehensive, representative, and potent medical congregations. I inherited a history of successes and achievements from those who preceded me in office. We need all of you to continue this impetuous march.

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ORIGINAL RESEARCH

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Factors associated with the survival of patients with implanted cardiac defibrillators in a cohort from Medellin, Colombia

Factores asociados a la supervivencia de pacientes portadores de cardiodesfibriladores en una cohorte de Medellín, Colombia

Jorge Enrique Sotelo-Narváez,* Luis Miguel Ruiz-Velásquez,‡
Julián Miguel Aristizábal-Aristizábal,§ Jorge Eduardo Marín-Velásquez,§ Juan Carlos Díaz-Martínez§

Keywords:
sudden cardiac death, implantable cardioverter defibrillators, cardiac pacing devices.

Palabras clave:
muerte súbita de origen cardiaco, cardiodesfibrilador implantable, dispositivos de estimulación cardiaca.

ABSTRACT

Introduction: sudden cardiac death accounts for 50% of cardiovascular deaths worldwide and 20% of mortality. The use of an implantable cardioverter defibrillator (ICD) is associated with the optimal management of cardiovascular diseases and positively impacts mortality. **Material and methods:** a retrospective cohort of 730 patients required an ICD and attended electrophysiology consultation in eight hospitals in Medellín, Colombia, between 2013 and 2020 and had a follow-up for at least six months with two controls. Adjusted and survival analyzes were performed. **Results:** 72% of patients were male. The most prevalent pathologies were arterial hypertension (71%) and dyslipidemia (46%). 56.7% of patients had ischemic heart disease. At the beginning of the follow-up, 72.9% had an ejection fraction (LVEF) of less than 35%, and echocardiographic follow-up found improvement in LVEF, less than 35% in 19.9%. 62.7% had an ICD for primary prevention, 20.3% received appropriate therapy due to ventricular tachycardia, and 11.2% and 14.7% had inappropriate therapy, usually caused by atrial fibrillation (8.5%). Survival analysis found that functional class NYHA III (HR 2.96, 95% CI 1.85-5.15), arterial hypertension (HR 2.182, 95% CI 1.23-3.86), inappropriate therapies, and age (HR 1.02, 95% CI 1.01-1.03) were associated with a significant decrease in survival in patients with an ICD. **Conclusion:** in this study, it was found that most of the patients were men, and the main indication of ICD was primary prevention. Age, NYHA III functional class, arterial hypertension, and inappropriate therapies were associated with a significant decrease in survival in patients with an ICD.

RESUMEN

Introducción: *la muerte súbita cardiaca representa 50% de las muertes de origen cardiovascular en el mundo y 20% de la mortalidad. El uso de cardiodesfibrilador implantable con el manejo óptimo de enfermedades cardiovasculares, impacta positivamente al reducir la mortalidad.* ***Material y métodos:*** *cohorte retrospectiva de 730 pacientes que requirieron un CDI y acudieron a consulta con electrofisiología en ocho hospitales en Medellín, Colombia, entre 2013 y 2020, que tuvieron al menos seis meses de seguimiento y dos controles. Se realizaron análisis ajustados de supervivencia.* ***Resultados:*** *eran hombres 72% de los pacientes, las patologías más prevalentes fueron hipertensión arterial (71%) y dislipidemia (46%); 56.7% tenían cardiopatía isquémica, al inicio del seguimiento 72.9% tenían una fracción de eyección (FEVI) inicial menor de 35%; al seguimiento ecocardiográfico se demostró una mejoría de la FEVI, que era menor a 35% en 19.9%. Tenían CDI por prevención primaria 62.7%, tuvieron una terapia 20.3%, usualmente taquicardia ventricular (11.2%) y presentaron alguna terapia inapropiada 14.7%, mayormente por fibrilación auricular (8.5%). El análisis de supervivencia encontró que la clase funcional NYHA III (HR 2.96, 95% IC 1.85-5.15), la hipertensión arterial (HR 2.182, 95% IC 1.23-3.86), las terapias inapropiadas y la edad (HR 1.02, 95% IC 1.01-1.03), se asociaron a una disminución significativa de la supervivencia.* ***Conclusión:*** *en este estudio se encontró que la mayoría de los pacientes eran hombres, la principal indicación fue por prevención primaria. La edad, clase funcional NYHA III, la hipertensión arterial y haber presentado terapias inapropiadas, se asociaron a disminución significativa de la supervivencia en pacientes portadores de un CDI.*

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INTRODUCTION

Sudden cardiac death (SCD) is the death of a cardiovascular cause, occurring less than one hour from the onset of symptoms when it is witnessed. Alternatively, unexpected death of cardiovascular cause in an individual who was observed to be alive 24 hours prior. SCD accounts for 50% of deaths of cardiovascular origin worldwide and about 20% of mortality in the general population.[1]

Appropriate therapy is a shock triggered by an episode of ventricular tachycardia or ventricular fibrillation. An inappropriate therapy is a shock triggered erroneously by another arrhythmia, whether it be sinus tachycardia, supraventricular tachycardia, or excess sensor sensitivity.

Using an implantable cardioverter defibrillator (ICD) with other pharmacological therapies has become a fundamental strategy for preventing SCD.[2-4] Although the most frequent indication for these devices worldwide is primary prevention,[5] in Latin America, secondary prevention is the predominant indication, with a low rate of inappropriate therapies and a mortality rate similar to the reported in the world literature.[6]

In 2018, Aristizábal et al. published a study about the prognostic impact of defibrillator shocks in a Colombian cohort showing that mortality was 12.8%, being 1.8 times higher in patients with ischemic heart disease, who likewise had a 65% higher risk of appropriate therapies, compared to non-ischemic heart disease.[7]

There are no extensive studies or registries documenting the main risk factors associated with survival in patients with cardioverter defibrillator implantation.

This study aims to follow up on this initial cohort of patients with cardioverter defibrillators and determine survival and associated factors in high complexity centers in the city of Medellín.

MATERIAL AND METHODS

A retrospective cohort of 730 patients with cardiomyopathy (of varied etiology) was carried out. The patient had a high risk of sudden death, required an ICD or cardiosynchronizer implantation, and attended the electrophysiology consultation. The follow-up was performed in eight different centers in Medellín, Colombia, between 2013 and 2020. Patients had a clinical and device six months follow-up with two controls. Patients without complete clinical history were excluded from the study.

Each follow-up appointment was performed by at least one teaching electrophysiologist accompanied by at least one electrophysiology resident. At the end of the consultation, an online data record was made in Google Drive.

All the information was obtained by review of medical records and complemented by telephone calls or an additional appointment for review if it was required. Calls and national death databases established the mortality of patients not attending rescheduled appointments.

The main objective of this study was to evaluate the survival, and related factors of patients with ICD attended in several clinics in the city of Medellin by the CES electrophysiology group between 2013 -2020.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range according to the normal distribution, and categorical variables as absolute numbers and percentages.

A univariate analysis was performed to characterize the study population. The nature of the variables was considered; in the case of quantitative variables, the Kolmogorov-Smirnov normality test was performed to define whether the quantitative variables are presented with averages or medians.

For the bivariate analysis, the associations with respect to survival were calculated independently for each factor. The Chi-square test of independence was used for qualitative variables, and for quantitative variables, the t of Students Test or Mann-Whitney U test (quantitative-qualitative) was used.

ORs and 95% confidence intervals were also calculated from binary logistic regression.

Differences in survival according to covariates were calculated with the Log Rank test.

The association between covariates and time-to-event presentation was calculated

using COX regression. A p-value of less than 0.05 was considered statistically significant. All analyses were performed with the software SPSS version 25.

RESULTS

This study included 730 patients with a mean age of 63 years. The youngest patient at the time of implantation was 16 years old, and the oldest was 90 years old. The characteristics of the population are described in *Table 1*.

Table 1: Socio-demographic characteristics.

Age (Mean ± SD)	
Male	63.6 ± 11.91
Female	62.1 ± 13.95
Gender (%)	
Male	72.5
Female	27.5
Comorbility (%)	
Arterial hypertension	71.1
Diabetes mellitus	24.0
Chronic kidney disease	12.5
Hypothyroidism	23.2
Dyslipidemia	46.3
Chronic obstructive pulmonary disease	12.9
Coronary artery bypass graft surgery	7.8
NYHA (%)	
I	40.7
II	41.5
III	13.6
IV	0.5
Ischemic cardiomyopathy	56.7
Non ischemic dilated cardiomyopathy	43.3
First LVEF (%)	
< 35	72.9
> 35	27.0
LVEF control < 35	19.9
Secondary prevention	37.3
Primary prevention	62.7
Appropriate therapy	20.3
Inappropriate therapy	14.7
Electrical storm	3.6
Death	23.5
Complications	15.1

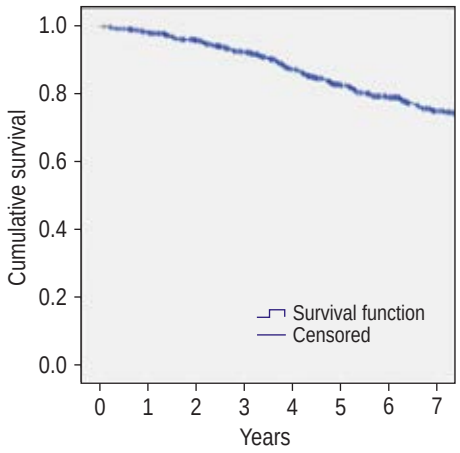

Figure 1: Kaplan Meier survival curve in patients with implanted cardioverter defibrillator implantation.

72% of patients were male, and the most prevalent pathologies were arterial hypertension (71%) and dyslipidemia (46%), while 24% of the patients had diabetes mellitus, 13% had chronic obstructive pulmonary disease, and 12% had chronic kidney disease.

Additionally, 364 patients (56.7%) had ischemic heart disease, of which 57 (8.1%) were surgically revascularized. 72.9% had an initial ejection fraction (LVEF) less than 35%, and 15% had LVEF greater than 50%; echocardiographic follow-up showed an improvement in LVEF less than 35% in only 19.9% of patients. 40% of patients were New York functional class (NYHA) I, 41% were NYHA II, and only 0.5% were NYHA IV.

62.7% of the patients had an ICD implanted for primary prevention. 20.3% of patients had appropriate therapy, in most cases for ventricular tachycardia (11.2%). 14.7% of the patients presented inappropriate therapy; the most frequent cause was atrial fibrillation (8.5%), followed by supraventricular tachycardia other than AF in 3.8%, noise 1.2%, electrode dysfunction 0.7%, and overdetection 0.3%. The electrical storm was detected in 3.6% of the study population, defined as 3 ICD discharge therapies in 24 hours.

Kaplan-Meier curves show the cumulative survival in the follow-up of patients; total mortality was 23.5%. *Figures 1, 2 and 3* show

the Kaplan-Meier curves of inappropriate therapy and arterial hypertension, respectively.

86.6% of patients did not present any complication associated with device implantation. Among those that did occur, the most frequent was electrode displacement (9.3%), followed by infection (1.8%) and hematoma (0.4%).

In the bivariate analysis, age, presence of hypertension (p = 0), NYHA functional class III (p = 0), inappropriate therapy (p = 0.046), and presented electrical storm (p = 0.049) were significantly associated with decreased survival.

Other variables, such as sex (p = 0.34), diabetes mellitus (p = 0.36), and dyslipidemia (p = 0.35), had no direct association.

Multivariate survival analysis was performed using the Cox Proportional Hazards Model. NYHA functional class III (HR 2.96, 95% CI 1.85-5.15), the presence of arterial hypertension (HR 2.182, 95% CI 1.23-3.86), and age (HR 1.02, 95% CI 1.01-1.03) were associated with decreased survival in patients with ICD *(Table 2)*.

DISCUSSION

Sudden cardiac death is responsible for 50% of deaths of cardiovascular origin worldwide[3,4,8] and about 20% of mortality in the general population.[1] ICD, in conjunction with

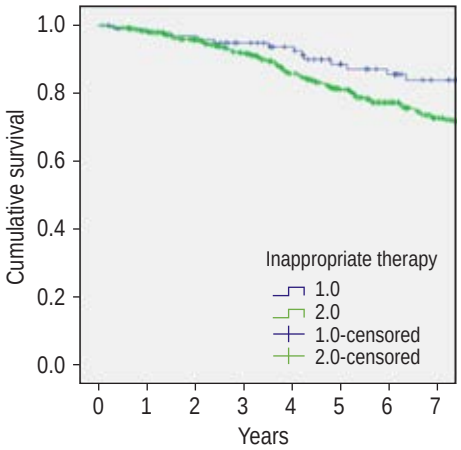

Figure 2: Kaplan Meier survival rate in patients with inappropriate implanted cardioverter defibrillator therapy.

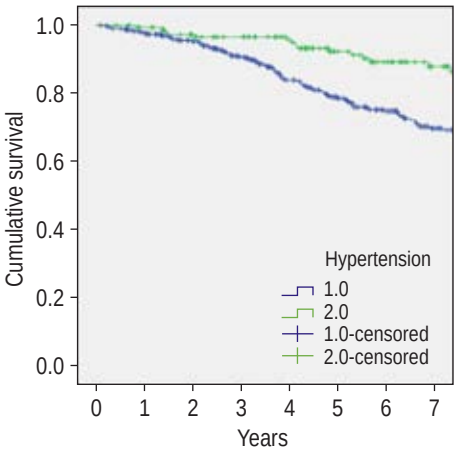

Figure 3: Kaplan-Meier survival rate in patients with arterial hypertension and implanted cardioverter defibrillator implantation.

pharmacological and non-pharmacological treatment, has been shown to decrease mortality related to sudden cardiac death.[9] In Colombia in 2018, Aristizábal et al. published a study about the prognostic impact of defibrillator shocks in a Colombian cohort, showing that mortality was 12.8%, being 1.8 times higher in patients with ischemic heart disease, who also had a 65% higher risk of appropriate therapies, compared to non-ischemic heart disease.[7]

In this study, the most frequent indication for implantation was primary prevention in patients with ischemic heart disease in 62% of cases, similar to what is reported in the world literature. Welsenes et al. published a long-term follow-up study of patients with implantable cardioverter defibrillators in primary and secondary prevention. 1302 (61%) patients received an ICD for primary prevention of sudden cardiac death and 832 (39%) patients for secondary prevention.[5]

In addition, we found that arterial hypertension was the most prevalent pathology in patients with ICD, regardless of their indication, and was the one most associated with decreased survival. Several studies have described hypertension as a recognized risk factor for sudden cardiac death.[10-12] A prospective study of 7,746 patients in Paris, France, found that the presence of arterial hypertension, and more specifically elevated systolic blood pressure, had an RR of 1.23

(1.02-1.46) for sudden cardiac death and an RR of 0.02-1.37 (1.19-1.56) for fatal acute myocardial infarction.[13]

At follow-up, it was found that 20.3% of the patients had appropriate therapy, in most cases due to ventricular tachycardia (11.2%). 14.7% of the patients had some inappropriate therapy. The most frequent cause was atrial fibrillation (8.5%), which was associated with increased mortality in our study. Although it is known that the presence of inappropriate therapies leads to significant myocardial injury, the increase in mortality is not so clear in the literature. Studies show that inappropriate therapies correlate with deterioration in the quality of life and increased mortality.[5,14] However, other recent studies have found no relationship between the presence of inappropriate therapies and mortality.[15,16]

The electrical storm was detected in 3.6% of the patients and was associated with a significant decrease in survival. These data correlate with those of different published studies. The MADIT II trial on ischemic heart disease as a primary prevention strategy reported an incidence of electrical storms of 4%.[17]

On the other hand, the complications inherent to implantation are a reality. The rate of complications reported for any adverse event varies between 12.4 to 22% for primary prevention studies and 8.0 to 22.8% for secondary prevention studies.[18] In this study, 13.4% of patients presented complications, with electrode displacement being the most frequent, representing 69% of all complications reported. Other complications, such as hematoma and pocket infection, were equally or less frequent than those found in the world literature.[19]

Table 2: Cox regression.

Characteristic	Hazard ratio	CI 95%	p
Age	1.02	(1.01-1.03)	0.028
Arterial Hypertension	2.182	(1.23-3.86)	0.007
NYHA (Class)			
I	Reference group		
II	1,25	(0.78-1.92)	0.349
III	3,095	(1.85-5.15)	0.000
IV	2,961	(0.401-21.87)	0.287

CONCLUSIONS

In this study of 730 patients followed for seven years, it was found that the main indication for ICD implantation was primary prevention for ischemic heart disease. The vast majority of patients had LVEF of less than 35% at the time of implantation. It showed marked improvement during follow-up, probably related to revascularization therapies and optimal medical management.

