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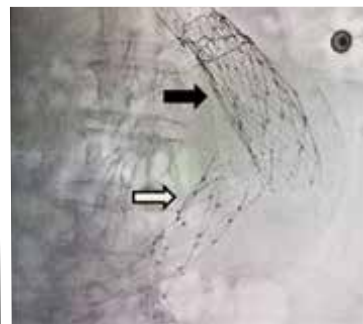
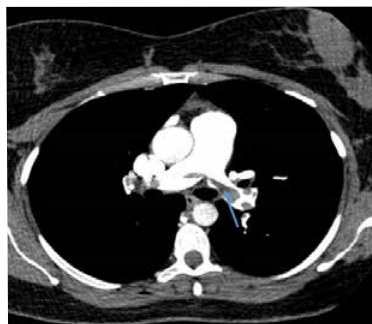
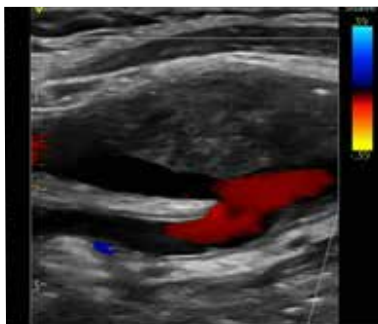
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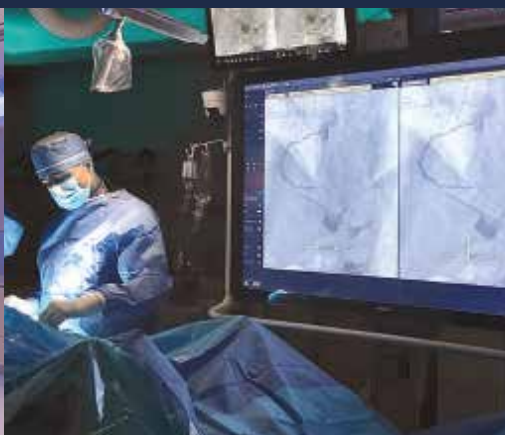
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Rediscovering the essential: the silent challenge of Familial hypercholesterolemia in Latin America.

Máxima Méndez Castillo

Clínica de Lípidos (Cli-LIPID), Santo Domingo, República Dominicana.

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ABSTRACT

Familial hypercholesterolemia (FH) remains widely underdiagnosed in Latin America, despite its high prevalence and strong association with premature cardiovascular disease. The study conducted in a subsidized population in Bucaramanga, Colombia, using the Dutch Lipid Clinic Network (DLCN) criteria, reveals the gap between clinical suspicion, genetic confirmation, and therapeutic control. Despite high adherence, only a third of patients achieved LDL-C goals, underscoring the complexity of the phenotype and the need for structured strategies. This editorial discusses the regional implications of these findings and emphasizes the need to strengthen screening, expand access to genetic testing and promote the development of lipid clinics. FH remains an unmet need in the region, and early detection represents a concrete opportunity to change the natural history of the disease.

Familial hypercholesterolemia (FH) is one of the most significant genetic disorders in cardiovascular prevention. Its impact does not spring only from its prevalence, higher than what was assumed for years, but from the lethal combination between a delayed diagnosis, a prolonged exposition to extreme levels of LDL-C and a natural history marked by premature CAD. In a continent where atherosclerotic disease is still the main cause of death, FH is a clinical challenge that remains silent, to a good extent because it is not sought with the necessary systematicity.^{1,2,3}

The study made in Bucaramanga provides several layers of reflection. First, it shows that the Dutch Lipid Clinic Network (DLCN) criteria, widely validated as a clinical tool, are still an efficient way to identify patients in risk, even in health care systems with limited resources.^{2,3,4,5,6,7,8} The evaluated cohort is representative of a frequent Latin American reality: elder patients, with a high load of co-morbidities, cared for in contexts where access to specialized follow-up is irregular. For only twenty people to meet the suspicion criteria does not imply a low prevalence; on the contrary, it reveals the structural problem: most are never even evaluated with an approach toward FH.

Another aspect deserving attention is the therapeutic gap. Adherence, close to 90%, suggests an appropriate commitment to treatment. However, only 30% reached LDL-C goals. This imbalance, observed also in international re-

gistris, exposes to converging realities: diagnostic inertia, patients arriving late, and therapeutic inadequacy before the genetic phenotype.^{3,4,9,10,11,12,13} Statins, even in high doses, are usually insufficient in patients with severe LDLR mutations. And without an appropriate diagnosis, stronger therapy combinations are hardly proposed.

The genetic component of the study enriches the clinical view. Identifying pathogenic variants in LDLR, along with APOE and PCSK9 mutations, confirms the value of genetics as a supplementary tool. Also, it displays a reality known by those working in the region: global databases do not reflect properly the Latin American genetic diversity, essentially associated to the high cost of genetic testing or the non-availability of the technique in said countries, reducing the identification of the variables known to be pathological, besides a significant number of variants of uncertain meaning, which may explain the behavior of this pathology in the region.^{1,2,14} This lack of representation leads to mutations being interpreted without a local population reference, limiting diagnostic accuracy. In spite of this, the information provided by molecular analysis is determinant to adjust therapy strategies and to start a family research, a crucial element in hereditary diseases.

The social dimension of the study is not to be overlooked either. Most patients belonged to low socioeconomic strata, a pattern that keeps repeating in Latin America. Financial

vulnerability limits access to tests, consultations and medications, and increases the chance for a diagnosis to be delayed for decades. The result is predictable: premature CAD, disabilities and death in ages where an active life is to be expected. FH, that could be detected in adolescence, is still diagnosed after the first coronary event, when damage is already significant.¹¹

Faced with this scenario, primary care emerges as an indispensable protagonist. It is clinicians, internists and clinical cardiologists who should suspect FH in the presence of persistently elevated LDL-C, a family history with early infarctions or the presence of xanthomas.^{10,12} Without the participation of the first level, no research system should prosper.

Likewise, the study points out the chance and the need to strengthen the lipid clinics in the region. These spaces allow to provide specialized care, adjust high-intensity treatments, coordinate cascade screening and perform continuing education. Where they exist, detection increases and results change. Where they don't, FH remains invisible.

The Bucaramanga experience shows that even with budgetary restrictions, directed genetic testing can be implemented, with a real clinical impact. It is an encouraging message for the region: no abundance of resources is required, but clarity in priorities.

Finally, this study is a reminder. FH is preventable, detectable and treatable. It is not a rare disease. It is not an incidental finding. It is a problem of public health. Under-diagnosing it is not due to lack of evidence, but to a lack of implementation. And it is precisely there where Latin American cardiology is called to lead a change.

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Editorial

Editorials express the opinions of their author(s), not necessarily those of the Editorial Committee of the Revista FAC.

Atrial fibrillation and bronchial asthma: two conditions linked by systemic inflammation

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ABSTRACT

Atrial fibrillation (AF) is known to be an arrhythmia characterized by uncoordinated atrial electrical activation. It is the most common sustained arrhythmia worldwide and is associated with significant morbidity and mortality. AF can range from asymptomatic (sub-clinical) to manifest episodes of arrhythmias (paroxysms) to permanent (formerly called chronic). Sometimes its first clinical manifestation can be a stroke (cerebrovascular event or cerebrovascular accident). Therefore, it is important to identify patients with a higher propensity to develop AF.

The association between AF and asthma is bidirectional. On the one hand, evidence suggests that AF shares a background of systemic inflammation with asthma. Asthma, being a systemic inflammatory disease, could be affecting the atria and thus favoring the development of atrial cardiomyopathy, which would predispose to the onset of AF.

In this issue of the Revista de FAC (Journal of FAC), Carlos Paterno et al. present the data from a retrospective study on 435 patients, of whom 93 were chronic and asymptomatic, a group that was compared with the rest, who had diseases categorized as "systemic autoimmune diseases" (SAIDs), such as psoriasis or rheumatoid arthritis, among others.¹ Although values of inflammatory activity were not compared directly, the authors compare both groups, considering them as subrogate to endothelial damage by inflammation: blood pressure values and the presence of atrial fibrillation (AF). Interestingly, neither blood pressure, nor AF frequency were different between both groups, so they assume there is similar systemic inflammation between asthma and the rest of SAIDs.¹

This editorial will focus on AF, asthma and inflammation. It is known that AF is an arrhythmia characterized by disorganized atrial electrical activation, being the most usual sustained arrhythmia at world level, and associated to a significant morbidity-mortality.² AF could be asymptomatic (subclinical), manifest episodes of arrhythmias (paroxysms) and finally be permanent (previously called chronic). At times, the first clinical manifestation could be stroke.³ Therefore, it is important to identify patients with a greater tendency to develop AF, and for this reason, there are different screening strategies. AF could be viewed from two angles: as a disease per se, or as a symptom of another disease.² For example for the second view, AF is frequently

found in acute pulmonary thromboembolism (PTE), where it is considered secondary to right atrium dilatation caused by hemodynamic alterations of pulmonary artery occlusion. Recently, the presence of atrial cardiomyopathy has been studied as a background for AF, mainly in cases where no direct cause for AF can be found (PTE, hyperthyroidism, acute ischemic heart disease, etc.).⁴

In terms of the pathophysiology of AF and its association with respiratory disorders, not considering the hemodynamic ones that have been described above for PTE, the proposed mechanisms include an elevated inflammatory activity, endothelial dysfunction and sympathetic activation; mechanisms mainly studied in sleep apnea.⁵ In the studies made in several laboratories, including ours, patients with sleep apnea were detected to possibly generate AF by common pathophysiological mechanisms, like increased sympathetic tone, intermittent hypoxemia, systemic inflammation and endothelial dysfunction.⁵ However, more recently, other respiratory diseases, such as asthma, are starting to also show an association with AF.

The association between AF and asthma is bidirectional. On one hand, evidence suggests that AF shares a background of systemic inflammation with asthma, and on the other, treatments for asthma, such as β_2 -adrenergic agonists, have been associated with a greater risk of arrhythmias.⁶ Although the main mechanism of action of β_2 -adrenergic agonists, such as salbutamol, is their bronchodilator effect,

they also have cardiovascular, uterine, metabolic and neurological effects.⁷ In regards to the heart, studies in asymptomatic patients show that salbutamol, administered by inhalation or orally, is associated with an increase in heart rate of 23 and 28%, respectively.⁷

Thus, asthma (as it is a systemic autoinflammatory disease, as the investigators of this publication point out) could be affecting the atria, and thus, favor the emergence of atrial cardiomyopathy, which would predispose to the appearance of AF. On the other hand, plenty of AF episodes in asthmatic patients could be the consequence of using bronchodilators with sympathomimetic properties (β_2 -adrenergic agonists), as with patients who already have supraventricular tachycardia.⁸ In this case, using this drugs in patients with the abovementioned substrate would make them act as AF “triggers”, through an increase in sympathetic tone.

In asthma, inflammation is mediated by numerous pathways. In the eicosanoid pathway, arachidonic acid is catalyzed by 5-lipoxygenase in leukotrienes, which are strong paracrine inflammatory substances, mainly formed in leukocytes. Leukotrienes mediate bronchoconstriction, mucus secretion and local edema in bronchioles. Leukotrienes has systemic effects; leukotriene receptors largely express in the heart and are intrinsically associated with the conduction system.⁹

Different inflammatory cytokines mediate ion channel function and atrial remodeling. Inflammation mediators have been described, such as C-reactive protein and interleukine-6, elevated in patients with AF, and their influence has even been demonstrated in AF ablation success.⁶

Tattersall et al. in 2020 raised the hypothesis that persistent asthmatic patients present a greater risk of developing AF, and that this association would be attenuated by adjusting the baseline markers of systemic inflammation. In the MESA (*Multi-Ethnic Study of Atherosclerosis*), a prospective longitudinal study in adults with no cardiovascular disease at the onset of the study, with a multi-ethnic cohort of 6615 participants with almost 13 years of follow-up, the aim was detecting the appearance of AF in these patients. They concluded that persistent asthma was associated with a 1.5 times increase in incident AF risk, that this association was not attenuated when adjusting baseline inflammatory biomarkers, and that persistent asthma could be associated to a higher relative risk of AF in women.⁹

Given the high prevalence of undiagnosed AF, which in turn may lead to severe consequences, such as thromboembolic events, heart failure and progression of AF, it is important to identify populations with a greater risk of developing AF, to make a diagnosis or start an early treatment of AF, and act timely on risk factors such as asthma, obesity and obstructive sleep apnea. Equally, in this association, it has been proven that treating obesity by weight-loss programs and treating sleep apnea in asthmatic patients improves the symptoms of asthma.

Current guidelines do not contemplate this association (AF and asthma), but it is evident that both pathologies share pathophysiological mechanisms, mainly systemic inflammation. When reviewing the 2020 and 2024 ESC guidelines on AF, between the risk factors and co-morbidities, COPD (chronic obstructive pulmonary disease) and sleep apnea are included, but asthma is not considered.^{10,11} The 2025 GINA guideline (*Global Initiative for Asthma*) suggests managing multi-morbidity, including co-morbidities like rhinosinusitis, obesity, anxiety/depression and gastroesophageal reflux, which may contribute to respiratory symptoms, and even contribute with a poor control of asthma, but do not take into account cardiovascular pathologies, among them AF.¹²

Our reflection, due to the prevalence of asthma and AF still increasing, is to consider this association, to seek it intentionally, and simultaneously, to carry out more investigations on the possible mechanisms of this association.

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Review Article

Contemporary use of antiarrhythmic drugs: practical messages for clinical cardiologists from the EHRA compendium

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Proarrhythmia; EHRA.

ABSTRACT

Antiarrhythmic drugs remain a cornerstone of rhythm and rate control in patients with cardiac arrhythmias, despite major advances in catheter ablation and device therapy. The EHRA Practical Compendium of Antiarrhythmic Drugs and its *European Heart Journal* editorial summarize 10 key messages that help clinicians use these agents more safely and effectively. The ABC indications framework (Appropriate, Back-up, Complementary) positions antiarrhythmic drugs alongside ablation and devices. A practical update of the Vaughan-Williams classification, understanding electrophysiological dynamics and pharmacokinetics, arrhythmia-specific drug selection, systematic proarrhythmic risk assessment, and careful use in comorbidities and special populations are the core themes. This article summarizes these messages with a clinical focus, supports scenario-based decision-making, and provides adapted tables and figure references to facilitate implementation in daily practice.

INTRODUCTION: WHY ANTIARRHYTHMICS STILL MATTER

The emergence of catheter ablation and therapy with devices has partially moved attention away from antiarrhythmic drugs (AADs). However, most patients with atrial fibrillation (AF) or other arrhythmias do not have access to invasive therapies, or else do not benefit from them fully, so AADs are still essential.¹

In Europe, only a minority of patients with AF undergo ablation, and around half are still in treatment with AADs after the procedure. Furthermore, AADs cannot be replaced in scenarios such as channelopathies, many ventricular tachycardias associated to structural heart disease, prevention of ICDs shocks and acute treatment in emergencies.²

The consensus document from the *European Heart Rhythm Association* (EHRA), published in *Europace* 2025, offers a practical summary of 91 pages and a supplement on the contemporary use of AADs, complemented by an editorial in the *European Heart Journal*, summarizing 10 key messages for clinicians.^{1,3} The goal of this article is moving these messages to the context of clinical cardiologists, emphasizing the practical aspects, and supporting on the editorial figures and selected tables from the summary.