Age, arterial hypertension, functional class, electrical storms, and inappropriate therapies were associated with significantly decreased survival. Optimal pharmacological and non-pharmacological treatment of cardiovascular risk factors in patients with ICD positively impacts survival and should always be considered during device evaluation.

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Cardiac amyloidosis with acute heart failure as a clinical presentation

Amiloidosis cardiaca con falla cardiaca aguda como presentación clínica

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Keywords: amyloidosis, infiltration, acute heart failure, echocardiography, case report.

Palabras clave: *amiloidosis, infiltración, falla cardiaca aguda, ecocardiografía, reporte de caso.*

ABSTRACT

Amyloidosis is a deposit disease, in which a specific protein precursor inadequately folds from its tertiary structure to a flatter one, generating multisystemic deposits that affect the organs' function. A non-systematic review of the literature was performed, and multiple reports of cardiac amyloidosis in the American and European populations were found. However, no cases of cardiac amyloidosis with acute heart failure were exhibited in elderly patients in Latin America. The case of an elderly patient who debuted with acute heart failure in which cardiac compromise due to amyloid deposits was evidenced is presented below. Clinical suspicion is fundamental, as cardiovascular involvement has increased in frequency in recent years, and a timely diagnosis often determines the prognosis.

RESUMEN

La amiloidosis es una enfermedad de depósito, donde un precursor proteico específico se pliega inadecuadamente desde su estructura terciaria a una de forma más plana, generando depósitos multisistémicos que comprometen la función de múltiples órganos. Se realizó una búsqueda no sistemática de la literatura, encontrando múltiples reportes de amiloidosis cardiaca en población estadounidense y europea, pero no se encontraron reportes de caso de amiloidosis cardiaca como presentación aguda de falla cardiaca en paciente anciano en Latinoamérica. Se presenta el caso clínico de una paciente de edad avanzada, quien debuta con falla cardiaca aguda de novo donde se pudo evidenciar un compromiso cardiaco por depósitos amiloides. La sospecha clínica es fundamental, ya que el compromiso cardiovascular ha aumentado en frecuencia en los últimos años, y un diagnóstico oportuno muchas veces determina el pronóstico.

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INTRODUCTION

Amyloidosis corresponds to a group of diseases in which there is an extracellular tissue deposition of fibrillar proteins called amyloids, which originated from an alteration in the folding of specific protein precursors. Amyloidosis ends up infiltrating and damaging the function of various organs such as the kidneys, liver, nervous system, and heart. When it invades the myocardium, it can compromise ventricular function (initially with diastolic dysfunction) and the conduction system, leading to a poor prognosis for the patient.[1]

In a non-systematic search of the literature using the terms «amyloidosis», «cardiac» and «compromise» in PubMed with the Mesh Terms: Heart and Amyloidosis, multiple reports of cardiac amyloidosis in American and European populations were found, but there were no case reports of cardiac amyloidosis, as an acute presentation of heart failure, in elderly patients in Latin America. However, here is a case of an elderly patient who debuted with de novo acute heart failure. Amyloid deposits were documented without other etiologies that explained her acute decompensation.

CASE PRESENTATION

A 76-year-old female patient with a history of arterial hypertension and difficult-to-manage

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atrial fibrillation (AF), anticoagulated with rivaroxaban, was admitted to the institution for 1-month for moderate dyspnea (mMRC 4) with decreased functional class, paroxysmal nocturnal dyspnea, orthopnea, bendopnea, lower limb edema grade III. With no history of ischemic heart disease, on physical examination with normal blood pressure and preserved ventricular function.

The patient first received symptomatic treatment with diuretics for dyspnea. An electrocardiogram (EKG) *(Figure 1)* and transthoracic echocardiogram *(Figure 2)* were performed for diagnosis.

The EKG showed Q waves in precordial leads from V1 to V4 with associated low voltage. The echocardiography showed a left ventricular ejection fraction (LVEF) of 48%, grade II diastolic dysfunction, biauricular dilatation, and ventricular hypertrophy with a septal predominance (thickness of 16 mm). Those characteristics are related to restrictive heart disease. In addition, an increase in cardiac tissue refringence was evidenced; there was not a specific strain pattern reported by the echocardiography. Other laboratory tests were normal, such as hemoleukogram, electrolytes, renal function, thyroid function, and glycemia.

Given these clinical and paraclinical findings, the Cardiology and Hemodynamics services decided to perform coronary arteriography to rule out coronary ischemic disease. Coronary arteries without significant obstructive lesions were reported. With this new information and associated with the EKG and echocardiography findings, an endomyocardial tissue biopsy was performed. The results showed positivity for red congo and apple-green birefringence with polarizing light, confirming the involvement of amyloid deposition. In an effort to define the extent of cardiac involvement, cardiac magnetic resonance imaging (MRI) was requested, but unfortunately, the patient's clinical condition worsened, and she died after the diagnosis was established.

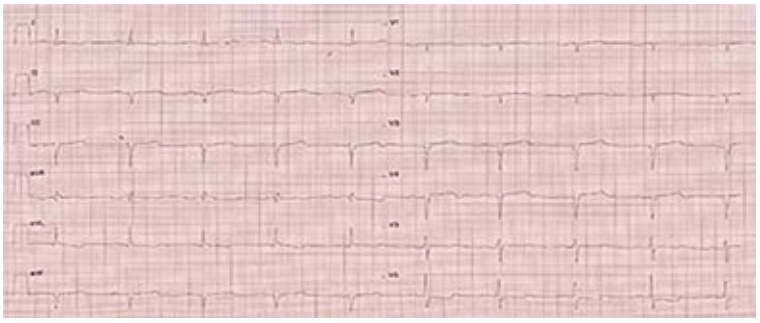

Figure 1: Electrocardiogram with the low-voltage QRS complex. Q waves in precordial leads simulating an old anteroseptal acute myocardial infarction (AMI).

DISCUSSION

Amyloidosis with cardiac involvement is divided into two main types that account for 95% of all cases. Amyloid light-chain or primary amyloidosis (AL amyloidosis) is explained by a clonal alteration of plasma cells due to the overproduction of light chains. On the other hand, Transthyretin Amyloidosis (ATTR) is produced by the misfolding of the hepatic protein transthyretin and can be acquired senile (ATTRwt) or hereditary (hATTR).[2] The prevalence of this pathology is relatively low, or it is underdiagnosed since deposits of the senile form have been found in up to 25% of older patients, most of whom are asymptomatic.[3] This prevalence has been increasing over the years due to the development of better diagnostic methods, greater knowledge of the disease, and a bigger number of patients (greater aging of the population).

Clinical diagnosis is not easy because of the wide spectrum of clinical presentations. Amyloidosis is usually presented as heart failure with preserved ejection fraction, dyspnea associated with exercise, AF, left branch bundle block, cerebrovascular events, or symptoms of right heart failure such as lower limb edema and ascites.[4] Paraclinical tests are fundamental; EKG shows lower voltage QRS complex or pseudo-infarction patterns, as reported, to confirm the diagnosis. AF may also be evidenced, which is relatively common, with a prevalence of 10 to 20% and significant morbimortality.[5]

The cornerstone in the diagnosis of amyloidosis is echocardiography. It provides characteristic patterns: concentric growth of the left ventricle with a more echogenic appearance than in patients with true hypertrophy. This is generated because amyloid deposits produce enlargement of the interventricular septum

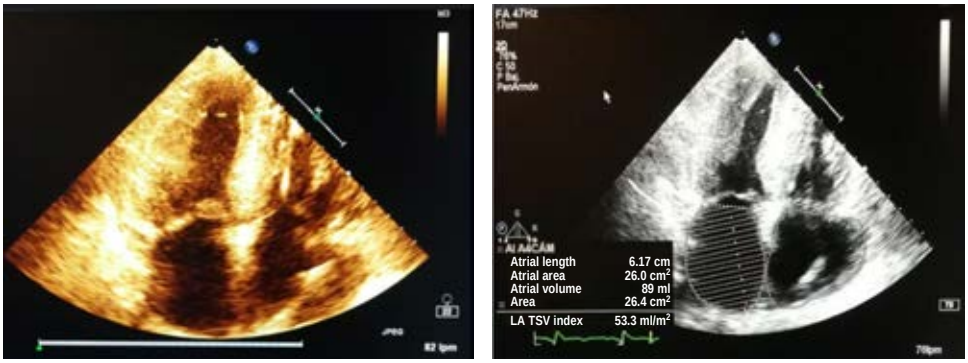

Figure 2:

Transthoracic echocardiogram. Apical four-chamber view showing left ventricular hypertrophy and left atrial enlargement.

of more than 12 mm and give a granular appearance to the myocardium.[6] As for the atria, a restrictive component can be appreciated with enlargement of chambers, contractility dysfunction in the absence of the transmitral A wave, and the tissue Doppler A wave in patients with sinus rhythm, in addition to an increased ventricular E/e ratio indicating an elevated ventricular pressure.[7] It should be emphasized that the Doppler findings depend on the patient's stage, demonstrating progressive infiltration in accordance with diastolic dysfunction.[8] The regional Strain is also an invaluable help since it has characteristics only seen in a few pathologies. The amyloidosis case is presented as a global compromise that preserves the apical zone in the bull's eye or Japanese flag.[9]

In the case described, several elements led to suspicion of cardiac amyloidosis, such as low-voltage QRS complexes, ventricular thickening with septal predominance, and increased echogenicity of the left ventricle. Unlike hypertrophic cardiomyopathy, which generates high voltages, amyloidosis infiltration generates low voltage.

Other imaging methods can be very useful, such as cardiac MRI, which shows diffuse late gadolinium enhancement in the subendocardium that does not follow the coronary distribution and has a sensitivity of 93%. Another imaging- resource is cardiac scintigraphy with Tc99m. It is a less invasive study compared to endomyocardial biopsy, which requires the injection of a radiotracer. Once injected, it binds to TTR amyloid fibrils, which is useful to differentiate between the different types of amyloidosis, showing intense marking in ATTR amyloidosis and none in AL.[3] Therefore, it is useful to differentiate ATTR from AL cardiac amyloidosis when a monoclonal protein is not identified by serum kappa/lambda free light chain ratio analysis or serum or urine protein immunofixation. A patient with strongly positive radionuclide imaging, associated with an absence of a plasma cell dyscrasia, is highly specific for ATTR cardiac disease, so tissue biopsy is not required.[10]

Confirming the diagnosis is with an endomyocardial biopsy, which is 100% sensitive. In this case, given the suspicion of cardiomyopathy of unknown origin. In the context of heart failure with echocardiographic signs of restriction and coronary angiography without lesions, it was decided to perform the procedure, which helped to establish the diagnosis. The biopsy result is also relevant because it differentiates amyloidosis from other types of infiltrative diseases and the specific type of amyloidosis, each with a specific treatment and prognosis.[11] There is also the possibility of performing a biopsy of other tissues, such as the subcutaneous fat of the abdominal wall. Nevertheless, this has a low sensitivity (14%) in ATTRwt amyloidosis, which can lead to false negatives.[3]

In patients diagnosed with cardiac ATTR amyloidosis, noninvasive sequencing of the TRR gene is useful for discriminating between wtATTR and hATTR. It is used in patients diagnosed with cardiac ATTR amyloidosis. Thus, diagnosis of hATTR allows for genetic counseling and disease-specific treatment.[12] However, it was not performed because our patient had already died.

In the case described, no other triggers for acute decompensation were found. The blood

pressure was controlled. The ventricular rate was normal, no ischemic cause was found, and there were no associated infections. The patient had good adherence to medical treatment, the paraclinical tests did not show metabolic alterations, and there was no different valvular or mechanical dysfunction that would explain the symptoms; thus, amyloidosis is attributed to the causal link of acute heart failure in this patient.

The main treatment and prognosis depend directly on the type of amyloidosis; thus, AL amyloidosis has a haemato-oncology-directed treatment with specific chemotherapeutics and usually has a worse prognosis.[13] On the other hand, ATTR amyloidosis is based on the management of heart failure with emphasis on the treatment of water overload, in addition to new therapies aimed at blocking or stabilizing the transthyretin tetramer or clearing the amyloid fibers. Recently, Tafamidis has shown a decrease in cardiovascular hospitalizations, 30-day mortality, and functional decline. The incidence of adverse events is similar in the tafamidis and placebo groups.[14] It stabilizes transthyretin tetramer by binding to the thyroxine-binding site of TTR tetramer and preventing dissociation of TTR tetramer into monomers, thus reducing TTR amyloid.[15]

For the treatment of hereditary TTR amyloidosis, new therapies have been released. Among these new therapies are ribonucleic acid (RNA)-targeted therapies that interfere with hepatic TTR synthesis (patisiran, inotersen, and vutrisiran). Diflunisal is a nonsteroidal anti-inflammatory drug that can stabilize the TTR tetramer in vitro and may prevent the formation of amyloid deposits in the heart.[16] Patisiran is approved for the treatment of peripheral nerve disease caused by hereditary transthyretin amyloidosis, and it may halt the progression of the cardiac manifestations of hATTR.[17] Inotersen is indicated for polyneuropathy of hATTR and benefits have also been shown for amyloid cardiomyopathy.[18] Organ transplantation is a definitive treatment option for patients with severe cardiac amyloidosis. Heart and liver transplantation has been used to treat hATTR; for AL amyloidosis, a heart transplant is recommended.[12]

Other authors, such as Bodard et al. in France, Franco et al. in Barcelona, and Fernandes et al. in Portugal report cases of acute heart failure due to amyloidosis similar to this one. They report elderly patients (93, 90, and 78 years old, respectively) with acute congestive heart failure symptoms and electrocardiographic and echocardiographic findings like this one, in whom amyloidosis was found by a salivary gland or subcutaneous fat biopsy.[19-21] The case's novelty is that no similar cases were found in Latin American populations.

CONCLUSIONS

Amyloidosis is an underdiagnosed multisystemic pathology due to its wide range of symptoms. We present a case of an elderly patient who debuted with acute heart failure. Amyloid infiltration was documented in echocardiography and endomyocardial biopsy. It is essential to make a timely diagnosis to offer specific treatment, especially in ATTR, since when this is associated with cardiac involvement, it has a worse prognosis.

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Restrictive cardiomyopathy in a paediatric patient: a case report

Miocardiopatía restrictiva en un paciente pediátrico: un reporte de caso

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Keywords:
restrictive cardiomyopathy, TNNI3 gene, diastolic heart failure, atrial remodeling.

Palabras clave:
miocardiopatía restrictiva, Gen TNNI3, insuficiencia cardiaca diastólica, remodelación atrial.

ABSTRACT

Restrictive cardiomyopathy is characterized by a severe diastolic impairment with a normal systolic function. It is the least common of all cardiomyopathies among paediatric patients. Restrictive cardiomyopathy has a poor prognosis and commonly requires a cardiac transplant. We present a case of a 12-year-old patient with four months history of heart failure symptoms and first-degree family history confirmed heterozygous mutation in the TNNI3 encoder. This paper is presented to emphasize the importance of genetic studies in families who have different cardiac phenotypes.

RESUMEN

La miocardiopatía restrictiva se caracteriza por una afectación diastólica severa acompañada de una función sistólica normal. Es la miocardiopatía menos común en la edad pediátrica. La miocardiopatía restrictiva tiene un pronóstico pobre y comúnmente requiere trasplante cardiaco. Presentamos el caso de una paciente de 12 años, con historia de cuatro meses de sintomatología de fallo cardiaco y un familiar de primer grado con mutación heterogenética del gen TNNI3 confirmada. Este artículo pretende enfatizar la importancia del estudio genético en familiares que tienen diferentes fenotipos cardiacos.