1. ABC MODEL OF INDICATION FOR A CONTEMPORARY USE OF AADS

The first key message is conceptual: to arrange indications of use of AADs by the ABC model (*Figure 1*).

- **A – Appropriate therapy:** AADs are the main or preferred treatment. They include rhythm control in AF not candidate or not a priority for ablation, pharmacological termination of AF/atrial flutter or well tolerated ventricular tachycardias (VT), and prevention of recurrence in patients who respond well and prefer pharmacological treatment.
- **B – Back-up therapy:** AADs are added when ablation, devices or other treatments are inefficient, inaccessible, contraindicated or not accepted by the patient. For instance, reduction of AF recurrence after a first failed ablation.
- **C – Complementary therapy:** AADs are integrated to invasive therapy to enhance its efficacy or cover vulnerable phases (blanking period after AF ablation, prevention of VT in carriers of ICDs, association to resynchronization, etc.).³

For clinical cardiologists, this outline helps to position each prescription: are AADs the best available option for

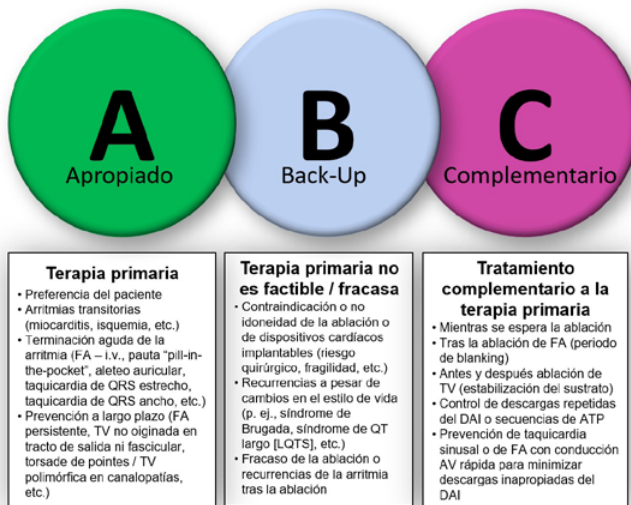


FIGURE 1A.

Indications of use of antiarrhythmic drugs by the ABC model

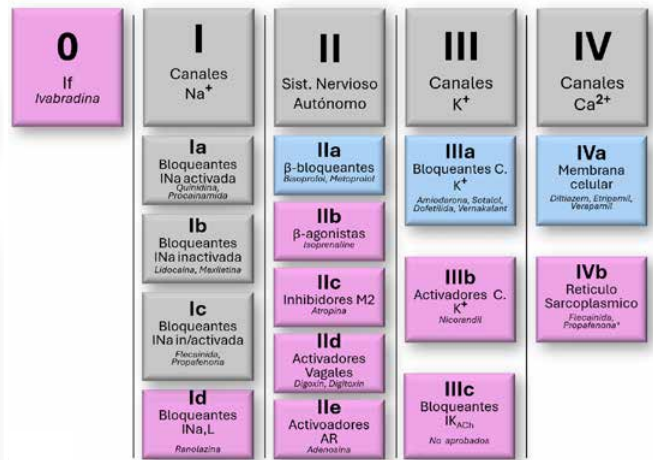


FIGURE 1B.

Simplified version of the classical Vaughan-Williams classification 2018 update

this patient? (A); do I use them as a “safety net” after the main therapy? (B); do I use them to complement or enhance another therapy? (C).

2. UPDATED AND PRACTICAL CLASSIFICATION OF AADS

The second key message is that the classical classification by Vaughan-Williams, although useful, is incomplete for current practice. The EHRA summary adopts a simplified version of the 2018 update, including new drugs (ivabradine, ranolazine, vernakalant, etc.) and reorganizes classes so that they are more useful for decision-making (Figure 1B, Table 1).⁴

In Table 1, the updated classification is outlined:

- **Class 0:** ivabradine (sinus node modulation)
- **Class I** (sodium blockers), with subclasses Ia, Ib, Ic and Id according to kinetics and effect on action potential duration
- **Class II** (adrenergic drugs), subdivided into beta blockers and sympathomimetic agents
- **Class III** (potassium channel blockers), with drugs of very varied use (amiodarone, dronedarone, sotalol, dofetilide, etc.)
- **Class IV** (non-dihydropyridine calcium channel blockers).

This classification is not just academic: it helps to anticipate effects (for instance, QT prolongation with many class III drugs), and to integrate pharmacology with the mechanism of the arrhythmia. The EHJ editorial underscores that even within a single class, there are relevant differences between drugs, which condition their efficacy and safety.

3. ELECTROPHYSIOLOGICAL AND PHARMACOKINETIC DYNAMICS: WHAT IS ACCURATE TO CHOOSE PROPERLY.

The third message approaches the “physiological layer”, explaining why a single AAD can be better to prevent rather than to end an arrhythmia, or vice versa.

3.1. Dependency on rate and binding kinetics

- **Direct dependency on use:** effect is increased at high rates. This is the case of flecainide or propafenone, which displays a more intense block at a faster rate, favoring tachycardia termination.
- **Reverse dependency on use:** the effect is emphasized in bradycardia. Sotalol extends QT more markedly at lower rates, which makes it useful to prevent AF, but increases the risk of torsades de pointes when rate decreases abruptly after tachycardia.

3.2. Pharmacokinetics and metabolism

The summary reviews absorption, liver metabolism, distribution and excretion of the main AADs, offering specific recommendations in chronic kidney disease and liver failure. Drugs such as amiodarone, dronedarone, verapamil or propranolol have a significant liver metabolism, and multiple interactions via CYP3A4 and P-gp, demanding caution when associating them with direct anticoagulants, antiplatelet drugs and other cardiovascular drugs. In clinical practice, this is translated into three simple rules:

1. Systematically review concomitant medication before starting AADs;
2. Adjusting doses in chronic kidney disease and liver failure and in fragile elderly patients;
3. Preventing combinations of QT-prolonging drugs (antiarrhythmics, macrolides or quinolones, antipsychotic drugs, etc.)

TABLE 1.

Simplified update of the Vaughan-Williams classification of antiarrhythmic drugs (AADs)

Class	Subclass	Main pharmacological target/action	Examples of drugs
HCN channel blockers			
0		Pacemaker current mediated by HCN channel (If)	Ivabradine
Na⁺ channel blockers			
I°	Ia	Nav1.5 (INa) in open state (intermediate dissociation)	Ajmaline, disopyramide ^(b) , procainamide ^(b) , quinidine/hydroquinidine ^(b,c,d)
I°	Ib	Nav1.5 (INa) in inactivate state (rapid dissociation)	Lidocaine, mexiletine ^(c) , phenytoin
I°	Ic	Nav1.5 in open/inactivate state (slow dissociation)	Antazoline ^(c) , cibenzoline, flecainide ^(d) , pilsicainide, propafenone ^(d)
I°	Id	Late Na ⁺ current	Ranolazine
Autonomous nervous system inhibitors and activators			
II	IIa	β-blockers	β1 blockers: atenolol, bisoprolol, esmolol, landiolol, metoprolol, nebivolol; β1 and β2 blockers: nadolol, propranolol; β1, β2 and α1 blockers: carvedilol, labetalol
II	IIb	β-blockers	Isoprenaline
II	IIc	Muscarinic receptor M2 inhibitors	Atropine
II	IId	Vagus nerve activators/ACh release	Digoxin, digitoxin
II	IIe	Adenosine A1 receptor activators	Adenosine
K⁺ channel blockers and activators			
III	IIIa	Unspecific K ⁺ channel blockers	Amiodarone ^(g) , dronedarone ^(g) , sotalol ^(h) , bretylium
III	IIIa	K ⁺ Kv11.1 (hERG) channel blockers	Dofetilide ⁽ⁱ⁾ , ibutilide ⁽ⁱ⁾ , nifekalant
III	IIIa	K ⁺ Kv1.5 (IKur) channel blockers	Vernakalant ^(k)
III	IIIb	K ⁺ Kir6.2 (KATP) channel activators	Nicorandil ^(l)
III	IIIc	GIRK1 and GIRK4 (IKACh) blockers	No approved medication
Ca²⁺ channel modulators			
IV	Iva	Bloqueadores no selectivos de membrana de superficie y de la corriente de Ca ²⁺ tipo L (ICaL) mediada por los canales Cav1.2 y Cav1.3	Bepridil, diltiazem, etripamil, verapamil
IV	IVb	Bloqueadores de canales de Ca ²⁺ del receptor de rianodina 2 (RyR2) del retículo sarcoplásmico intracelular	No approved medication
Mechanosensitive channel blockers			
V		Bloqueadores del canal del receptor potencial transitorio (TRPC3/TRPC6)	No approved medication
Gap junction channel blockers			
VI		Bloqueadores de conexinas Cx (Cx40, Cx43, Cx45)	No approved medication
«Upstream» target modulators			
VII		IECA, ARNI, antagonistas del receptor de mineralocorticoides, inhibidores de SGLT2, estatinas	Atorvastatin, enalapril, lisinopril, losartan, candesartan, sacubitril, spironolactone, etc.

AADs, antiarrhythmic drugs; **ACEIs**, angiotensin-converting enzyme inhibitors; **ACh**, acetylcholine; **ARNI**, angiotensin receptor-neprilysin inhibitor; **Cav**, calcium channels; **HCN**, hyperpolarization-activated cyclic-nucleotide-gated channels; **Nav**, sodium channels; **Kv**, potassium channel; **TdP**, torsades de pointes. **a** Beta blockers of Nav1.5/Na⁺ differ according to their binding state and their dissociation kinetics, conditioning its therapeutic role and its effects on cardiac action potential. Open/inactivate state blockers (slow dissociation kinetics) such as flecainide and propafenone, bind preferentially with open and inactivate Na⁺ channels, and dissociate slowly. They significantly reduce conduction velocity, particularly during tachycardia, which makes them efficient in atrial and ventricular arrhythmias (class Ic). Open state blockers (rapid dissociation), such as lidocaine and mexiletine, bind with open channels but dissociate fast, allowing a selective action in ischemic or depolarized tissue, not affecting normal conduction (class Ib). Inactivate state blockers (intermediate dissociation kinetics), such as quinidine and amiodarone, firmly bind to the resting state of Na⁺ channels, prolonging the refractory period and reducing reentrant arrhythmias (class Ia, with multiclass effects in the case of amiodarone). Na⁺ late current inhibitors, such as ranolazine, act on the persistent inflow of Na⁺ ions during the plateau phase, reducing Ca²⁺ overload and afterdepolarizations. This mechanism is particularly beneficial in ischemic conditions and to prevent arrhythmias such as TdP. **b** Class Ia AADs present secondary anticholinergic activity (class IIc), which is important for disopyramide, moderated for quinidine and mild for procainamide. This anticholinergic effect may produce sinus rate acceleration by reducing parasympathetic influence on the heart. **c** Quinidine and mexiletine also present a secondary effect of K⁺ channel block (class III), contributing to their capacity to extend repolarization and modulating action potential duration, increasing antiarrhythmic efficacy in specific conditions. **d** Catheter ablation is recommended as first-line option. **e** Beta blockers are recommended as first-line treatment for heart failure, but have a low efficacy to prevent sustained episodes of ventricular tachycardia in this scenario. **f** Vernakalant can be administered to patients with structural heart disease, as long as they do not present severe aortic stenosis, recent acute coronary syndrome or moderate to severe heart failure. **g** In regions where there is no vernakalant available, as well as IV class Ic drugs recommended by the AHA/ACC/HRS 2023 AF guidelines. **h** They may present limited efficacy if there is elevated adrenergic tone. **i** Vagal maneuvers are first-line option. **j** Electrical cardioversion is the first-line choice.

4. SAFE PRESCRIPTION: BASAL EVALUATION, START AND FOLLOW-UP

The summary emphasizes on safety not depending only on the drug, but also on the scenario where it is started.

4.1. Basal evaluation before starting AADs

Before prescribing an AAD that could extend QRS or QT, it is advisable:

- 12-lead ECG (QRS, QTc, U waves, previous bradyarrhythmias or tachyarrhythmias)
- Echocardiogram to document systolic function, hypertrophy and valvulopathy
- Renal and liver function, electrolytes (K+, Mg2+)
- In amiodarone, thyroid, lung and basal ophthalmological evaluation.³

4.2. Starting in the hospital or as outpatient treatment?

EHRA proposes a pragmatic strategy:

- Admission recommended for class Ia and some class III drugs (dofetilide, ibutilide) due to risk of early proarrhythmia
- Ambulatory start with adequate monitoring in patients with no structural heart disease for class Ic, amiodarone (oral), dronedarone or ranolazine, with serial ECGs within the first 24-72 h or in early visits
- Reinforcing patients' education on warning symptoms (dizziness, syncope, more intense or prolonged palpitations, heart failure worsening).

4.3. Structured follow-up

Once maintenance dose has been established, follow-up should include:

- Periodical ECG (at least once a year, and before if there are modifications made on doses or concomitant medications)
- Specific monitoring according to drug (for instance, thyroid testing, liver function and serial chest X-rays or CT in prolonged treatment with amiodarone).

5. SELECTION OF AADS ACCORDING TO TYPE OF ARRHYTHMIA

Table 2 (adapted from Table 3 from the EHRA summary) outlines the AADs recommended by the clinical guidelines of the European Society of Cardiology according to the type of arrhythmia, differentiating prevention and termination, and taking into account the presence or not of structural heart disease (Figure 2).^{5,6,7}

5.1. Atrial fibrillation (AF) and atrial flutter (Figure 3)

- In patients with no significant structural heart disease, the first-line options for rhythm control include flecainide, propafenone, dronedarone and sotalol, saving amiodarone for selected cases
- In the presence of relevant structural heart disease (ventricular dysfunction, severe hypertrophy, extensive CAD) amiodarone is prioritized, and in specific scenarios, sotalol as well, avoiding class Ic
- The pill-in-the-pocket approach with flecainide or propafenone in selected paroxysmal AF is still a useful strategy when its safety has been proven in a monitored environment (Figure 4)

5.2. Supraventricular tachycardias (SVT) with no AF

In atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentry tachycardias (WPW) and focal atrial tachycardias, ablation is frequently the preferred option, but AADs are still an alternative or bridge.

- Beta blockers and verapamil/diltiazem are the first choice for most SVT with no manifest accessory pathway
- Flecainide and propafenone are saved for patients with no structural heart disease, who are not candidates for ablation or who refuse it.

5.3. Premature ventricular contractions and ventricular tachycardias

The choice depends on the presence of structural heart disease and the clinical context (idiopathic vs scar) (Figure 5).

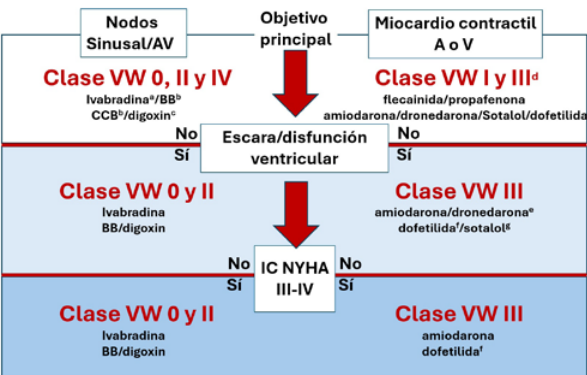


FIGURE 2. Recommendations from the clinical guidelines of the European Society of Cardiology according to the type of arrhythmia, indication of prevention or termination and presence of structural heart disease.