INTRODUCTION

Restrictive cardiomyopathy (RCM) is a heart muscle disease that leads to diastolic dysfunction with preserved systolic function in the early stages. The cardiac muscle is affected by abnormal stiffness affecting the ventricle; this leads to increased diastolic pressure in the atrium, causing hypertrophy.[1] RCM represents approximately 2.5-5% of all cases of cardiomyopathies in children. RCM is the least common of three original subtypes of cardiomyopathies: hypertrophic, dilated, and restrictive. The etiology is considered idiopathic. However, with recent advances in genetics, it has been found that sarcomere genes may play an essential role in its genesis.[2] Other possible infiltrative diseases have been identified in adults (Amyloidosis, Sarcoidosis, Hereditary Haemochromatosis, and Fabry's disease).[3]

The phenotype of the condition can manifest in first-degree relatives with different modes of inheritance. There have been reports of autosomal dominant (most common form), autosomal recessive, X-linked, and mitochondrial modes of inheritance. The different phenotypes and modes of inheritance encourage diagnostics screening and diagnosis during genetic counseling for families with members known to have the condition.[4,5] Therefore, the collaboration between cardiology clinicians and geneticists is essential for correctly diagnosing and treating these patients. The American College of Medical Genetics and Genomics (ACMG) recommends the study of 59 genes related to phenotypic manifestations of cardiomyopathies.[6] The best-described genes in the genesis of RCM are DES, TTR, TNNI3, TNNT2, MYH7, TPM1, FLNC, GLA, MYBPC3, ACTC1, MYL2, and MYL3.

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Because of the genetically monogenic disease characteristic, RCM can manifest with at least one of the genes mentioned above.[4]

The TNNI3 gene encodes subunit I of cardiac troponin. This protein uses intracellular calcium as a sensor regulating the interaction between thick and thin myofilaments. Subunit I is responsible for the inhibitory function of the protein. It prevents the interaction of Actin and Myosin in the absence of Ca^{2+}. The malfunction of this subunit produces alterations in Ca^{2+}, leading to stiffness of the ventricle.[7]

Clinically, patients can report shortness of breath, chest pain, fatigue, and lower limb edema. On examination, patients can present with an S4 gallop rhythm on auscultation, pulmonary crackles, and wheezing. Thorax X-rays can show atrial hypertrophy and pulmonary congestion. The ECG can be abnormal in most cases with wide P waves, conduction disturbances, and ventricular repolarization due to branch involvement, leading to AV blocks. Echocardiography reveals a variable degree of bilateral atrial hypertrophy and significant diastolic dysfunction. Tricuspid and mitral regurgitation are common findings. There are no defined diagnostic criteria for RCM in children; however, the left atrium size is often used as a reference for diagnosis. Some guidelines recommend additionally measuring the mitral valve E/A ratio, which is > 2 in advanced diastolic dysfunction stages. Cardiac MRI may be a diagnostic alternative to demostrate the atrial cavity and ventricular myocardial enlargement of the atrial cavity due to infiltrative diseases; therefore, it is usually more helpful in adults than children.[8-10]

Treatment is aimed at secondary causes when present. In adults, the treatment objective is to reduce the protein production that affects the myocardium in cases where genetic disorders cause RCM and supportive measures until cardiac transplantation is possible. Loop diuretics and aldosterone inhibitors are preferred over other antihypertensive medications such as ACE inhibitors and ARBs. They are not well tolerated because of their hypotensive effect. Creatinine and electrolytes must be monitored during their use.

Additionally, β-blockers and calcium antagonists are not commonly indicated because they may reduce the heart rate affecting the optimal cardiac output for patients with normal heart rates. However, they can be used in some presentations. Digoxin's use is limited for tachyarrhythmias management because the preserved systolic function may lead to digitalis intoxication. Amiodarone may be considered for this function.[3,9] RCM has a poor prognosis, the worst among all myocardiopathy. Studies show that patient mortality after diagnosis 2-3 years without cardiac transplantation is 50 and 75% at five years.[8,10]

CASE PRESENTATION

A 12-year-old Honduran patient with no previous medical history was admitted with a one-day history of hemoptysis associated with a 4-month background of non-productive cough, shortness of breath, and palpitations. The patient seemed to have low weight for her age and appeared chronically ill on examination. The physical examination revealed a height of 154 cm and a weight of 35.45 kg for a body surface of 1.23 m^2. An abdominal examination revealed hepatomegaly, but the rest of the physical examination was unremarkable. Family history revealed that her half-sister had been diagnosed with hypertrophic cardiomyopathy at the age of 15.

One of the first-degree relatives of the patient had genetic investigations which reported a heterozygous mutation in gene TNNI3, classified as a variant of uncertain significance associated with Dilated cardiomyopathy 2A (OMIM:611880), Dilated cardiomyopathy 1FF (OMIM: 613286), Restrictive cardiomyopathy familial 1 (OMIM: 115210), Hypertrophic cardiomyopathy 7 (OMIM: 613690), all of which have an autosomal dominant inheritance pattern. A diagnosis of cardiomyopathy was suspected due to the clinical presentation and family history. Findings in the initial chest X-ray *(Figure 1)* revealed cardiomegaly, bilateral atrial enlargement, and pulmonary congestion, and those on the ECG *(Figure 2)* showed a sinus rhythm, bilateral atrial enlargement, and right ventricle strain supported the suspected diagnosis. The echocardiogram *(Figure 3)* confirmed the bilateral atrial dilation (LA; 34.8 cm^2, RA: 34.1 cm^2), an E/A ratio

greater than 2, and a PSAP of 47 mmHg, and a left atrial volume of 154 cm^3. Using the recommendations for chamber quantification by the European Society of Cardiology, those values were classified as severely abnormal as the atrial volume was above 73 mL. Therefore, indicating severe damage to the left atrium. Abdominal ultrasound confirmed hepatomegaly with dilation of suprahepatic veins. PCR SARS-CoV-2 was negative.

Figure 1: Image corresponding to chest X-ray on arrival. Cardiomegaly with notable biatrial hypertrophy and pulmonary venous congestion.

Figure 2: Electrocardiogram on arrival. Sinus tachycardia and bi-atrial enlargement.

After considering the patient's history, physical examination, and investigation results, the parent team concluded that the patient was suffering from restrictive cardiomyopathy. Genetic investigations were considered to confirm the mutation present, but this was not pursued due to the difficult access and elevated cost of the test in the country. As part of the initial management, we started furosemide 20 mg IV TDS, Spironolactone 25 mg PO OD, Enalapril 5 mg PO BD, and Aspirin 100 mg PO OD. After discharge, the patient had another admission due to persistent symptoms and hyponatremia. The patient's medications were adjusted during the second admission, and new ones were added (Furosemide 40 mg PO TDS, Bisoprolol 2.5 mg PO OD, Amlodipine 2.5 mg daily PO OD). Unfortunately, given the poor clinical response to medical treatment, a cardiac transplant has been considered the best treatment option. However, Honduras has no access to public or private transplant services.

DISCUSSION

In Honduras, a developing country, most investigations for these cardiovascular conditions are difficult to access. This case is of a 12-year-old female with a reserved prognosis due to a poor response to medical treatment. The patient should undergo a heart transplant as soon as possible, but unfortunately, there are no private or public transplant services in Honduras. The family history of a 21-year-old maternal sister with a known diagnosis of hypertrophic cardiomyopathy with a TNNI3 gene mutation represents an essential aspect of this case, helping establish a clinical diagnosis in the absence of available genetic investigations.

The TNNI3 gene mutation has been associated with hypertrophic, dilated, and restrictive cardiomyopathy *(Table 1)*.[11] Although our patient lacks genetic investigation due to financial limitations, the mode of inheritance (autosomal dominant inheritance mainly, but autosomal recessive, X-linked, and mitochondrial-transmitted disease can occur),[12] clinical presentation, and echocardiogram findings helped conclude the diagnosis. Echocardiograms are essential in developing countries where most genetic investigations are not readily available.

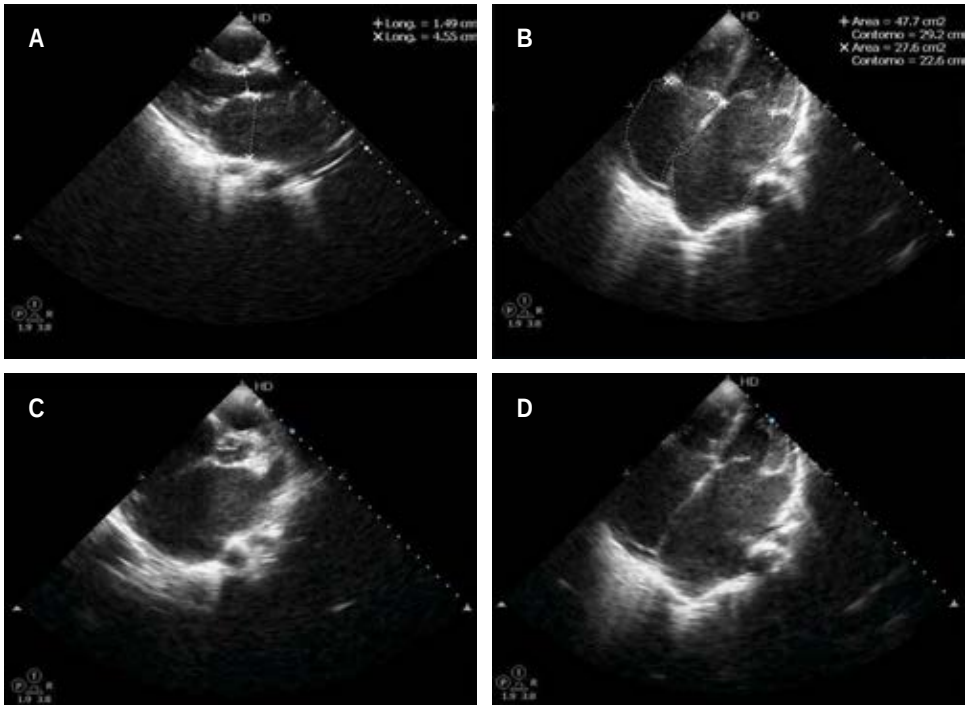

Figure 3:

Transthoracic echocardiography. **A)** Parasternal long axis view. The left atrium shows hypertrophy. **B** and **D)** four cardiac chamber views. Severe atrial dilation without ventricular compromise can be seen. **C)** Parasternal short axis view. Important dilation on the left atrium, including cardiac appendage.

Table 1: Family's echocardiographic analysis. It shows how the same gene may affect the same family members with different disease phenotypes.

										Left atrium				
	Age	Sex	Age of symptomatology onset	ECG	LVD mm	LVS mm	ISVD mm	LVPWD mm	LVEF %	Diameter mm	Area cm^2	Volume cm^3	RA cm^2	E/A ratio
Patient	12	Female	12	Biatrial growth	32.20	22.20	5.21	3.26	60.00	45.50	47.70	154.00	27.60	> 2
Relative	26	Female	15	Left ventricular Hypertrophy	38.10	20.40	16.00	12.80	80.00	31.10	14.30	43.00	12.60	Normal

ECG = electrocardiogram. LVD = left ventricle in diastole. LVS = left ventricle in systole. IVSD = interventricular septum in diastole. LVPWD = left ventricle posterior wall in diastole. LVEF = left ventricular ejection fraction. RA = right atrium. Age is represented in years.

Echocardiograms help recognize the phenotype of the different cardiomyopathies following diagnostics criteria.[13,14]

Diagnostic criteria

There are no established diagnostic criteria for RCM in the pediatric age. Therefore, diagnosis can be based on a thorough clinical and physical evaluation, a complete patient and family history, and various specialized investigations. In this case, the patient arrived for the first time at the hospital with critical cardiac symptoms such as progressive dyspnoea, cough, and palpitations. Chronic disease evidence was appreciated at first sight due to her cachexic

look. The patient's relative had a confirmed cardiac diagnosis at a young age. A complete cardiac study was made considering all the previously mentioned.

The patient's X-rays, combined with clinical findings, confirmed a global cardiac illness. The electrocardiogram revealed the presence of atrial hypertrophy, which led to echocardiography to determine atrial involvement and measure how much this impacted cardiac function. The echocardiogram reported an atrial diameter of 45.5 mm and an area of 47.7 cm^2. According to the European Society of Cardiology,[15] the patient had a severe compromise of both her left and right atria. Even though the FEV was not affected, the E/A ratio showed a restrictive filling pattern due to the atrial compromise. In conclusion, a diagnosis of restrictive cardiomyopathy was an adequate diagnosis according to both clinical and echocardiographic data.

Management

The management is usually directed at to controlling congestive symptoms. Loop diuretics, as mentioned before, represent the main stem of treatment. Loop diuretics help control pulmonary congestion, peripheral edema, and ascites. However, RCM represents challenging management because it requires close monitoring if diuresis is overdone, causing a further decline in stroke volume and causing hypotension.[16] The management requires a tailored approach based on an individual case. As part of the initial management of our patient, loop diuretics, Aldosterone Inhibitors, and Angiotensin-Converting Enzyme Inhibitors were used. Even though scientific studies discourage the use of Enalapril as an antihypertensive, in this particular case, it was used as part of heart failure therapy, which is why only 5mg was indicated. Nonetheless, the patient required an adjustment to the therapy because of a poor response. Although not recommended due to their effect on heart rate,[3] the need to use Calcium Channel Blockers and Beta-blockers represented an improvement in the clinical course. At this stage, these medications were beneficial because the patient had persistent tachycardia. Low doses of Bisoprolol were prescribed for Warfarin failure afterward. A heart transplant represents a definitive treatment option given the limited effective medical therapies, poor mechanical support options and a genetic risk factor that leads to rapid progression or sudden death. It is known that overall waitlist mortality for children with RCM is around 10% and increases if patients require mechanical support while on the waitlist. After a transplant, patients can have a five-year survival of around 77%. Improved risk stratification methods will help identify patients who can benefit from a transplant early in the disease.[11]

CONCLUSIONS

In this case, a clinical diagnosis of restrictive cardiomyopathy is established in a paediatric patient with a family background of TNNI3 gene mutation. We considered this case relevant because of various reasons. First, it reminds us of the importance of genetic investigations in relatives of a patient with cardiomyopathy, highlighting the old paradigm of clinical cardiology and genetic investigations, which is not common in developing countries. Second, it helps us understand the impact of one genetic defect on the different phenotypes of diseases in a single organ. Third, restrictive cardiomyopathy is not the most common in the paediatric population.

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Residual mitral regurgitation grade 2+ after transcatheter edge-to-edge mitral valve repair: Epic fail?

Regurgitación mitral grado 2+ después de la reparación valvular mitral transcatéter borde a borde: ¿un gran fracaso?

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Keywords:
functional mitral regurgitation, mitral valve, mitral valve insufficiency, mitral valve repair, transcatheter edge-to-edge mitral valve repair.

Palabras clave:
insuficiencia mitral funcional, válvula mitral, insuficiencia valvular mitral, reparación valvular mitral, reparación valvular mitral borde a borde transcatéter.

ABSTRACT

Cardiac surgery and interventional cardiology have been pursuing the idea of working together to build a critical process for patients, from which an appraisal is made of long-term procedural outcomes. The sole intention is to avoid therapies which fail to solve the pivotal issues of clinical significance to patient well-being. One such example is the efficacy of transcatheter edge-to-edge mitral valve repair (TEER) in treating the functional mitral regurgitation (FMR), a critical parameter being the presence of post procedural residual, or recurrent mitral regurgitation (MR). The impact that this has in relation to the patient's survival, mortality, and rehospitalization for heart failure rates, should be emphasized before making any special assumptions. Roughly half of patients after TEER experienced post procedural MR 2+ (grade 2/4 by echocardiography) within the first year. In fact, the aforementioned has been greatly ignored in the current guidelines for valvular heart disease, giving a recommendation Class IIa for TEER in FMR. Therefore, whether MR 2+ after TEER influences the patient post procedural outcome in the short and longer terms, requires careful consideration.

RESUMEN

La cirugía cardiaca y la cardiología intervencionista han estado persiguiendo conjuntamente la idea de trabajar juntos para construir un progreso crítico destinado a nuestros pacientes, a partir de lo cual estamos obligados a rendir cuentas de nuestros resultados a largo plazo. Todo lo anterior está orientado a evitar promesas poco realistas y medidas prácticas que no logran resolver el problema principal. En este punto, surge de nuevo la misma antigua pregunta sobre la eficacia de la reparación mitral borde a borde transcatéter (TEER) en el tratamiento de la insuficiencia mitral funcional (IMF) o primaria. Un punto crítico y de inflexión es la insuficiencia mitral (IM) residual o recurrente después del procedimiento sin anuloplastia. Se debe enfatizar el impacto que ésta tiene en relación con las tasas de supervivencia, mortalidad y rehospitalización por falla cardiaca del paciente, antes de hacer algunas suposiciones especiales. Aproximadamente casi la mitad de los pacientes después de TEER tenían IM 2+ (grado 2/4 por ecocardiografía) dentro del primer año. De hecho, lo anterior ha sido ignorado en gran medida en las guías actuales para la enfermedad cardiaca valvular, dando una clase de recomendación IIa para TEER en IMF o primaria. Por lo tanto, si la IM 2+ después de TEER afecta o no el resultado del paciente debe revisarse nuevamente, así como su impacto en la clase de recomendación para TEER en las actuales guías clínicas.