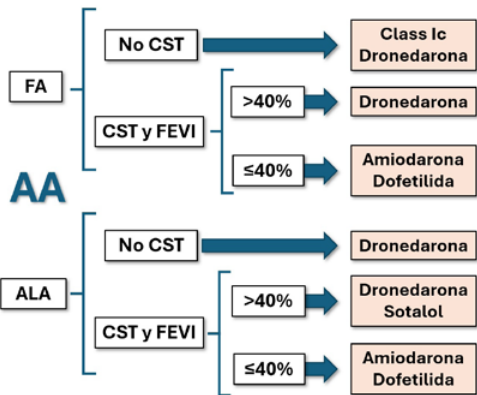


FIGURE 3. Selection of antiarrhythmic drugs in atrial fibrillation and atrial flutter

TABLE 2.

Antiarrhythmic drugs and other recommended agents for different heart rhythm disorders according to clinical practice guidelines. When two options are offered, it is advised to use the second alternative AAD as substitute option. The cells in green show high evidence / recommendation, those in yellow medium, and those in orange weak.

Tachycardia prevention					
Rhythm disorder	First choice AADs	Strength of recommendation	Second choice AADs	Strength of recommendation	ESC guideline (year/topic)
Sinus tachycardia ^a	Ivabradine, beta blockers	Medium	Alternative or combination	Medium	2019 SVT
Focal atrial tachycardia (focal AT)	Beta blockers, calcium antagonists (CCB) or class Ic drugs	Medium	Alternative		2019 SVT
Atrial flutter (AFL)	Beta blockers or CCB ^b	Medium	Amiodarone ^c	Low	2019 SVT
Atrial fibrillation (AF) – no structural heart disease (SHD) or heart failure (HF)	Class Ic drugs or dronedarone	High	Alternative		2024 AF
AF – with SHD or HFpEF/HFmrEF	Dronedarone	High	Alternative		2024 AF
AF – HFrEF	Amiodarone	High			2024 AF
Non-preexcited paroxysmal supraventricular tachycardia (SVT)	Beta blockers or CCB ^e	Medium ^e	Alternative	Medium	2019 SVT
Polymorphic ventricular tachycardia/ventricular fibrillation (PVT/VF) with SHD or ischemia	Beta blockers and K ⁺ /Mg ²⁺ replenishment	High	Amiodarone	Medium	2022 VA
Premature ventricular contractions (PVC) / idiopathic VT in outflow tract or fascicular	Beta blockers or CCB or class Ic drugs ^e	Medium ^e	Alternative		2022 VA
Idiopathic PVC/VT of another origin	Beta blockers or CCB	High	Alternative or ablation		2022 VA
VT with SHD	Beta blockers	High ⁱ	Amiodarone or sotalol	Medium	2022 VA
Torsades de pointes (TdP)/VF without SHD	Nadolol/propranolol (LQTS 1 and 2, CPVT). Mexiletine (LQT3). Quinidine (LQTS, idiopathic VF, ERS, Brugada)	High and Medium	Flecainide (CPVT)	Medium	2022 VA
Tachycardia termination/control					
Rhythm disorder	First choice AADs	Strength of recommendation	Second choice AADs	Strength of recommendation	ESC guidelines (year/topic)
Focal AT	IV adenosine	Medium	IV CCB, IV beta blockers	Medium	2019 SVT
AFL	IV ibutilide/dofetilide	High	Amiodarone	Low	2019 SVT
AFL	Beta blockers or CCB ^b	Medium	Amiodarone ^c	Low	2019 SVT
AF – with no SHD or HF	IV vernakalant ^f ; IV flecainide / propafenone or «pill-in-the-pocket»	High	Alternative: ibutilide ^k		2024 AF
AF – with SHD/HF	IV vernakalant ^f ; IV amiodarone	High	Alternative		2024 AF
AF – without SHD or HF (HR control)	Beta blockers, CCB or digoxin ^d	High	Alternative		2024 AF
AF – with SHD or HF (HR control)	Beta blockers or digoxin	High	Alternative		2024 AF
Narrow QRS complex tachycardia	IV adenosine	High	IV CCB, IV beta blockers	Medium	2019 SVT
Wide QRS complex tachycardia	IV adenosine	High	IV procainamide	Medium	2019 SVT
Preexcited SVT	Class Ic drugs or ibutilide or IV procainamide	Medium ^g	Alternative		2019 SVT
Preexcited AF	Ibutilide or IV procainamide	Medium	Class Ic drugs	Low	2019 SVT
PVC/idiopathic VT of outflow tract or fascicular	Beta blockers (outflow tract) or IV CCB (fascicular)	High	Alternative		2022 VA
VT with SHD or of unknown origin ^h	IV procainamide	Medium ⁱ	Amiodarone	Low	2022 VA
TdP/VF with no SHD	Mg ²⁺ , K ⁺ , beta blockers (congenital LQTS). Isoprenaline (acquired LQTS, idiopathic VF, ERS, Brugada). Verapamil, quinidine (idiopathic VF)	High / Medium			2022 VA
PVT/VT with SHD or ischemia	Beta blockers and K ⁺ /Mg ²⁺ replenishment	High	Amiodarone	Medium	2022 VA

ADD, antiarrhythmic drugs; AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; CCB, calcium channel blockers; CPVT, catecholaminergic polymorphic ventricular tachycardia; ERS, early repolarization syndrome; ESC, European Society of Cardiology; HF, heart failure; HFpEF/HFmrEF/HFrEF, heart failure with preserved / mildly reduced / reduced ejection fraction; HR, heart rate; LQTS, long QT syndrome; PISP, pill-in-the-pocket; PVTs, premature ventricular contractions; PVT, polymorphic ventricular tachycardia; SHD, structural heart disease; SVT, supraventricular tachycardia; TdP, torsades de pointes; VA, ventricular arrhythmias; VF, ventricular fibrillation; VT, ventricular tachycardia. **a** Management of reversible causes is the first-line option. **b** Used for heart rate control with scarce effect on atrial flutter prevention. **c** Sotalol and dofetilide are also recommended in the AHA / ACC / HRS 2023 AF guidelines, and in this consensus, dronedarone is identified as another reasonable alternative to amiodarone. **d** Catheter ablation is advised as first-line option. **e** Beta blockers are recommended as first-line choice to treat heart failure, but present a low efficacy to prevent sustained episodes of VT in this scenario. **f** Vernakalant can be administered to patients with SHD but no severe aortic stenosis, recent acute coronary syndrome or moderate to severe heart failure. **g** In areas where there is no vernakalant available, as well as IV class Ic drugs recommended by the AHA / ACC / HRS 2023 AF guidelines. **h** They may have a limited efficacy if there is elevated adrenergic tone. **i** Vagal maneuvers are the first-line option. **j** Electrical cardioversion is the first-line choice.

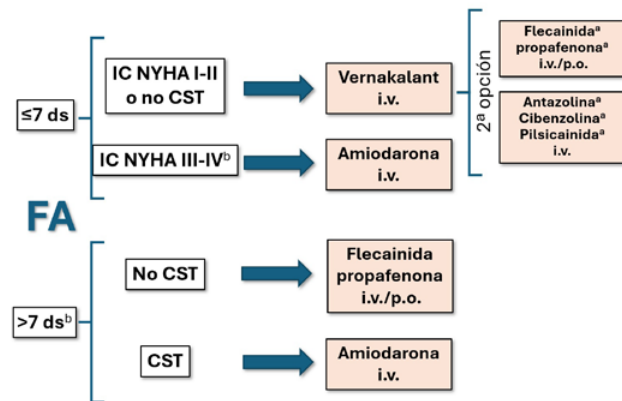


FIGURE 4.

Pill-in-the-pocket approach with flecainide or propafenone in paroxysmal AF

- In well tolerated idiopathic ventricular arrhythmias, beta blockers and verapamil are usually the first line; flecainide, propafenone or sotalol are considered in absence of structural heart disease
- In structural heart disease, amiodarone and sotalol are the reference drugs, in combination with beta blockers and devices (ICD).

Table 3 (adapted from Table 4) lists the typical indications and the scenarios where AADs should not be used, per drug, providing a quick view on “when yes and when no” for each AAD.

6. INTEGRATION WITH ABLATION, DEVICES AND OTHER THERAPIES

One of the differential messages of the summary is the integrating view of AAD with other rhythm control strategies:

- In AF, many patients benefit from a combined approach: AAD to reduce the arrhythmic load, facilitate cardioversion or manage recurrence, along with ablation when indicated
- In carriers of ICD, AADs (amiodarone, sotalol, beta blockers) reduce the incidence of ventricular tachycardias, and therefore, of appropriate and inappropriate shocks
- In channelopathies (LQTS, Brugada, catecholaminergic polymorphic VT), quinidine, mexiletine, or specific beta blockers are integrated with non-pharmacological strategies (sympathetic denervation, ICD, avoidance of triggering drugs).

This integration is reflected in several of the figures of the EHJ editorial (Figures 4, 6, 7 and 8), illustrating the position of AADs within practical clinical decision-making circuits.

7. RISK OF PROARRHYTHMIA: IDENTIFICATION, PREVENTION AND MONITORING

Proarrhythmia is the main weakness of AADs. The summary devotes an extensive section to this problem, and

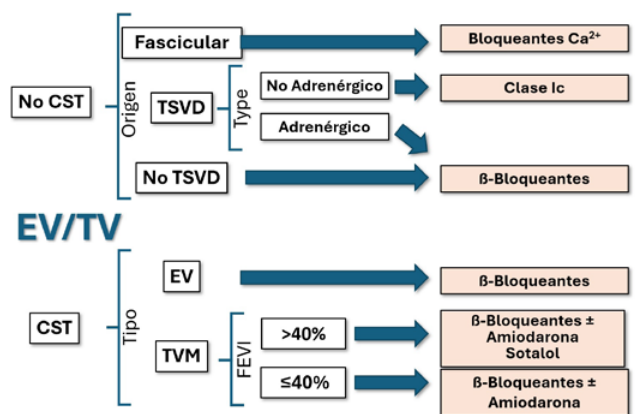


FIGURE 5.

Selection of antiarrhythmic drugs in premature contractions and ventricular tachycardias

offers both a risk table per drug, and a list of predisposing factors (Tables 4 and 5).

7.1. Risk according to drug

Table 4 (Table 10 of Europace) classifies the risk of proarrhythmia (low, intermediate and high) and the typical type of induced arrhythmia (torsades de pointes, monomorphic VT, bradyarrhythmias, etc.) for the main AADs of classes I through IV and other agents.³

Some practical aspects:

- Torsades de pointes is associated mainly with many class III drugs (sotalol, dofetilide, ibutilide) and certain class Ia drugs (quinidine, disopyramide), particularly in combination with additional risk factors
- QRS prolongation with class Ic may precipitate monomorphic VT or VF in ischemic structural heart disease or cardiomyopathy
- Beta blockers and non-dihydropyridine calcium channel blockers usually present a low risk of torsades-like proarrhythmia, but may induce significant bradyarrhythmias in specific patients.

7.2. Predisposing factors

Box 12 of the summary (Table 5 in this article) details the factors increasing the risk of torsades de pointes: female gender, advanced age, prolonged basal QTc, bradycardia, hypokalemia, hypomagnesemia, heart failure and renal or liver insufficiency, among others.

In practice, clinical cardiologists should:

1. Adjust electrolytes before and during treatment with QT-prolonging AADs
2. Avoid combinations of QT-prolonging drugs, except under a very justified indication
3. Reassess QTc periodically after dose modifications, introduction of new drugs or appearance of symptoms.

TABLE 3.

Typical indications and contraindications of the main antiarrhythmic drugs (AADs)

The conditions for the indications and contraindications are expressed between brackets.

Modified VW class	AAD	Main indications	It should not be used/main contraindication
IIB	Ivabradine	Inappropriate sinus tachycardia	Cardioversion of atrial fibrillation
IA	Ajmaline	AF termination (with preexcitation); termination of monomorphic VT (MVT) with no significant structural heart disease	Brugada syndrome (BrS); heart failure with reduced ejection fraction (HFrEF)
IA	Quinidine	Prevention of polymorphic VT (PVT) in channelopathies	Long QT interval
IA	Procainamide	Termination of MVT with structural heart disease (SHD)	HFrEF
IA	Disopyramide	Prevention of vagotonic AF	HFrEF
IB	Lidocaine	Termination of PVT/ischemic VF	Bradycardia
IB	Mexiletine	Prevention of TdP in LQT3	Bradycardia
IB	Phenytoin	Termination of junctional ectopic tachycardia (JET) by digitalis toxicity	Bradycardia
IC	Flecainide / Propafenone	Prevention/termination of idiopathic AF; WPW syndrome	BrS; SHD
ID	Antazoline	Termination of idiopathic AF	Bradycardia; SHD
ID	Ranolazine	Prevention/termination of AF	Long QT interval
IIA	Beta blockers β_1 (e.g., bisoprolol, metoprolol)	Rate control in AFL/AF; idiopathic VT/PVC	Bradycardia
IIA	Beta blockers $\beta_1+\beta_2$ (e.g., nadolol, propranolol)	Prevention of TdP in LQT1 and LQT2; catecholaminergic polymorphic VT (CPVT)	Bradycardia
IIB	Isoprenaline	TdP in acquired LQTS; PVT in BrS	CPVT
IIC	Atropine	Sinus bradycardia	Inappropriate sinus tachycardia
IID	Digoxin	Rate control in AF/AFL	Amyloidosis
IIE	Adenosine	Termination of paroxysmal supraventricular tachycardia (PSVT)	Asthma/COPD
Modified VW class	AAD	Main indications	Should not be used/main contraindication
III	Amiodarone	Prevention/termination of AF/AFL in HFrEF; prevention/termination of MVT with SHD	Bradycardia
III	Dronedronarone	Prevention of AF/AFL in SHD	Permanent AF; HFrEF
III	Dofetilide	Prevention of AF/AFL in HFrEF	Long QT interval
III	Ibutilide	Termination of AFL	Long QT interval
III	Sotalol	Prevention of MVT with SHD	Chronic kidney disease (CKD)
III	Vernakalant	Termination of AF ≤ 7 days of evolution	Aortic stenosis; NYHA III/IV
IV	Verapamil / Diltiazem	Rate control in AF/AFL; prevention/termination of fascicular VT	MVT with SHD; HFrEF

ADD, antiarrhythmic drugs; AF, atrial fibrillation; AFL, atrial flutter; BrS, Brugada syndrome; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; HFrEF, Heart failure with reduced ejection fraction; JET, junctional ectopic tachycardia; LQTS, long QT syndrome; LVEF, left ventricular ejection fraction; MVT, monomorphic ventricular tachycardia; PVCs, premature ventricular contractions; PVT, polymorphic ventricular tachycardia; RVOT, right ventricular outflow tract; SHD, structural heart disease; TdP, torsades de pointes; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White.

8. SPECIAL POPULATIONS AND SITUATIONS

The summary devotes a chapter to situations in which physiology or comorbidities substantially modify the benefit-risk profile of AADs:

- Pregnancy: beta blockers are preferred (with specific caution), avoiding amiodarone and dronedarone due to their potential fetal toxicity
- Children and fetuses: they require specific experience, and often, referral to reference centers
- Elderly patients: greater risk of adverse effects, interactions and accumulation of drugs; it is advised to start with low doses, monitor closely and frequently review concomitant medication
- Heart failure: the choice of AADs in LVEF reduction is particularly delicate; amiodarone is prioritized in many situations and class Ic is avoided
- Renal or liver insufficiency: they require dose adjustment, and in some drugs, they should be avoided completely

TABLE 4.