INTRODUCTION

The first objective of this paper is to provide an overview about the impact of residual or recurrent mitral regurgitation (MR) 2+ (grade 2/4 by echocardiography) after transcatheter edge-to-edge mitral valve repair (TEER) in treating the functional mitral regurgitation (FMR). The second objective is to review the results in terms of residual or recurrent MR after TEER, which have featured in the most significant trials and reports within the literature of recent years.

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Extreme caution should be exercised regarding the definition of a «good result» after TEER, in consideration of echo parameters utilized for this purpose. The definitions discussed herein are useful in considering the success or failure of MV repair, by accepted practices, irrespective of the approach being surgical or percutaneous. As such, it must be referenced in order to be adequately defined. Hence, a «standard acceptable good result» must be adopted, in order to provide a realistic outcome after TEER in the real-life scenario. However, since the reference point between surgery and TEER is completely different at present, the final outcome for TEER in terms of residual or recurrent MR needs to be revisited.

Most of the current protocols studying the efficacy of TEER consider MR ≤ 2+ as a «good result». Hence, the most common practice in catheter-based techniques is to omit the importance of residual or recurrent MR2+. As a result, the big trials do not show the impact of having the above pathological condition. However, according to what has been previously published in literature related to cardiac surgery, the most effective way of defining success after MV repair procedure is the presence of MR ≤ grade 1+ (grade 1/4 by echo). Moreover, the value of the outcome is highly dependent upon whether this variable is incorporated into the success definition.

IMPACT OF MITRAL REGURGITATION 2+ IN SURGICAL SERIES

Over the years, surgical experience has demonstrated the negative impact of residual or recurrent MR ≥ 2+ after MV repair. In this framework, Enriquez-Sarano et al. have highlighted how much the presence of MR affects patient survival. Special consideration must be given to the fact that MR ≤ 1+ is the only degree that does not negatively affect survival. All the others, including MR 2+, 3+ and 4+ (grades 2, 3, and 4/4) negatively affect the patient survival ($p > 0.01$).[1]

There is a general agreement that residual MR > 1+ is a risk factor for moderate or severe MR at follow-up.[2] De Bonis et al. found that the only predictor of recurrence for MR ≥ 3+ was the presence of residual MR > 1+ at hospital discharge (HR: 5.7; 95% CI, 1.6-20.6; $p = 0.007$).[3] Chang et al. figured out that, by applying logistic regression, one of the most important independent prognostic factors for recurrence of MR, was residual MR ≥ 2+ after hospital discharge.[4] Suri et al. have stressed the risk of having mild intraoperative residual MR 1+ in the operating room progressing towards MR ≥ 3+, is associated with adverse left ventricular remodeling, poor outcome and death (HR: 1.72).[5] Obata et al. found that when residual MR was more than 2.0 cm^2 color Doppler flow area on intraoperative TEE, the MR increased to ≥ 3+ during the follow-up period.[6] Residual MR should be targeted to less than 2.0 cm^2 color Doppler flow area during echocardiographic study.

Rizza et al. compared patients with postoperative residual MR ≤ 1+ vs MR2+, and they found a higher incidence for the use of inotropics in the intensive care unit ($p = 0.12$) and a longer in-hospital stay, involving patients with residual MR 2+ ($p = 0.18$).[7] In general terms, residual MR reduces the efficacy and durability of MV repair.[8]

At this point, it can be shown that the analysis of results backed up by surgical experience, clearly shows the negative impact of residual MR2+ on patients' survival, especially in the long-term. Consequently, the implicit hypothesis of the «acceptable» good result as MR ≤ 2+ after TEER, is likely to be untrue. Furthermore, there is no logic to support why the outcomes from TEER should be analyzed using different criteria to those from surgical MV repairs.

INCIDENCE OF MITRAL REGURGITATION 2+ IN TRANSCATHETER EDGE-TO-EDGE MITRAL VALVE REPAIR SERIES

If the primary aim of treatment is to obtain a post procedural MR reduction as residual MR ≤ 1+, it is highly striking that according to some European reports, half of the patients receiving TEER had a residual MR ≥ 2+ at 1-year follow-up.[9-13]

In a European multicenter registry by Adamo et al., 184 consecutive patients with FMR who underwent successful TEER procedure were analyzed. Of them, 47% showed residual or

recurrent MR 2+ at 1-year follow-up.[10] In the ACCESS-EU study by Maissano et al., 48.3% had MR2+ at 1-year follow-up after TEER.[11] The TCVT (transcatheter valve treatment sentinel pilot registry), is part of the European Society of Cardiology EuroObservational Research Programme. From this study, two reports have come to light. Nickenig et al. reported the results of 628 consecutive patients who underwent TEER. In this study, success after TEER was defined as having equal or less than moderate (≤ 2+) after TEER. In this context, 59.1% of patients with FMR had residual MR 2+ after 12 months follow-up.[12] In similar conditions, Pighi et al., reported up to 61.5% of patients with post procedural MR2+ after 1-year follow-up.[13]

In the EVEREST-II trial, 30% of patients had residual or recurrent MR2+ after 5-year follow-up.[14] In the MITRA-FR trial, up to 32% had residual or recurrent MR2+ or greater, after 12 months of follow-up. More specifically, nearly 25% experienced MR 2+ in the same interval.[15] As the occurrence of residual or recurrent MR after TEER is neither mentioned in the original COAPT trial publication by Stone et al. nor in the supplementary material,[16] data coming from Stone et al. have been included in this review.[17] At 1-year follow-up, 25.7% of patients had recurrent MR2+. Later, at 2-years follow up, 21.9% had MR2+.[17] At 3 years, the only mention of residual or recurrent MR after TEER, appears cited as MR ≤ 2+ in 98.8% of cases.[18] Therefore, in the COAPT trial, there is no clear or exact representation of the severity of MR after TEER *(Table 1)*.

Table 1: Incidence of mitral regurgitation 2+ in transcatheter edge-to-edge mitral valve repair.

Author	Year	MR 2+ (%)	Follow-up (year)
Pighi[13]	2017	61.5	1
Nickenig[12]	2014	59.1	1
Maisano[11]	2013	48.3	1
Adamo[10]	2019	47.0	1
Feldman[14]	2015	30.0	5
Stone[17]	2018	25.7	1
Obadia[15]	2018	25.0	1

MR 2+ = mitral regurgitation grade 2/4, also called «moderate».

IMPACT OF MITRAL REGURGITATION 2+ IN TRANSCATHETER EDGE-TO-EDGE MITRAL VALVE REPAIR SERIES

Regarding the impact of residual or recurrent MR after TEER, Buzzatti et al. demonstrated in a multivariate analysis, that post procedural MR 2+ was the only factor associated with a further development of MR ≥ 3+ (adjusted HR: 6.71; 95% CI, 3.48-12.90; p < 0.001) and worse outcomes, including impacts on survival and quality of life, when compared to MR ≤ 1+.[19] Reichhart et al. showed that patients with residual MR ≤ 1+ at discharge and 12-month follow-up after TEER, had better outcomes compared to patients with residual MR 2+ or ≥ 3+ (p = 0.029).[20]

In the GRASP-IT registry (Getting Reduction of mitrAl inSufficiency by Percutaneous clip implantation in ITaly), a retrospective multicenter study, Adamo et al. identified the recurrence of MR as the most important predictor for all-cause mortality alone (HR: 2.17, 95% CI: 1.42-3.31, p < 0.001) and combined with HF hospitalization (HR: 2.20, 95% CI: 1.52-3.19, p < 0.001), at 5-year follow-up.[21] Buzzatti et al. analyzed 339 patients who underwent TEER, of whom 68.8% had FMR. At 5-year follow-up, residual MR2+ was identified as the most important predictor for all-cause death in univariate [p < 0.001; HR: 2.71: 1.73-4.25] and multivariate analyses [p < 0.001; HR: 4.18: 1.87-9.37]. In addition, residual MR2+ was also the most important factor for MR ≥ 3+ recurrence in univariate [p < 0.001; HR: 5.01: 2.70-9.29] and multivariate analyses [p < 0.001; HR: 4.67: 2.49-8.74] in patients with FMR after TEER at 5-year follow-up.[22]

«MODERATE» OR «GRADE 2+» MITRAL REGURGITATION MEANS THE SAME?

Current 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease cited that the categorization of MR severity as mild, moderate, or severe is highly dependent on several factors, of which echo parameters are of paramount importance.

However, several shortcomings need to be pointed out. Firstly, there is a clear difference between FMR in Stage A (MR grade 0) and Stage B (MR grade 1+ or 2+). Secondly, however, no differences are highlighted between MR 1+ and 2+ (Stage B). Thus, the same echo parameters are applicable for both of them (ERO < 0.40 cm^2, regurgitant volume < 60 mL, and regurgitant fraction < 50%).[23] This is especially important, because the final outcomes with residual MR ≤ 1+ or MR2+ after operation are completely different, regardless surgical or percutaneous approach.

In addition, the 2019 American Society of Echocardiography guidelines score the severity of MR as only mild, moderate and severe. According to this, semiquantitative echo values are used for this purpose; namely, for mild: effective regurgitant orifice area (EROA) < 0.2 cm^2, regurgitant volume (RVol) < 30 mL, and regurgitant fraction < 30%; moderate: EROA between 0.2 and 0.39 cm^2, RVol between 30 and 59 mL, and regurgitant fraction between 30 and 49%; and severe: EROA > 0.4 cm^2, RVol > 60 mL, and regurgitant fraction > 50%.[24] Therefore, there is no reason to classify the MR as «moderate-to-severe», whatever the presentation. The foregoing indicates the nature of the conflict in measuring TEER performance. This must be resolved by selecting more correct, reliable definitions for echo parameters, since these criteria are the key point to the measurement of procedural performance and outcome.

MR ≤ 2+ IS NOT A «GOOD RESULT» AFTER TEER

The main problem is how to classify MR2+ as a robust independent parameter. If we apply the above criteria, all cases cataloged as MR 2+ should be considered to be «moderate» MR, but not «less than moderate», mild, or any other lesser classification. Furthermore, the «moderate-to-severe» terminology of MR 3+ can be confusing and should be avoided in all definitions. Consequently, the implicit hypothesis of MR ≤ 2+ as an «acceptable good» result after TEER is likely to be untrue; MR2+ after TEER should be considered a risk factor of poor prognosis, especially in the long-term. The target must be MR ≤ 1+ after MV repair, regardless of the approach. The same condition is equally applicable, whatever surgical or percutaneous MV repair.

HOW AN UNREALISTIC «ACCEPTABLE GOOD» RESULT AFTER TEER HAS INFLUENCED THE CURRENT GUIDELINES FOR THE MANAGEMENT OF VALVULAR HEART DISEASE

Based upon the available literature, current guidelines for the management of VHD recommend TEER for special cases of primary and FMR. For cases with primary or organic MR, with high or prohibitive surgical risk as operative mortality > 8%, anatomy suitable for TEER and life expectancy > 1 year, the recommendation for TEER is class IIa. For cases with secondary or FMR, with no requirements for coronary artery bypass grafting, as a result of heart failure, in stage D for FMR with no adequate response to guideline-directed medical treatment, with left ventricular ejection fraction < 50%, pulmonary systolic artery pressure < 70 mmHg, left ventricular end systolic diameter < 70 mm, TEER appears as a class IIa recommendation.[23]

This being the case, current clinical guideline recommendations for the use of TEER in MR should be reviewed. It is important to realize that all these recommendations emanate from the analysis of studies and reports in which MR2+ after TEER has been taken as an optimal or acceptable result. Furthermore, given these unfavorable circumstances, these recommendations for the use of TEER should be reappraised, under the precept that MR2+ is a suboptimal result, that negatively affects the patient's survival, quality of life and hemodynamics.[25,26]

CONCLUSIONS

In conclusion, the key observations of this review are: 1) the classification to measure the degree of MR commonly used in daily practice should be reviewed and adapted in a clearer and more concise way than currently, especially to measure the performance after TEER; 2) echo parameters for this purpose should be uniformly utilized for all cases, regardless of the approach; 3) current echo parameters to measure the

performance of MV repair are totally different for surgery and catheter-based techniques, such as TEER; 4) MR 2+ is frequently downgraded in TEER studies; 5) MR 2+ does impact the final outcome in terms of survival, quality of life, recurrent MR ≥ 3+ after MV repair, regardless of the approach. In this context, TEER is no exception to this observation.

If the parameters that govern the physical laws of cardiovascular hemodynamics are the same for any individual, then the same criteria should apply for both surgery and TEER. Thus, the results of MV repair should be clearly expressed as successful, only if the residual MR is ≤ 1+. That means that the final target, in terms of echo values, should always be a residual MR ≤ 1+ after MV repair, regardless of a surgical or transcatheter approach.

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A minireview of high blood pressure prevalence in some contemporary hunter or fisher-gatherer communities

Una minirrevisión de la prevalencia de la presión arterial alta en algunas comunidades contemporáneas de cazadores o pescadores-recolectores

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Keywords:
blood pressure, high blood pressure, hunter-gathering communities, lifestyle, acculturation.

Palabras clave:
presión arterial, hipertensión arterial, comunidades de cazadores-recolectores, estilo de vida, asimilación cultural.

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ABSTRACT

Introduction: high blood pressure (HBP) is a risk factor for cardiovascular diseases, the leading cause of mortality worldwide. HBP intertwines hypertensive phenotypes and lifestyle traits. Systolic blood pressure rises with age, and HBP is frequent in older ages. This minireview describes the population mean blood pressure (BP) and the prevalence of HBP in communities of fishing-hunting and gathering individuals. **Material and methods:** the data on BP values or HBP prevalence were analyzed in different databases from contemporary studies on hunters-fishers and gatherers communities. **Results:** sixteen articles were selected from tribes of Central and South America, Africa, and Asia. Communities with little or no influence from modern civilization showed low BP values, regardless of gender or age. HBP prevalence was in most of them between 0 and 10%, with few exceptions. Acculturation changes this BP pattern. The concept that HBP, especially the isolated systolic HBP that affects the elderly, is an inevitable consequence of age seems unsustainable considering these data. **Conclusion:** high blood pressure (HBP) is not fatally linked to aging but results from the relationship between heredity and environment, a consequence of an unhealthy lifestyle related to civilization. This fact emphasizes the role of behavioral strategies in promoting better metabolic and cardiovascular health.

RESUMEN

Introducción: *la hipertensión arterial sistémica (HAS) es un factor de riesgo de enfermedades cardiovasculares, las primeras causas de mortalidad mundial. En la génesis de la HAS se entrelazan fenotipos hipertensivos y rasgos del estilo de vida. La presión arterial sistólica aumenta con la edad y la HAS es frecuente en edades avanzadas. Esta minirrevisión describe los valores promedio de la presión arterial (PA) poblacional y la prevalencia de la HAS en las comunidades de cazadores-pescadores y recolectores actuales.* ***Material y métodos:*** *se analizaron los datos de los valores de PA y la prevalencia de HAS de comunidades contemporáneas de cazadores-pescadores y recolectores en diferentes bases de datos.* ***Resultados:*** *dieciséis artículos fueron seleccionados de estudios de tribus de América del Sur y Central, África y Asia. Las comunidades con poca o nula influencia civilizatoria moderna tuvieron cifras de PA bajas, independientemente del género y la edad. La prevalencia de la HAS varió entre 0 y 10%, con pocas excepciones. La asimilación cultural modificó este patrón. El concepto de que la HAS, especialmente la de tipo sistólica aislada que afecta a los ancianos, es una consecuencia inevitable de la edad, parece insostenible de acuerdo con estos datos.* ***Conclusión:*** *la HAS no está fatalmente ligada a la edad, sino que es el resultado de la relación entre la herencia y el ambiente, consecuencia del estilo de vida poco saludable relacionado a la civilización. Este hecho refuerza la importancia de las estrategias conductuales que promueven una mejor salud cardiovascular y metabólica*

INTRODUCTION

The relationship between certain diseases and civilized society has long been a topic of interest for evolutionary biologists, ecologists, physiologists, physicians, nutritionists, anthropologists, sociologists, and historians.[1] The poorly defined concept of «civilization diseases»[2]

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refers to a set of maladies, unknown or with very low prevalence in the pre-agricultural and pre-historical ages (from the Paleolithic to Neolithic eras). The emergence and epidemiological spread of these ailments depended on nutritional and socio-cultural changes when human beings abandoned their nomadic lives and the hunting-fishing and gathering activities, settling first in villages and then in cities, obtaining their food supply from agriculture and livestock, and dialectically opposing their lifestyle traits with their genetic nature developed over millennia.[3] Remarkably, among these «civilization diseases», high blood pressure (HBP) is one of the best examples of these diseases resulting from the convergence of hereditary predisposition and certain lifestyle features, such as the type of nutrition, the consumption of salt and alcohol, obesity, sedentarism, and psychosocial stress, among other factors.[4]

HBP is currently the most prevalent cardiovascular disease and one of the most critical factors of death and disability worldwide, associated with dyslipidemia, tobacco consumption, obesity, and diabetes. HBP is one of the main promoter factors of coronary, cerebral, and peripheral atherosclerosis, heart failure, chronic renal disease, atrial fibrillation, vascular dementia, and vision loss, among other complications.[5]

Blood pressure (BP), especially systolic blood pressure (SBP), rises with age, and older adults have a higher prevalence of HBP. Even among those who were not hypertensive at younger ages, upon reaching old age, a considerable proportion of them showed elevation of BP, particularly SBP and pulse pressure, yielding to the modality known as isolated or predominant systolic arterial hypertension).[6-9] Is this fact consubstantial to human aging? Or, on the contrary, are these changes linked to age, another consequence of a civilized lifestyle?