Risk of proarrhythmia and typical forms of proarrhythmia of different antiarrhythmic drugs (AADs). The background is shown in black, beige or white to indicate high, moderate or low risk of proarrhythmia, respectively.

Class	Drug	Risk	Type of proarrhythmia
0	Ivabradine	Low	Bradycardia, AV block, AF
Ia	Quinidine	High	TdP
Ia	Procainamide	Moderate	AV block, monomorphic VT ^b , TdP
Ia	Disopyramide	Low	Bradycardia
Ib	Mexiletine / Lidocaine	Low	Bradycardia, AV block
Ic	Flecainide	Moderate	AFL ^a , monomorphic VT ^b , bradycardia
Ic	Propafenone	Moderate	AFL ^a , monomorphic VT ^b , bradycardia
Id	Ranolazine	Low	QT prolongation
IIa	Beta blockers	Low	Bradycardia, AV block
IIb	Isoprenaline	Low	Sinus tachycardia, PAC, PVC, VT
IIc	Atropine	Low	Sinus tachycardia, paradoxical AV block ^d
IId	Digoxin / Digitoxin	Moderate	AV block, junctional tachycardia, polymorphic VT, AT with AV block
IIe	Adenosine	Moderate	Transient sinus bradycardia and AV block, AF, PAC, PVC
III	Amiodarone	Low	Bradycardia, AFL ^a
III	Dronedarone	Low ^e	Bradycardia
III	Dofetilide	High	TdP
III	Ibutilide	High	TdP
III	Sotalol	High	TdP, bradycardia
III	Vernakalant	Low	Sinus bradycardia, non-sustained VT (NSVT)
IV	Verapamil	Low	Bradycardia, AV block
IV	Diltiazem	Low	Bradycardia, AV block

FA, fibrilación AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; AV, atrioventricular; NSVT, non-sustained ventricular tachycardia; PAC, premature atrial contractions; PVC, premature ventricular contractions; TdP, torsades de pointes; VT, ventricular tachycardia. **a** In patients with AF. **b** In patients with structural heart disease. **c** In patients with sinus node dysfunction or AV conduction disorders. **d** AV block worsening in ECG, like AV block progression from second degree to complete block when atropine increases sinus rate. **e** High risk when combined with digitalis, as dronedarone reduces renal excretion of digitalis agents, enhancing associated risks. The combination may also increase the probability of AV block and other proarrhythmic effects.

- Channelopathies and familial heart diseases: the summary offers specific recommendations (for instance, use of quinidine in Brugada, mexiletine in LQTS3, etc.), integrating evidence and clinical experience.

9. NEW DRUGS AND FORMULATIONS BEING DEVELOPED

Most evidence is still focused on classical antiarrhythmic drugs, but there is a small but active line of development of new drugs and formulations. The most advanced example is etripamil, a short-acting calcium channel blocker administered intranasally, close to being approved for home self-administration to terminate AV nodal-dependent tachycardia.⁸ In the same line of management “on demand”, an inhaled formulation of flecainide is being evaluated, which may offer a fast cardioversion of AF of recent onset.⁹

In addition, the summary mentions other compounds in earlier stages of research, like budiodarone, HDAC6 inhi-

bitors, and small-conductance potassium channel blockers (SK channels). All of them are considered now experimental strategies, with no role yet in usual critical practice or recommendations from guidelines, but show the possible ways for a future renewal of antiarrhythmic therapy.

10. PRACTICAL IMPLICATIONS FOR CLINICAL CARDIOLOGISTS

From the 10 key messages in the EHJ editorial and the EHRA summary, some operative conclusions are drawn for daily consultation:

1. AADs remain essential: ablation and devices do not substitute the need for an expert use of drugs.
2. The ABC model helps to prioritize: it forces us to question whether AADs is the main therapy (A), back-up (B) or complementary (C), and to document this logic in clinical history.

TABLA 5.

Clinical risk factors and electrocardiographic signs related to torsades de pointes (TdP)

Risk factors of TdP	ECG signs indicating risk of TdP
• Age >65 years^a • Female gender^a • Congenital long QT syndrome (clinical or subclinical by incomplete penetrance, mono or polygenic) • Personal history: - History of syncope - History of TdP or significant bradycardia - Nausea, vomit, diarrhea or current use of laxatives • Structural heart disease: - Myocardial ischemia - Heart failure - Left ventricular hypertrophy • Systemic disorders: - Renal or liver insufficiency - Hypothyroidism - Subarachnoid bleeding - Hypothermia • Electrolytic disorders: - Hypopotassemia (<3.5 mmol/L) - Hypocalcemia (<8.5 mmol/L) - Hypomagnesemia (≤0.7 mg/dL) • Drugs: - Medication extending QT - Diuretic treatment - Drug interactions • Signs in ECG	• Bradycardia (<60 bpm), including recent conversion from AF • QTc >500 msec • QT increase >60 ms in regard to baseline • T-wave alternans • T or U wave distortion • Premature ventricular contraction and non-sustained VT triggered after a pause

AF, atrial fibrillation; ECG, electrocardiogram; VT, ventricular tachycardia.

^a Age and gender per se are not enough to contraindicate specific antiarrhythmic drugs, although a closer monitoring and control of other risk factors are recommended.

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3. A practical classification and basic understanding of pharmacodynamics allow to anticipate desired and undesired effects, to better choose the drug and to explain patients what is the goal with each treatment.
4. Safety depends on context: thorough basal evaluation, informed decision on in-hospital or outpatient start, and structured monitoring are as important as the drug's choice.
5. Selection should be specific for each arrhythmia, but always integrated with the rest of the strategy (anticoagulation, comorbidities management, ablation, devices).
6. Proarrhythmia can be prevented to a large extent if risk factors are identified, the appropriate drug is chosen, and there is an adequate monitoring.
7. Special populations require caution and adapting more than global prohibitions.

All in all, the EHRA summary provides a “map” for a contemporary use of AADs. This article attempts to translate it to the area of Spanish-speaking clinical cardiologists, integrating conceptual figures and practical tables that may serve as quick support for decision-making.

Original Investigation Reports

Early Reperfusion Project for Patients with ST-Segment Elevation Acute Coronary Syndrome in the Public Sector of the Alto Valle of Río Negro. Science and Policy Interface: A technical offering to policy makers to achieve health results.

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Acute Myocardial Infarction,
Percutaneous Coronary Intervention,
Thrombolysis.

ABSTRACT

Introduction: in the Alto Valle of Río Negro (RN) in 2017, a healthcare issue was identified where hospitals do not routinely use thrombolytics (TBL) for immediate treatment of ST-Segment Elevation Acute Coronary Syndrome (STEMI) and instead refer patients for primary percutaneous coronary intervention (PCI).

Objective: to formulate an early reperfusion project that includes pre-hospital/hospital thrombolysis and PCI under the " Infarction Code" (IC) protocol to reduce the years of potential life lost (YPLL) observed in this population and to increase patient engagement.

Materials and Methods: the project was formulated using the methodology of socio-sanitary project development from a perspective of macromanagement.

Results: prioritizing PCI as the main strategy, STEMI patients from hospitals in the Eastern Health Zone should be referred to Sanatorio Juan XXIII (Level A1) or Clínica Roca (Level A2). Patients from the Western Health Zone should be referred to Fundación Médica (Level A1) or Policlínico Modelo de Cipolletti (Level A2), with direct access to the hemodynamics room. The arrival times from Catriel and El Cuy are at the threshold for PCI within 120 minutes; therefore, these patients should receive (unless contraindicated) fibrin-specific TBL followed by referral for a pharmaco-invasive strategy.