This minireview is aimed to support the already established concept, but not shared by all that HBP is not an inevitable fact of advanced age. We analyzed data collected in the literature about BP values, or HBP prevalence, found in contemporary times in some communities that get their food from hunting (or fishing) and gathering activities, as our ancestors did in the Stone Age. The elucidation of this fact has undoubted practical value because it points the way forward for primary prevention.[10] The goal is not the impossible return to the primitive tribal style of life, but to learn from the culture of our ancient ancestors some customs and practices that made it unlikely the presence of diseases that today are the leading public health problems of human society.

MATERIAL AND METHODS

This review aims to describe the average population BP and the prevalence of HBP, estimated in observational studies on human communities that in current times still live by the norms of primitive hunting-fishing and gathering societies. We examined databases from the National Library of Medicine (NIH), the National Center for Biotechnology Information (NCBI), MEDLINE/PubMed, and Sciencedirect, with no publication date or sample size restriction. Medical Subjects Headings: blood pressure, high blood pressure (or hypertension), and hunter-gathering communities (and the Boolean terms «and» and «or» to make more precise the search) were selected to identify those articles focused on habitual BP and the prevalence of HBP in these societies. Inclusion criteria encompass studies written in English in which BP was quantitatively measured, and the prevalence of hypertension was estimated. Other types of communications were excluded, such as clinical cases, scientific or philosophical reflections, letters to the editor, brief notes, abstracts, and duplicate articles. We consider the cut-off values of BP signaling HBP (BP $\geq$ 140/90 mmHg), as it is recommended by the Task Force of the European Society of Cardiology (ESC), the European Society of Hypertension (EHS),[11] and the Mexican Official Norm on hypertension (DOF - Diario Oficial de la Federación, 2017).[12] Additionally, we considered other sources, like previous reviews of special ethnic groups.[13-16]

RESULTS

Of all databases consulted, sixteen articles were selected. Groups were divided by geographical areas in Central and South America *(Table 1)*,[17-23]

Table 1: Southern and Central America's hunter-fishers-gatherers' communities.

Ethnicity	Kuna	Kuna	Yanomami Yekwana	Tsimane	Yanomami	Xingu	Carajas
Geographic place	Ailigandi island, San Blas archipelago, off the Caribbean coast of Panama	Ailigandi and Ticantiki, islands, San Blas archipelago, off the Caribbean coast of Panama	Venezuela	Bolivian Amazonia	Brazilian Amazonia	Brazilian Amazonia	Amazon basin of tropical Northern Brazil, on the shores of two southern tributaries of the Amazon river
Number	133	142	155 Yanomami: 72 Yekwana: 83	2,248	400	198	89
Gender, %	M: 39 F: 61	–	Yanomami M: 54 F: 46 Yekwana M: 40 F: 60	F: 52.6 M: 47.4	F: 200 M: 200	–	M: 46 F: 43
Age [years]	35-42	18-82	Yanomami: 22.4 Yekwana: 22.2	F: Normotensives: 38 Hypertensives: 66.5 M: Normotensives: 39.3 Hypertensives: 65.8	25-59	–	16-61+
SBP*	98.2 ± 1.2	–	Yanomami: 95.4 ± 8.7 Yekwana: 104.0 ± 10.6	F: 108 M: 113	95.4	F: 96.2 M: 103.3	Age: 16-20 M: 109.5 F: 96.0 Age: 21-30 M: 109.8 F: 104.1 Age: 31-40 M: 107.3 F: 105.4 Age: 41-50 M: 100.9 F: 100 Age: 51-60 M: 109.0 F: 98.0 Age: > 61 M: 110.3 F: 108.0
DBP*	58.4 ± 0.7	–	Yanomami: 62.9 ± 8.5 Yekwana: 66.1 ±95	M: 70 F: 66	61.4	F: 61 M: 64.4	Age: 16-20 M: 72.5 F: 69 Age: 21-30 M: 72.9 F: 70.7 Age: 31-40 M: 70.5 F: 72.2 Age: 41-50 M: 69.1 F: 69.4 Age: 51-60 M: 70.3 F: 67.7 Age: > 61 M: 69.7 F: 64.7

Contenido

Continue to Table 1: Southern and Central America's hunter-fishers-gatherers' communities.

Ethnicity	Kuna	Kuna	Yanomami Yekwana	Tsimane	Yanomami	Xingu	Carajas
MBP*	71.3	< 40 years: 81 ± 2 41-60 years: 77 ± 1 > 60 years: 80 ± 2	Yanomami: 73.7 Yekwana: 78.7	M: 84.3 F: 80	72.3	–	Age: 16-20 M: 84.3 F: 78 Age: 21-30 M: 85.3 F: 82 Age: 31-40 M: 82.3 F: 83 Age: 41-50 M: 79.7 F: 79.3 Age: 51-60 M: 83 F: 78 Age: > 61 M: 83.3 F: 79.3
HBP prevalence, %	–	2.2	–	M: 5.2 F: 3.9	0	1	–
Reference	17	18	19	20	21	22	23

SBP = systolic blood pressure. DBP = diastolic blood pressure. MBP = mean blood pressure, HBP = high blood pressure.
* Data expressed in millimeters of mercury [mmHg].

Africa *(Table 2)*[24-30] and Asia *(Table 3)*.[14,31] Data from those geographical places are shown in *Tables 1 to 3*.

Lowenstein, in 1961, described the population average arterial pressures of two Indian tribes (Mundurucus and Carajas) living in the tropical Amazon basin in northern Brazil, reporting that BP remains low throughout the adult life of these individuals.[23] BP tended to increase with age in Mundurucus Indigenous people but not in the Carajas group. The two tribes differ in their lifestyle, being the Carajas more attached to their primitive culture, while the Mundurucus had lost part of the lifestyle of their ancestors as westernized Brazilians had somehow partially acculturated them.

DISCUSSION

We are heirs to a long lineage that began when the great apes were evolutionarily separated from the first of our oldest direct ancestors, the «hominins», Like the archaic «Homos» that succeeded them, in the first millennia of the existence of «Homo sapiens», these beings lived under the norms of the tribal nomad society, dedicated to hunting or fishing, and gathering tasks. The term «civilization», whose etymology comes from the Latin word civitas (city), defines that stage of the development of human society that brought undoubted benefits but, at the same time, among many negatives, even catastrophic aspects, gave rise to numerous threatening risks to human health, which continue to weigh on contemporary human society. Civilization did not arise from one moment to another. The Neolithic age (the transition between the Stone Age and civilized eras) began 10,000 or 12,000 years ago and was characterized by slow and gradual changes in humans' food supply and social organization. Among the many facts that define civilization are the abandonment of nomadism and settlement in villages or cities, the invention of writing, pottery, agriculture and livestock, the origin of structured religions ruled by a priestly caste, the very birth of science, the end of the egalitarian society norms with the apparition of private property, and the differentiation of the human society in social classes (with the introduction of slavery), the development of the

Table 2: African hunter-gatherers' communities.

Ethnicity	Traditional pygmies	Hadza	Traditional pygmies	Pygmies	Luo	!Kung Bushmen	Bushmen
Geographic place	Southern Cameroon	Northern Tanzania	Cameroon	Cameroon	Nairobi, Kenya	Republic of Botswana	Souhern Ganzhi, Kalahari desert
N	94	46	20	150	310	152	78
Gender, %	M: 39 F: 61	M: 41 F: 59	M: 46 F: 54	M: 55 F: 45	–	M: 52 F: 48	M: 54 F: 46
Age [years]	23-46	18-60	33-35	38 ± 12	20-65	15-83	15-65
SBP*	119 (110-129)	Age: 18-39 115.90 ± 14.37 Age: 40-59 123.12 ± 19.73 Age: > 60 126.07 ± 17.48	122 ± 4	107 ± 12	M: 122.9 F: 129.2	Age: 30-39 M: 120 F: 113 Age: 50-59 M: 118 F: 123 Age: 70-83 M: 117 F: 123	Age: 12-17 M: 107.5 ± 14.9 F: 108.3 ± 9.1 Age: 18-35 M: 110.1 ± 11.7 F: 112 ± 15 Age: 40-55 M: 107.5 ± 11.2 F: 117.5 ± 12.9 Age: 60-65 M: 107.6 ± 9.9 F: 113.8 ± 19.2
DBP*	73 (66-78)	Age: 18-39 69.96 ± 11.49 Age:40-59 74.97 ± 29.26 Age: > 60 69.63 ± 11.28	83 ± 2	71 ± 11	M: 69.7 F: 72.5	Age: 30-39 M: 75 F: 73 Age: 50-59 M: 72 F: 76 Age: 70-83 M: 66 F: 68	Age: 12-17 M: 68 ± 13.4 F: 69.7 ± 8.9 Age: 18-35 M: 66.9 ± 5.3 F: 68.8 ± 8.7 Age: 40-55 M: 63.1 ± 6.7 F: 70.8 ± 5.7 Age: 60-65 M: 67.8 ± 5.5 F: 69.6 ± 9.0
MBP*	88 (81-93)	Age: 18-39 85.3 Age: 40-59 91 Age: > 60 88.7	97 ± 3	83 ± 10	M: 87.7 F: 93	Age: 30-39 88.2 Age: 50-59 89.5 Age: 70-83 84.7	Age: 12-17 M: 81.0 F: 82.7 Age: 18-35 M: 81.3 F: 83.3 Age: 40-55 M: 77.7 F: 86.3 Age: 60-65 M: 83.3 F: 84.7

Continue to Table 2: African hunter-gatherers' communities.

Ethnicity	Traditional pygmies	Hadza	Traditional pygmies	Pygmies	Luo	!Kung Bushmen	Bushmen
HBP prevalence‡	2.2	Age: 18-39 4.95 Age: 40-59 21.28 Age: > 60 25.93	–	3.3	–	–	–
Reference	24	25	26	27	28	29	30

SBP = systolic blood pressure. DBP = diastolic blood pressure. MBP = mean blood pressure, HBP = high blood pressure.
* Data expressed in millimeters of mercury [mmHg].
‡ Data expressed as a percentage.

institutions that together make up the State, the introduction of bronze crafting, the complete evolution and consolidation of the patriarchally family, and the creation of all kind of artistic expressions, including a pearl of extraordinary architectural wisdom and capabilities.[32,33]

Also took place a profound dietary revolution, characterized by the introduction of cereals as a nutritional fundament, as well as the consumption of meat of cattle modified by domestication, dairy and poultry products, the use of salt as a flavoring and food preservative agent, and the consumption of alcoholic beverages, among many others. In contrast with civilized people, our primitive nomad ancestors consumed the healthier meat of wild animals, fruits, nuts, roots, and abundant vegetables with a high dietary fiber, calcium, and potassium content. At the same time, cereals, milk, and dairy products were not components of their usual diet.[34] They did not ingest more salt than the natural constituent of their food, while the consumption of alcohol and tobacco was utterly unknown to them. Besides, women and men were generally lean and endowed with splendid physical fitness. Of course, they did not have an easy life. Many died young due to infections, parasite infestations, obstetric complications, injuries, and other accidents caused by the vicissitudes inherent to wildlife. Still, they were free of the chronic-degenerative epidemics that overwhelm civilized humans, particularly in modern times.[3]

One of the epidemiological traits in modern societies is the population age-dependent increment of SBP and a high prevalence of HBP, particularly in advanced ages. In the elderly, the mechanism responsible for the sustained increment of SBP is the altered aged-linked mechanic properties of the elastic arteries, which are due to senescent structural changes (extracellular matrix dystrophy, calcification, atheromatous and hypertensive arteriosclerosis, among others).[5]

At the present times, it is difficult to find «pure» hunter-fisher-gatherer societies because complete cultural isolation is now rather impossible. For that reason, it is noticeable that those contemporary primitive societies show a certain degree of acculturation (promoted by trade, religious, political, governmental, academic, or

Table 3: Asian hunter-fisher-gatherers communities.

Ethnicity	Negrito	Lau	Aita
Geographic place	Peninsular Malaysia	Northeast Malaita islets, Solomon Islands. Oceania	Bougainville island mountains, Solomon Islands, Oceania
Number	Deep forest communities: 197	178	169
Gender‡	M: 43.2 F: 56.8	M: 77 F: 101	M: 81 F: 88
Age (years)	18-80	15-65	18-64
Systolic blood pressure*	Deep forest communities: 130 ± 23	M: 122 ± 3.5 F: 128 ± 3.2	M: 111 ± 3.1 F: 106 ± 3.9
Diastolic blood pressure*	Deep forest communities: 84 ± 15	M: 81 ± 3.2 F: 83 ± 3.7	M: 72 ± 1.9 F: 67 ± 5.1
Mean blood pressure*	Deep forest communities: 99.3	–	–
High blood pressure prevalence‡	39.2 ± 7.0	M: 7.8 F: 9.9	M: 0 F: 0
Reference	14	31	31

* Data expressed in millimeters of mercury [mmHg].
‡ Data expressed as a percentage.

«charitable» intromissions, and migratory flows) and, because some hunter-gatherers, besides their hunting or fishing activities, practice pastoralism, and forest gardening-herbalism or swidden agriculture.

Some authors consider that three hundred groups worldwide that can be regarded as predominantly hunter (or fisher)-gatherers exist. They encompass ~10 million people,[35] an impressive number, considering that direct man-made destruction of many habitats and the environmental disasters due to climate change have limited the ecological possibilities of this form of life.

This review shows that HBP is unknown or rare in these societies living under the norms of the Stone Age. Population average BP pressures are less than 120/80 mm Hg, in all genders, in all age groups, and in tribe persons of different ecological regions. Except for Malaysian Negrito deep forest inhabitants, who have a high prevalence of HBP, which is unusual in other similar tribal groups,[14] and the Tanzanian Hadza ethnic group in whom an HBP prevalence of 21-26% was observed, in the rest of tribal communities, BP values were low, and the prevalence of HBP was less than 10% or completely absent. The isolation of the Malaysian Negrito community favors inbreeding and the more frequent occurrence of hypertensive phenotypes. The Hadza group has been somehow «contaminated» by their neighbor's more acculturated ethnic groups.

Concerning age, in most cases, older people had almost the same BP as the younger group members. *Table 4* shows that in the Amazonian Yanomami, average population blood pressure was similar in both genders and all age groups.[21] Why were our ancient ancestors not assailed by HBP? A low salt consumption played a role because its excess is one of the etiopathogenic mechanisms of hypertension, but by no means is it the only one. Among behavioral and nutritional protective factors against HBP, vascular damage, and early aging and frailty, are included the lifelong maintenance of physical activity, the absolute absence of tobacco smoking and ingestion of alcoholic beverages, and a healthy diet with high content of dietary fiber and rich in nutraceuticals, as polyphenols (epicatechin or quercetin) or carotenoids (as lycopene) and of course, with low salt content.

Although, in general, aging is associated with a natural decline of all organic functions, civilized life (particularly the western type of

modern civilization) has two antagonistic but simultaneous effects. On the one hand, it accelerates vascular aging, promoting chronic vascular diseases (atherosclerosis, hypertensive, and senescent calcinotic arteriosclerosis), yielding a pandemic outburst of acute and chronic vascular syndromes, principally from cardiac or cerebral origin. At the same time, high-tech medicine, and pharmacological advances, have decreased the mortality caused by these syndromes, at least in developed countries, though sometimes costly but effective therapeutic interventional or surgical procedures.[36] Those who survive the acute vascular syndromes, thanks to these interventions, are often affected later by disabling conditions such as heart failure, neurological or kidney deficiencies, and vascular dementia.

Aging is a natural, inevitable process but is not necessarily associated with frailty, disabling, or threatening diseases. The contemporary hunter-fisher and gatherers tribe persons' features signal that HBP and other «civilizations diseases» do not fatally accompany old age.

On the other hand, a large body of data suggests that acculturation (adopting a different cultural pattern) promotes the emergence of the typical chronic-degenerative diseases of civilization. Noticeably, the extraordinarily high consumption of polyphenols (epicatechin) from cacao beverages, for example, in the Panamanians Kuna Indigenous people, is associated with almost the absence of HBP and with a low incidence of cardiovascular diseases, diabetes, and cancer. This protection is not due to genetic influence because the people of this ethnic group, when acculturated, acquire the pathology of civilized human society.[18]

Table 4: Mean population values of blood pressure in both genders and different age groups in Yanomami Indians.

Gender and age group, years	Systolic blood pressure*	Diastolic blood pressure*
Men		
20-29	100	59
30-39	106	61
40-49	102	52
50-59	104	65
Women		
20-29	91	50
30-39	91	54
40-49	95	54
50-59	90	58

* Data expressed in millimeters of mercury [mmHg].
Taken from: Mancilha-Carvalho J et al.[21]

CONCLUSION

Data from this review strengthen the concept that HBP is not consubstantially linked to aging but instead to the unhealthy lifestyle that most of the modern, westernized world population has adopted. Although it is impossible to return to the past, it is always advisable to look back to learn about the healthier lifestyle of our primitive ancestors. We can introduce behavioral changes that promote better metabolic and vascular health, such as a moderate restriction of salt and alcohol, a greater consumption of vegetables and fruits, a lean weight, the habit of physical exercise, and total avoidance of tobacco smoking.

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Consensus statement

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Consensus Statement of the Mexican College of Interventional Cardiology and Endovascular Therapy on percutaneous coronary treatment with drug-coated balloon. The COMECITE DCB consensus statement+

Declaración de Consenso del Colegio Mexicano de Cardiología Intervencionista y Terapia Endovascular sobre el tratamiento coronario percutáneo con balón recubierto de fármaco. La declaración de consenso COMECITE

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Keywords:
drug coated balloon, coronary angioplasty, in-stent restenosis, coronary restenosis, coronary drug eluting balloon.

Palabras clave:
balón medicado, angioplastia coronaria, reestenosis intrastent, reestenosis coronaria, balón medicado coronario.

ABSTRACT

Percutaneous coronary intervention (PCI) is currently the prevalent revascularization method for the last forty years due to its efficacy, low complication rate, and minimal invasion with still pending restenosis solution. The dominant strategy to improve PCI for long-lasting benefits is the utilization of drug-eluting stents (DES), even though the current in-stent restenosis (ISR) rate is ≈10%, plus the inconvenience of foreing body insertion, thrombosis risk, bleeding in high-risk patients, jailing branches potential and possible multiple metal layers after ISR treatment. Drug coated-balloon (DCB) may reduce restenosis without leaving a foreign body and adding metal layers. Several expert group consensus statements and updating report publications, support their utilization for almost a decade. The present paper is from the Mexican College of Interventional Cardiology and Endovascular Therapy (COMECITE) statement regarding current DCB utilization and recommendations in ISR, small vessels, bifurcations, left anterior descendent/left main coronary and acute myocardial infarction.

RESUMEN

La intervención coronaria percutánea (ICP) es actualmente el método de revascularización prevalente durante los últimos 40 años debido a su eficacia, baja tasa de complicaciones y mínima invasión, con el inconveniente de la restenosis. La estrategia dominante para mejorar la ICP para obtener beneficios a largo plazo es la utilización de stents liberadores de fármacos, aunque la tasa actual de restenosis intrastent es ≈10%, aparte de otros inconvenientes como la inserción de cuerpo extraño, riesgo de trombosis, hemorragia en pacientes de alto riesgo, potencial de atrapamiento de ramas y posibilidad de múltiples capas de metal después del tratamiento de la restenosis intrastent. El balón recubierto de fármaco puede reducir la restenosis sin dejar un cuerpo extraño ni agregar capas de metal, su uso está respaldado por declaraciones de consenso de grupos de expertos y actualizaciones de publicaciones de informes durante casi una década. El presente artículo es de la declaración del Colegio Mexicano de Cardiología Intervencionista y Terapia Endovascular (COMECITE) con respecto a la utilización actual del balón medicado coronario y recomendaciones en restenosis intrastent, vasos pequeños, bifurcaciones, descendente anterior izquierda/coronaria principal izquierda e infarto agudo de miocardio.

+ The statement is endorsed by *Colegio Mexicano de Cardiología Intervencionista y Terapia Endovascular* (COMECITE).

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INTRODUCTION

Percutaneous coronary intervention (PCI) is a worldwide non-surgical procedure that has become the prevalent revascularization method for the last forty years. It yields evident benefits, including efficacy, low complication rate, and minimal invasion; nonetheless, there is a justified research line to improve artery patency by reducing the rate of acute or delayed failure of the treated vessel.[1]

The current dominant strategy to improve PCI for long-lasting benefits is the drug-eluting stent (DES) due to significantly less target lesion revascularization (TLR),[2] even though, the current in-stent restenosis (ISR) rate is ≈10%. Stents impose a foreign body, thrombosis risk or bleeding in high-risk patients, and jailing branches potential. The metal layer in the arterial wall becomes significant after second or more stents to treat (ISR).[3] Another issue is small-vessel coronary artery disease (SVD) restenosis, which ranges from 25.8% with a stent to 34.2% in the balloon angioplasty population,[4] and bifurcation lesion restenosis, ranging from 4.6-6.7% in the main branch and 13.2-14.7% in the side branch.[5] Giuseppe Di Gioia et al. recently published a systematic review of clinical outcomes following bifurcation PCI techniques. They found a TLR of 10.2% with provisional stenting, 8.9% with the crush, 7.5% with culotte, 6% with double kissing (DK) crush, and 11.5% with T small protrusion (T/TAP).[6]

Drug coated-balloon (DCB) is a novel tool to reduce restenosis without leaving a foreign body and adding metal layers. It is supported by expert group consensus statements and updated report publications for almost a decade. The stent should be reserved exclusively for significant residual stenosis or flow-limiting dissection.[7,8]

The authors' purpose is to review historical publications and meta analysis in every scenario to make agreements and recommendations.

MATERIAL AND METHODS

The Mexican College of Interventional Cardiology and Endovascular Therapy (COMECITE for the name in Spanish: *Colegio Mexicano de Cardiología Intervencionista y Terapia Endovascular*) formed the consensus group with a designated chairman and co-chairman who later distributed functions to the rest of the members. Every member searched and analyzed relevant publications about coronary DCB in ISR, SVD, and bifurcation settings, using Cochrane Handbook[9] for systematic reviews of interventions and AMSTAR 2 (a measurement tool to assess systematic reviews) which is a critical appraisal tool for systematic reviews that includes randomized or non-randomized study trials of healthcare interventions.[10] The members also reviewed single papers regarding special DCBs for special anatomical conditions. The consensus group discussed every paper in an expert panel format, nominal group technique, and anonymous Dolphy survey.[11]

The authorship for publication follows the International Committee of Medical Journal Editors (ICMJE).[12]

Statistical analysis

The consensus group used the Forest Plot[13] with Number Cruncher Statistical Systems (NCSS) program and the Funnel Plot[14] with the NHS improvement program. The consensus considered TLR as an effective endpoint and major cardiovascular events (all-cause or cardiovascular death, myocardial infarction, or target lesion thrombosis) as a safety endpoint. DCB vs DES trials analyzed ISR, SMD, and bifurcation lesion scenarios.

Tables 1 to 3 shows the analysis with the Cochrane Manual of systematic reviews of interventions and AMSTAR 2. Funnel plots and the Egger test[15] explored publication bias or small-study effect. The Funnel plot is a graphic design that verifies deviations in the publications in systematic reviews and meta-analyses. High-precision trials are in the triangle's midline, while low precision is in the triangle's lateral regions.

The Forest Plot, known as the Blobbogram, is a graph showing the results of a group of trials evaluating three aspects: the intervention's neutrality, superiority, or inferiority through the odds ratio (OR). On the other hand, the

heterogeneity index analyzes the clinical and methodological differences between the participants and interventions. The criterion is $\chi^2 < 0.05$ or inconsistency index, whose formula is $I^2 = (Q\text{-}df/Q)\ x100\%$. Heterogeneity is low at approximately 25%, moderate at approximately 50%, and high at approximately 75%.

RESULTS

The consensus analyzed thirteen trials with 2,262 patients for ISR, six trials with 1,559 patients for SMD, six trials with 417 patients for bifurcation lesions, one meta-analysis comprising 5,711 patients with diverse bifurcation techniques, and several single papers for particular scenarios.

In-stent restenosis

The comparative trials' efficacy endpoint for ISR indicates no significant difference between DCB versus DES 1.26 OR (95% confidence interval, 0.80-1.99, p = 0.07) with a 47.89% heterogeneity index (moderate) *(Figure 1)*. The comparative trials' safety endpoint for ISR indicates no significant differences between DCB versus DES 0.79 OR (95% confidence interval, 0.55-1.15, p = 0.22) with a 0% heterogeneity index *(Figure 2)*. The funnel plot efficacy showed

Table 1: In-stent restenosis trials.

Trial	Design	Year	n	Scenario	Material
AGENT[43]	1:1, Open-Label, Core Lab, CEC	2019	125	Restenosis in-stent BMS or DES	PCB: 3 µg/mm^2 iopromide, ATBC 2 µg/mm^2
BIOLUX-RCT[44]	2:1, Open-Label, Core Lab, CEC	2018	229	Restenosis in-stent BMS or DES	SES, PCB 3 µg/mm^2 BTHC
DARE[45]	1:1, Open-Label, Core Lab, CEC	2018	278	Restenosis in-stent BMS or DES	EES, PCB 3 µg/mm^2 iopromide
ESSENTIAL[46]	Open-Label, Core Lab, CEC	2019	30	Restenosis in-stent BMS or DES	3 µg/mm^2 paclitaxel organic ester
ISAR-DESIRE[47]	1:1, Open-Label, Core Lab, CEC	2013	340	Restenosis in-stent DES	PES, PCB 3 µg/mm^2 iopromide
PACCOCATH[48]	1:1, Open-Label, Core Lab, CEC	2006	52	Restenosis in-stent BMS and DES	PCB 3 µg/mm^2 iopromide and POBA
PEPCAD II[49]	1:1, Open-Label, Core Lab, CEC	2009	131	Restenosis in-stent BMS	PES, PCB 3 µg/mm^2 iopromide
PEPCAD CHINA[50]	1:1, Open-Label, Core Lab, CEC	2014	221	Restenosis in-stent DES	PES, PCB 3 µg/mm^2 iopromide
RESTORE[51]	1:1, Open-Label, Core Lab, CEC	2018	172	Restenosis in-stent DES	EES, PCB 3 µg/mm^2 iopromide
RIBS IV[52]	1:1, Open-Label, Core Lab, CEC	2015	309	Restenosis in-stent DES	EES, PCB 3 µg/mm^2 iopromide
RIBS V[53]	1:1, Open-Label, Core Lab, CEC	2014	189	Restenosis in-stent BMS	EES, PCB 3 µg/mm^2 iopromide
SEDUCE[54]	1:1, Open-Label, Core Lab, CEC	2014	50	Restenosis in-stent BMS	EES, PCB 3 µg/mm^2 iopromide
TIS[55]	1:1, Open-Label, Core Lab, CEC	2016	136	Restenosis in-stent BMS	EES, PCB 3 µg/mm^2 iopromide

CEC = clinical events committee. BTHC = butyryl-tri-hexyl-citrate. ATBC = acetyl tributyl citrate. BMS = bare metal stent. DES = drug-eluting stent. PCB = paclitaxel-coated balloon. SES = sirolimus-eluting stent. EES = everolimus-eluting stent.

Table 2: Small vessel disease trials.

Trial	Design	Year	n	Scenario	Material
BASKET 2[56]	1:1, Open-Label, Core Lab, CEC	2018	758	Small vessel	EES, PES, PCB 3 µg/mm^2 iopromide
BELLO[57]	1:1, Open-Label, Core Lab, CEC	2012	182	Small vessel	BMS, PES
PEPCAD[58]	Open-Label, Core Lab, CEC	2010	118	Small vessel	PCB 3 µg/mm^2 iopromide, BMS bailout
PICCOLETO[59]	1:1, Open-Label, CEC	2010	57	Small vessel	PES, PCB 3 µg/mm^2 PTX DMSO (d(i)m(ethyl)s(ulf)o(xide)
PICCOLETO II[60]	1:1, Open-Label, CEC	2020	214	Small vessel	EES, PCB ≈2 µg/mm^2
RESTORE[61]	1:1, Open-Label, Core Lab, CEC	2018	230	Small vessel	EES, PCB 3 µg/mm^2 iopromide

CEC = clinical events committee. EES = everolimus-eluting stent. PES = paclitaxel-eluting stent. PCB = paclitaxel-coated balloon. BMS = bare metal stent. PTX DMSO = paclitaxel dimethyl sulfoxide.

Table 3: Bifurcation trials.

Trial	Design	Year	n	Scenario	Material
PEPCAD V[62]	Open-Label, Core Lab, CEC	2011	28	DCB in MB and SB + BMS in MB	BMS, PCB: 3 µg/mm^2 iopromide
DEBUIT[63]	1:1:1, Open-Label, Core Lab, CEC	2012	117	1. DCB in MB and SB + BMS in MB 2. BMS in MB and POBA in SB 3. PES in MB and POBA in SB	PES, BMS, PCB 3 µg/mm^2 PTX DMSO
BABILON[64]	1:1, Open-Label, Core Lab, CEC	2014	108	1. DCB in MB and SB and BMS in MB 2. Provisional T stent with DES	DES, BMS, PCB 3 µg/mm^2 iopromide
DEBSIDE[65]	Open-Label, Core Lab, CEC	2015	50	PES in MB and DCB in SB	PES, PCB 2.5 µg/mm^2 BTHC
SARPEDON[66]	Open-Label, CEC	2015	50	DES in MB and DCB in SB	DES, PCB 3 µg/mm^2 BTHC
PEPCAD-BIF[67]	1:1, Open-Label, Core Lab, CEC	2016	64	DES in MB and 1. POBA in SB 2. DCB in SB	PCB 3 µg/mm^2 iopromide

CEC = clinical events committee. PCB = paclitaxel-coated balloon. MB = main branch. SB = side branch. BMS = bare metal stent. POBA = plain old balloon angioplasty. DES = drug-eluting stent. PES = paclitaxel-eluting stent. BTHC = butyryl-tri-hexyl-citrate. DCB = drug-coated balloon. PTX DMSO = paclitaxel dimethyl sulfoxide.

a low precision in the ISAR-DESIRE 3 DCB trial *(Figure 3)*, and the TIS DES trial for safety *(Figure 4)*.

The DEB-Dragon-Registry, comprising 1,117 patients showed similar TLR (11.2% versus 11.2%; HR, 0.91 [95% CI, 0.55-1.51], p = 0.707), target vessel revascularization (TVR) (13.4% versus 14.2%; HR, 0.86 [95% CI, 0.55-1.36], p = 0.523), and device-oriented composite endpoint (14.2% versus 14.2%; HR, 0.91 [95% CI, 0.58-1.42], p = 0.667) between the thin-strut DES and DCB, respectively after propensity score matching. The device-oriented composite endpoint comprised cardiac death, target lesion revascularization, and target vessel myocardial infarction, together.[16]

Small vessel disease

The comparative trials' efficacy endpoint for SVD indicates no significant differences between DCB versus DES 1.05 OR (95% confidence interval, 0.60-1.86, p = 0.97) with a 24.38% heterogeneity index (low) *(Figure 5)*. The comparative trials' safety endpoint for SVD indicates no significant differences between DCB versus DES 0.95 OR (95% confidence interval, 0.56-1.61, p = 0.76) with a 20.91% heterogeneity index (low) *(Figure 6)*. The Funnel Plot for efficacy, showed low precision in PICCOLETO DCB, PEPCAD DCB + BMS, BASKET 2 DES, and BASKET 2 DCB trials *(Figure 7)*, and in PICCOLETO DCB, RESTORE DCB, and RESTORE DES trials for safety *(Figure 8)*.

Her et al, in retrospect, enrolled 227 patients according to reference vessel diameter (RVD) > 2.5 and < 2.5 mm. The primary endpoint was late lumen loss after six months of follow-up. The secondary endpoint was target vessel failure where no differences were observed.[17]

Lesions in bifurcations

DES is significantly superior to DCB in bifurcation technique efficacy endpoint 1.56 OR (95% confidence interval, 0.59-4.10, p = 0.006) with heterogeneity index (high) *(Figure 9)*. DES is significantly superior to DCB in bifurcation technique safety endpoint 1.49 OR (95% confidence interval, 0.91-2.42, p = 0.02) with a 60.63% heterogeneity index (moderate) *(Figure 10)*. The Funnel Plot found low precision in the DEBUIT BMS + POBA trial for efficacy *(Figure 11)* and the DEBUIT BMS + POBA trial for safety *(Figure 12)*.

BMS + POBA vs Culotte technique shifts efficacy and safety favor the 2 DES technique, but DCB provisional stenting has no significant differences from DK-Crush and Crush techniques.

Several metanalyses report significantly less lumen loss of DCB versus plain old balloon dilatation in the side branch and safe outcomes when treating the main vessel.[18-21] DCB appears to be a good option for the «keep it simple and safe» principle of the European Bifurcation Club.[22]

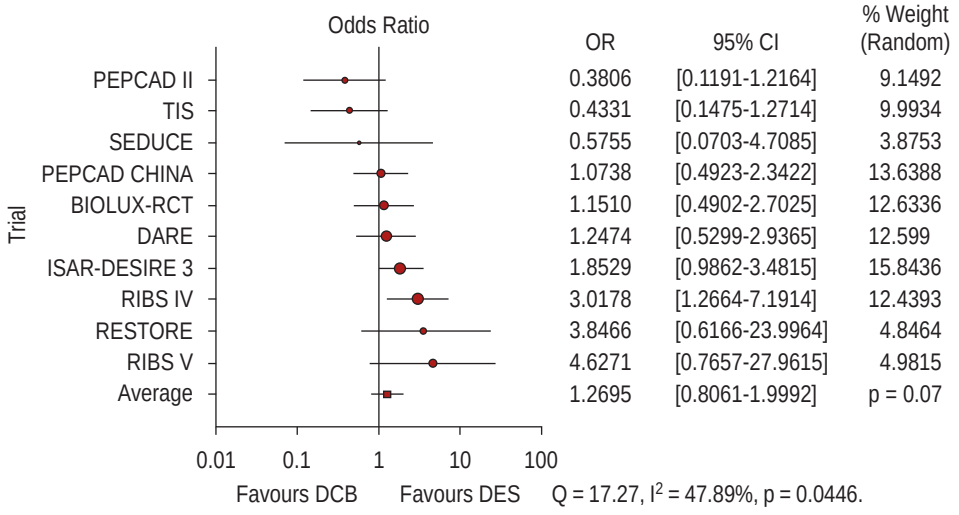

Figure 1:

Target lesion revascularization for in-stent restenosis; DCB versus DES.
DCB = drug-coated balloon.
DES = drug-eluting stent.

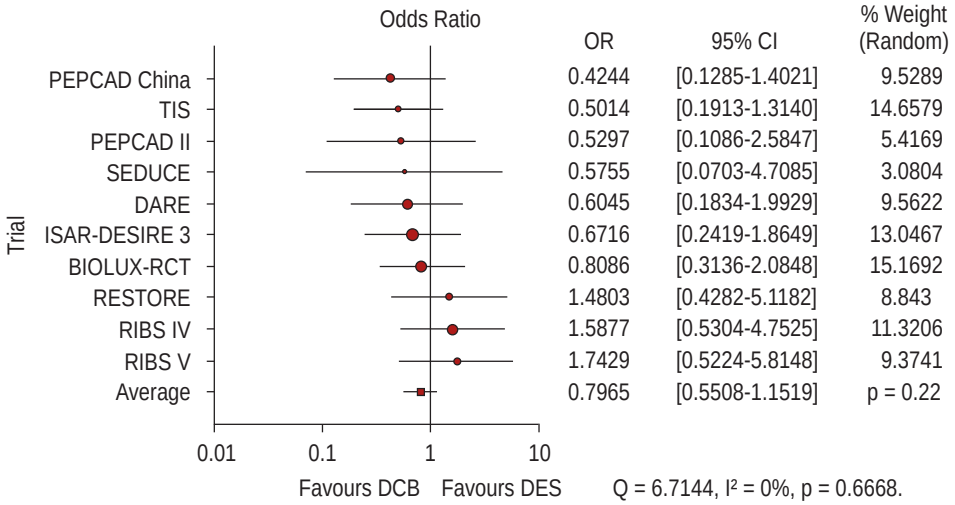

Figure 2:

Major cardiovascular events for in-stent restenosis; DCB versus DES. DCB = drug-coated balloon. DES = drug-eluting stent.

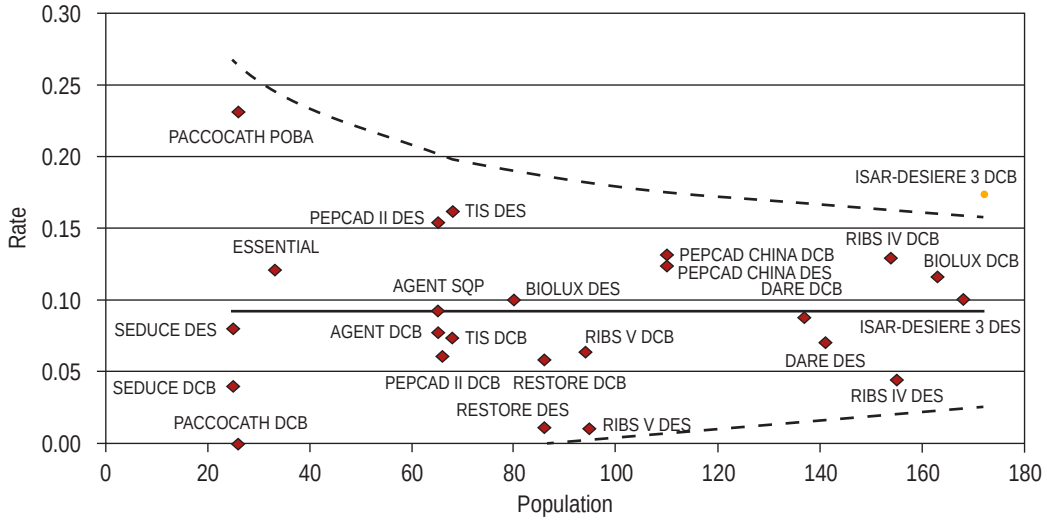

Figure 3:

Funnel plot, TLR in ISR; DCB versus DES. TLR = target lesion revascularization. ISR = in-stent restenosis. DCB = drug-coated balloon. DES = drug-eluting stent.

Figure 4:

Funnel plot, MACE in ISR; DCB versus DES. MACE = major adverse cardiovascular events. ISR = in-stent restenosis. DCB = drug-coated balloon. DES = drug-eluting stent.

ISR in left anterior descendent coronary artery

Prado Jr et al, in 2014, published a case report of ISR in ostial left anterior descendent (LAD), using a paclitaxel-eluting balloon, after seven months of follow-up the patient was symptom-free and had no angiographic restenosis.[23] Yee ST et al, in 2021, presented an ostial LAD ISR treated using a DCB, with success.[24]

ISR in the left main coronary artery

Shetty R et al. published a case report of ISR in an unprotected left main bifurcation and previously failed venous grafting two years before, using sirolimus-eluting kissing balloons. The patient remained asymptomatic with a negative stress test after a six-month follow-up.[25]

Maximkin et al. reported a 4-year follow-up of DCB in the treatment of left main coronary artery bifurcation. Provisional T stenting is associated with a significantly lower frequency of MACE and side branch restenosis compared with the two-stent technique.[26] Kitani et al. evaluated the efficacy and safety of DCB after directional coronary atherectomy (DCA) with a 12-month follow-up in 129 patients. They concluded that DCA/DCB provides good clinical outcomes and minimal side branch damage.[27]

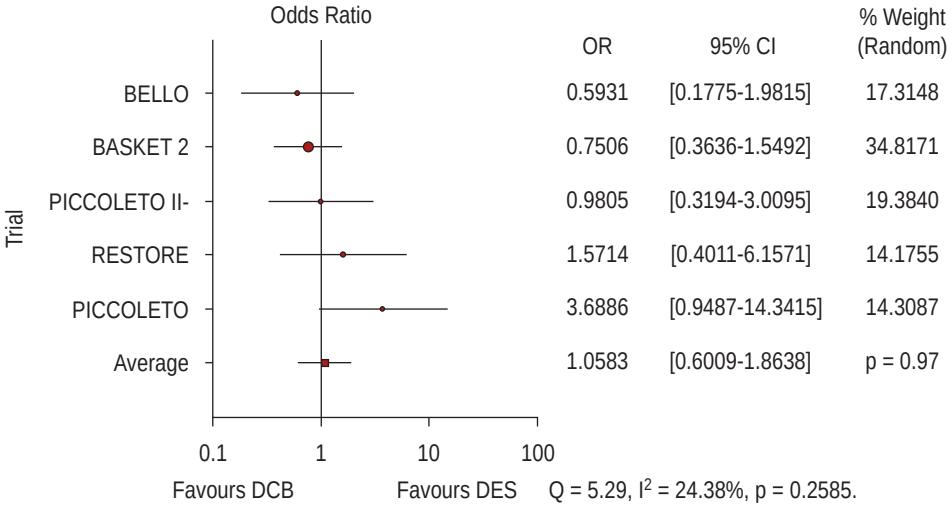

Figure 5:

Target lesion revascularization for SVD; DCB versus DES.
SVD = small vessel disease.
DCB = drug-coated balloon.
DES = drug-eluting stent.

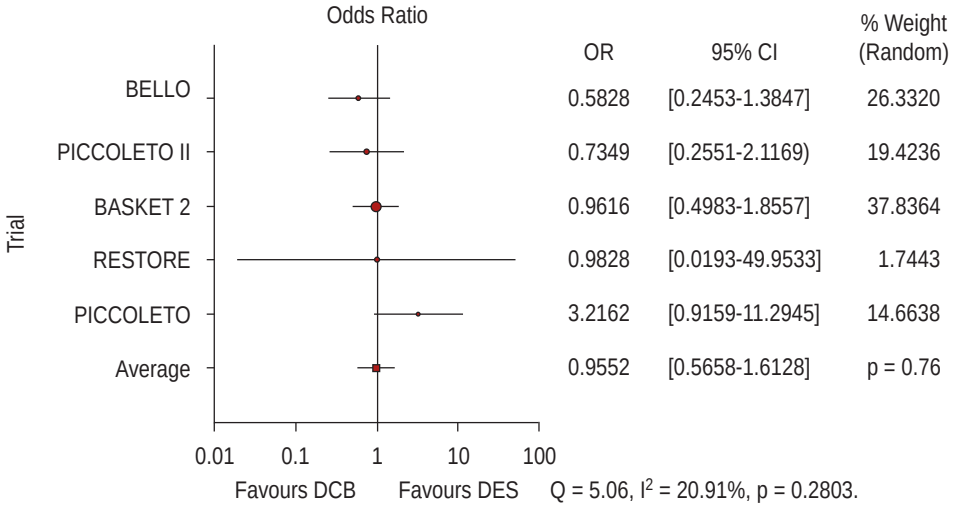

Figure 6:

Major cardiovascular events for SVD; DCB versus DES.
SVD = small vessel disease.
DCB = drug-coated balloon.
DES = drug-eluting stent.

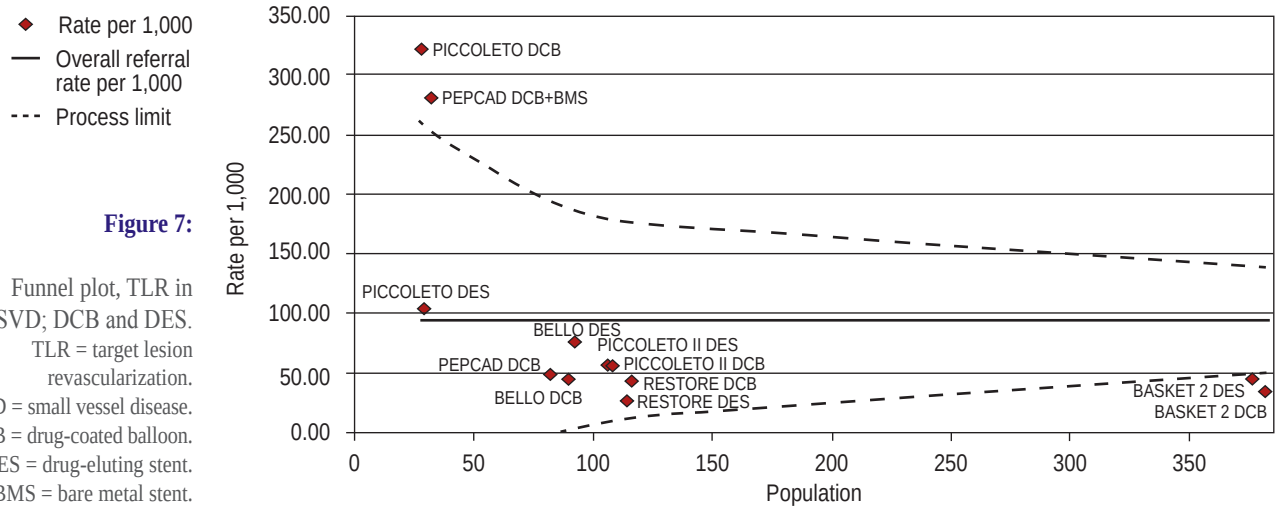

Figure 7:

Funnel plot, TLR in SVD; DCB and DES.
TLR = target lesion revascularization.
SVD = small vessel disease.
DCB = drug-coated balloon.
DES = drug-eluting stent.
BMS = bare metal stent.

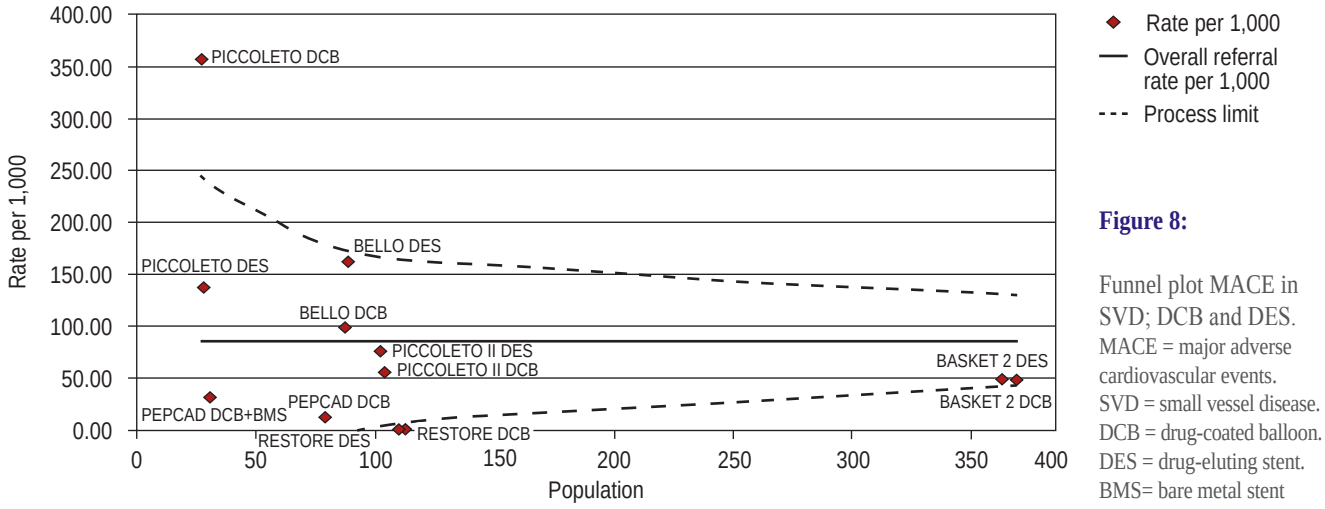

Figure 8:

Funnel plot MACE in SVD; DCB and DES.
MACE = major adverse cardiovascular events.
SVD = small vessel disease.
DCB = drug-coated balloon.
DES = drug-eluting stent.
BMS= bare metal stent

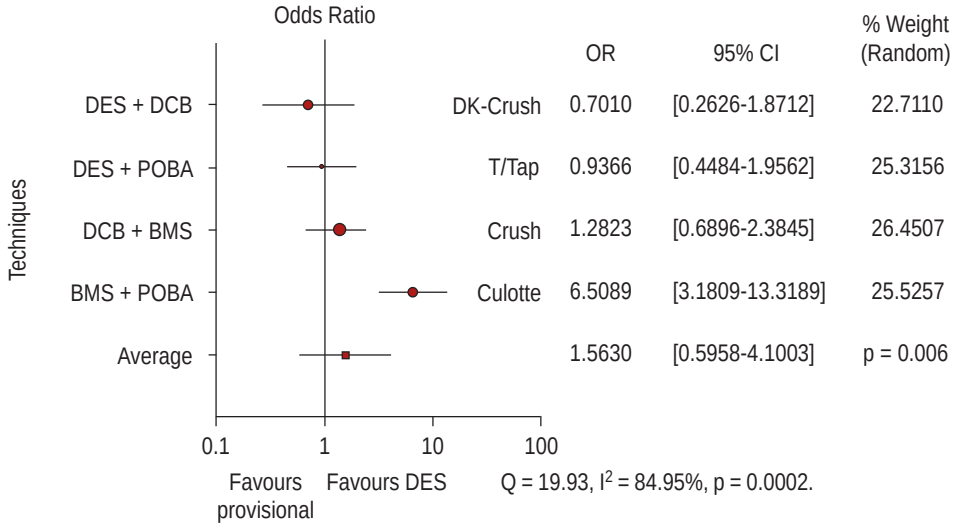

Figure 9:

Target lesion revascularization for bifurcation lesions; DCB versus DES.
DCB = drug-coated balloon.
DES = drug-eluting stent.

Acute myocardial infarction

Several publications inform comparable results in AMI, for DCB versus DES in single centers for AMI.[28]

The REVELATION trial compared fractional flow reserve (FFR) after randomized treatment with plain balloon angioplasty on 120 patients who received either DCB or DES during ST-segment elevation AMI intervention. Thrombus aspiration was performed in 78% with DCB and 83% with the DES group; 18% of suboptimal results received a bare-metal stent, and after nine months of follow-up, the DCB strategy was non-inferior to DES, and seemed to be safe and feasible.[29] This justifies the more recent finding of better one-year lumen loss for DCB versus DES in the setting of ST-elevation AMI (-0.12 ± 0.46 mm versus 0.14 ± 0.37 mm, $p < 0.05$), without significant major adverse events (11% versus 12%).[30]

The PEPCAD NSTEMI trial compares DCB versus BMS and DES in Non-ST-elevation AMI in 210 patients of whom, 62% have a multi-vessel disease and 31% were diabetics. 104 were randomized to DCB and 106 to stent treatment, 56% were treated with BMS, and 44% DES. After nine months, the primary endpoint was target lesion failure (cardiac or unknown death, reinfarction, and target

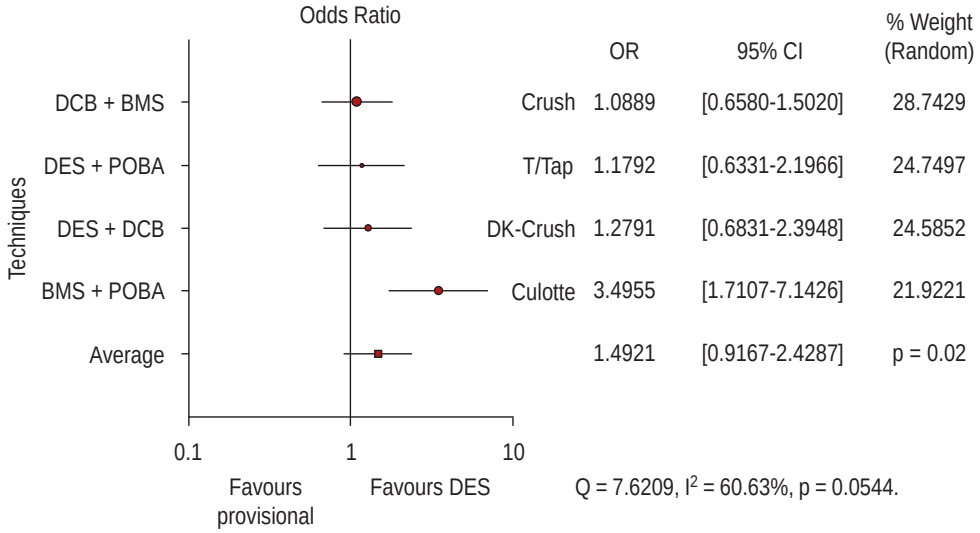

Figure 10: Major cardiovascular events for bifurcation lesions; DCB versus DES.
DCB = drug-coated balloon. DES = drug-eluting stent.

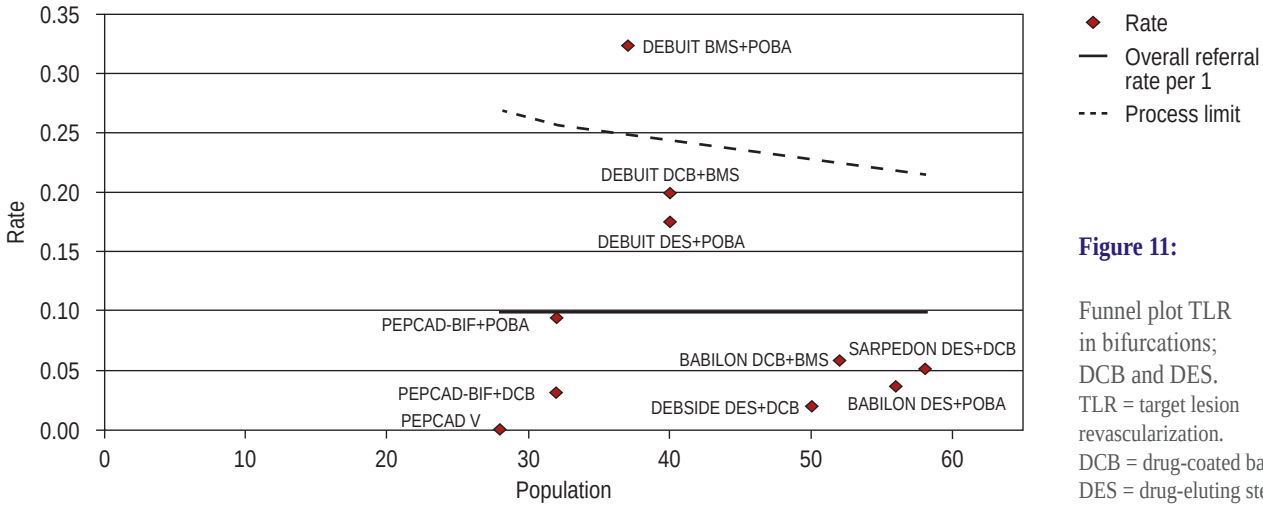

Figure 11:

Funnel plot TLR in bifurcations; DCB and DES.
TLR = target lesion revascularization. DCB = drug-coated balloon. DES = drug-eluting stent.

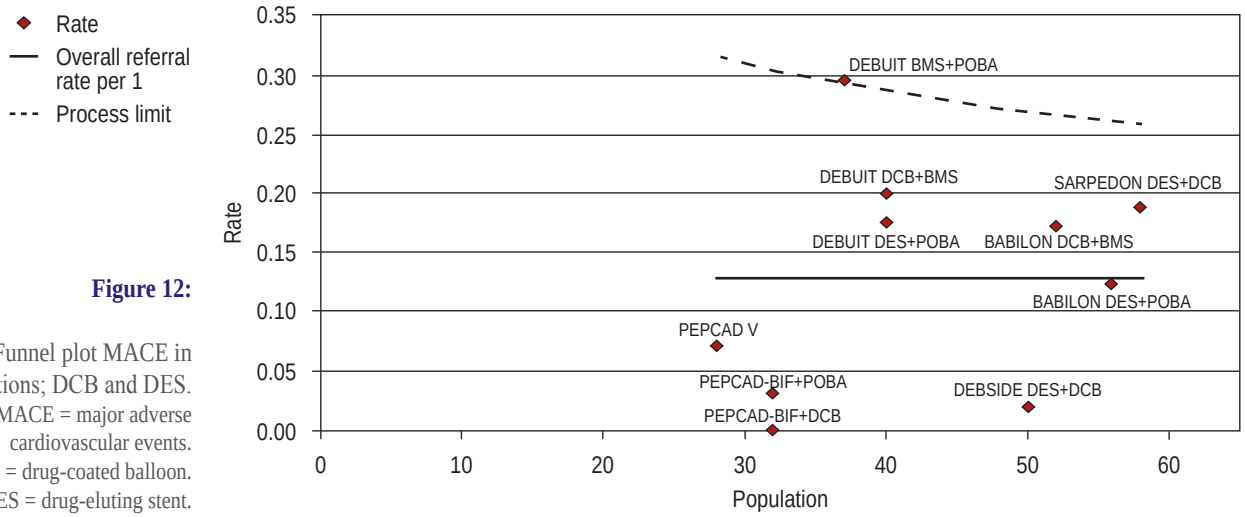

Figure 12:

Funnel plot MACE in bifurcations; DCB and DES. MACE = major adverse cardiovascular events. DCB = drug-coated balloon. DES = drug-eluting stent.

lesion revascularization). Secondary endpoints included major adverse cardiovascular events. DCB was non-inferior to stenting with BMS or DES.[31]

DISCUSSION

DCB treatment requires an initial dilatation with semi, non-compliant, or super high-pressure balloon on a 1:1 balloon-vessel ratio. Residual stenosis ≤ 30%, absence of flow-limiting dissection, and guide-wire evaluation with FFR ≥ 0.75 or iFR ≥ 0.89 would be considered a good result for DCB deployment preparation. Intracoronary image improves plaque evaluation and treatment with cutting or scoring balloon, ablation, or shockwave; DCB inflation duration must last at least sixty seconds at nominal pressure.[32,33] FFR predicts clinical outcome after balloon angioplasty with event-free survival rates at 6, 12, and 24 months of 92 ± 5%, 92 ± 5%, and 88 ± 6%, respectively, for FFR ≥ 0.90 after plain old balloon coronary angioplasty.[34]

There is significant coronary stenting contraindication or stent-less preference for several reasons such as planned non-cardiac surgery, high bleeding, and lesions that easily develop stent fracture. Iijima et al. published their experience in 118 *de novo* lesions not suitable for DES implantation 40% with very small vessel disease, 3% planned non-cardiac surgery, and 19% for high bleeding risk. TLR was the primary endpoint and suboptimal lesion preparation before DCB treatment was the secondary endpoint. Optimal lesion preparation is defined as TIMI flow grade 3, minor coronary dissection and residual stenosis ≤ 30%, suboptimal lesion preparation was 2.5%, three patient bailout stenting, 115 patients treated with DCB. TLR occurred in eight patients after an 8-month follow-up. Intracoronary image, Rotablator, conventional, cutting, and non-slip element balloon were used to optimize lesion preparation; they concluded DCB should be considered initially.[35] Ybarra et al case report suggested DCB benefits from plaque modification strategy during staged CTO treatment.[36]

Dissection after plain balloon angioplasty is a problem that may cause discomfort and overwhelm in some operators who use unnecessary coronary stenting, especially after good prognostic mild A and B-type dissections. DEBATE II showed that moderate dissections (type C) had a better prognosis if restrained for further treatment, including stenting; the explanation may relate to possible positive remodeling and major late luminal gain.[37,38]

DCB and DES in TLR effectiveness and safety are similar. RIBS IV trial is the only one with a statistically significant difference; however, its development did not follow the German consensus recommendations emphasizing the 1:1 balloon-to-vessel ratio; on the other hand, the funnel plot heterogeneity analyses index is moderate in efficacy with 0% heterogeneity in safety.

DCB and DES in SVD efficacy and safety are comparable without statistically significant differences and a wide heterogeneity index. The PEPCAD trial utilized BMS as a bailout with very high restenosis (45%); in the PICOLLETO 2 trial, DCB was superior to the everolimus-eluting stent considering in-lesion late luminal loss and comparable in clinical outcomes.

The BASKET-SMALL 2 Trial showed similar outcomes on SVD treated either with DCB or DES, without significant difference in diabetic versus non-diabetic patients. However, the people with diabetes had less target vessel revascularization with DCB.[39]

Bifurcation trials significantly differ in effectiveness and safety between DCB and DES, showing high and moderate heterogeneity indices respectively. DES is superior to BMS and plain old balloon angioplasty (POBA), and DK-Crush has the lowest TLR in DES techniques, highlighted as the gold standard DES procedure, even though compared with DCB there is no significant difference.

The DEFINITION-II Trial informs significant improvement in clinical outcomes by comparing the double stenting technique vs provisional stenting in complex coronary bifurcation lesions. In this trial, 22.5% of the provisional stent group required a side branch stent,[40] limiting the reliability of the final results.

The difference between regular balloon primary angioplasty versus stenting in ST-elevation myocardial infarction involves further interventions but there are no significant differences in mortality or reinfarction.[41] Coronary stenting during ST-elevated AMI has several inconveniences, especially related to insufficient time to know every detail of the patients and how many times a bleeding tendency is evident after stent placement. On the other hand, the generalized vasoconstriction precludes the accurate reference diameter, causing the risk for undersized stents. These issues might be the reason for more major adverse events and cardiac death for DES treatment to ST-elevation AMI.[42]

The main findings of this consensus are:

DCB and DES are equally effective and safe in IST. The clinical advantages of DCB include less risk for stent thrombosis, less bleeding in high-risk patients, shorter time of dual or triple antiplatelet therapy, avoidance of metal layers, and jailing side branches.

DCB in vessels with a diameter less than 3 mm (SVD) is a good option; the PICOLLETO-2 trial reports significantly less lumen loss with DCB vs everolimus-eluting stent and comparable clinical outcomes.

DCB in bifurcations is a promising tool. Provisional stenting in non-complex bifurcation lesions showed long-term benefits compared to a two-stent strategy.

Recommendations

1. The target lesion must receive proper preparation before DCB deployment: pre-dilatation with the conventional balloon, semi-compliant, non-compliant, or super high pressure could be used with a balloon-to-vessel ratio of 1:1, ≤ 30% residual stenosis, and dissection type A, B, C, and E is permitted. Consider prolonged inflation at low pressure for severe dissections before stenting.
2. The preparation may include plaque ablation with a cutting balloon, scoring balloon, laser, and shockwave.
3. The DCB must receive gentle management, avoiding touching the balloon and avoiding any friction with the system.
4. Consider DCB as a stand-alone therapy in *de novo* lesions in segment or bifurcation lesions for high-risk bleeding patients.
5. DCB should be the standard method to treat restenosis from either BMS or DES, equivalent to DES but nothing left behind.
6. Consider DCB over DES to treat *de novo* lesions in small vessels, especially in people with diabetes and bifurcations.
7. Consider DCB in potential stenting complications such as severe angulation, angle difference, bifurcation with > 50% side branch stenosis, hinge motion, severe calcification, chronic total occlusion (CTO), eccentricity, and atherosclerotic lesion associated with myocardial bridging.
8. Consider DCB for multi-vessel coronary artery disease.
9. Consider DCB in acute coronary syndromes, including ST and non-ST elevation

myocardial infarction and thrombus aspiration needed before DCB deployment.
10. Consider pressure wire, a physiological assessment for better outcomes. FFR ≥ 0.84 or iFR ≥ 0.89.
11. IVUS or OCT aid to treatment evaluation is not essential after DCB deployment unless suboptimal results or complications and pre/post stenting.
12. Consider being part of a DCB registry.

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Ohlsson J, Wranne B. Noninvasive assessment of valve area in aortic stenosis patients with. J Am Coll Cardiol 1986; 7: 501-508.

Six or more authors

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