Conclusions: the situation in the Alto Valle of RN requires immediate, collective, and coordinated actions among different stakeholders to enable network-based treatment of STEMI under the IC protocol, aiming to increase the average life years gained (LYG) and to enhance patient engagement.

INTRODUCTION

Health, particularly care for acute myocardial infarction (AMI) in the public sector of Alto Valle de Río Negro (RN), presents room for improvement; to take advantage of this, it is necessary to identify management problems, both in structure and processes: identifying them is the foundation to formulate projects to solve them. Decision making emerges from the identification of problems, the establishment of priorities, proposal of alternatives, formulation of a project and evaluation.

Planning is the continuing process of anticipating resources and services necessary to achieve specific goals according to an established order of priorities, choosing the optimal solution(s) among many alternatives, taking into consideration the context of currently known internal and external difficulties, or that can be expected in the future. A

project is an interrelated set of planned activities, an instrument of change within preexisting processes constituting a scenario of interaction between different actors with diverse interests and perspectives, where information is exchanged, groups and institutions are brought together, alliances and/or conflicts are generated as part of the process. As actions develop, evaluation is constituted to provide feedback on planning and management of projects; this planning/execution/evaluation process is an indivisible whole with permanent feedback.^{1,2}

According to a previous investigation in Alto Valle de RN, a sanitary problem has been detected: it is unlikely for early reperfusion treatment to be applied in patients with ST-segment elevation acute coronary syndrome (STEACS), and for the maximum number of these patients to be treated according to their incidence; hospitals do not usually use fi-

brinolytic agents for the immediate care of infarction, and these patients are referred to undergo PTCA, regardless of the time elapsed since diagnosis.³ During the development of the study, it was observed that the time window (TW) for PTCA was prolonged with a median of 200 minutes (IQR: 120-480) or a mean of 336±290, and only 26 patients were treated in year 2017; from these, 25 with good course, and one patient died, representing 15 total years of potential life lost (YPLL); taking into account the population and incidence of AMI, 50.5 total YPLL were not recorded due to lack of treatment of patients in 2017.³

STEACS presents multiple barriers in the public health sector of Alto Valle, which prevent a proper treatment: causes attributable to patients, like delaying to consult, deficit in prehospital-hospital care, lack of human resources (HR) in number and quality, deficit in technological resources, lack of treatment and training of staff, and absence of coordinated regional networks that would facilitate a fast referral to complexity centers, prioritizing times to act.³

Large distances make delays to PTCA to be prolonged. Every 30 minutes of delay to perform PTCA entails an increase in yearly mortality of 7.5%.⁴ Faced with the alternative to choose a reperfusion method before the patient, we should take into account that, if a delay exceeds 120 minutes, the best treatment will not provide the expected benefits.^{5,6,7,8}

A lack of coordination becomes evident in social and health care policies, as well as system fragmentation that removes regulation power from the State. This problem is universal; so, formulating an early reperfusion project is relevant, so much so that both the WHO and the World Heart Federation (WHF) are working to achieve a 25% reduction in early mortality by chronic noncommunicable diseases (NCDs) by 2025.⁹

The hypothesis is that formulating an early reperfusion project within five years would reduce YPLL, would achieve more life years gained (LYG) and a higher number of patients with STEACS would be treated in Alto Valle de RN.

The aim of the project is reducing cardiovascular morbimortality by STEACS in the public health sector of Alto Valle de RN.

General aim: formulating an early reperfusion project with prehospital/hospital thrombolysis and PTCA for Alto Valle de RN, with Infarction Code (IC) protocol.

Specific aims:

1. Improving prehospital/hospital care of patients with STEACS by treating more patients and using prehospital/hospital fibrinolysis and/or PTCA, as it may correspond in hospitals of Alto Valle de RN.
2. Implementing a network of regional care for prehospital management of patients with STEACS to administer reperfusion therapy fast and efficiently.
3. Establishing a protocol of IC to act.

GOALS OF THE GENERAL AIM OF THE PROJECT:

- Achieving early reperfusion in STEACS within 120 minutes by PTCA as priority strategy, 5% in the first year, 10% in the second, 25% in the third, 30% in the fourth and 60% in the last year.
- Decreasing mortality by STEACS in Alto Valle of RN between 20 and 25% per year, until obtaining by the end of the project, a reduction of approximately 50% of yearly mortality.
- Achieving increasing the treatment of patients with STEACS per year, following the ratio obtained in the city of Rosario: 52%, 150%, 9%, 14% and 28% respectively.¹⁰

Goals of specific aim (SA) 1 of the project:

- Obtaining the HR needed for emergency services, 50% within the first 6 months, 100% within 18 months.
- Obtaining 100% of necessary equipment for a fast diagnosis of STEACS in all ERs of hospitals in Alto Valle within the first 3 months.
- Obtaining 100% of necessary supplies for a fast diagnosis of STEACS in all ERs of hospitals of Alto Valle within the first 3 months.
- Acquiring high complexity ambulances necessary to move patients, for all hospitals, two per month, until completing a fleet of twelve ambulances within 6 months.
- Achieving building adequacy of ER services, 100% within the first 6 months.
- Disseminating and communicating patients and relatives at the time of discharge, as well as to the general population, the need to consult fast when precordial pain appears or when there are symptoms compatible with AMI.¹¹

Goals of SA2 of the project:

- Establishing a coordination, monitoring and feedback main office, 100% within the first 6 months, following the IC protocol.
- Categorizing centers and services according to FAC recommendations within the first 6 months.⁷
- Referring patients to private care centers for PTCA, with direct admission to the hemodynamics ward, 50% within the first 6 months, 100% within one year.
- Achieving prioritizing beds in private centers for STEACS, 50% within the first six months, 100% within one year.

Goals of SA3 of the project:

- Recording personal and origin data of patients, history, clinical characteristics, data on infarction and procedure, etc., according to ANNEX 1, 100% within the first 3 months.
- Systematic quantification of timing, 100% within the first 3 months.
- Reaching a maximum time since first medical contact (FMC)-ECG and diagnosis ≤10 min, 50% within the first 3 months, 100% within one year.

- Reperfusing the infarction culprit artery (ICA) with PTCA before 120 minutes since FMC, 5% within the first year, 10% in the second, 25% in the third, 30% in the fourth and 60% in the last year.¹²
- Reaching a maximum time since the diagnosis of STEACS to thrombolytics (TBL) infusion in a prehospital/hospital context of 10 minutes, 50% within 6 months, 100% within one year, in the case of patients with no access to a center with PTCA before 120 minutes.¹³
- Achieving access to TCA, in the case of TBL without reperfusion criteria, hemodynamic failure, electrical instability or ischemia worsening, 50% within the first 6 months, 100% within the first year.
- Achieving pharmacoinvasive strategy within 2-24 hours after successful thrombolysis, 50% within the first 6 months, 100% within one year.¹⁴
- Achieving the systematic recording of processes and results, 50% within the first year, 100% within the second year.
- Writing guidelines for clinical practice and protocols to act 100% within the first 3 months.
- Achieving the training of HR 50% within the first 6 months, 50% within the second semester.
- Achieving the training of HR on IC protocol, 50% within the first 3 months, 50% within the second trimester.
- Achieving certification, 50% of the staff within the first 6 months, 50% in the second semester.
- Achieving participation in the Federal Registry of Cardiovascular Diseases (REFECV by its acronym in Spanish), 50% within the first 6 months, 50% within one year.
- Achieving the obligation to report STEACS to the National System of Epidemiological Surveillance (SINAVE by its acronym in Spanish), 50% within the first 6 months, 50% within one year.

MATERIALS AND METHODS

We applied the methodology to formulate socio-sanitary projects from a perspective of macro-management, by which decisions related to public health care policies, actions by authorities to direct a social group toward specific goals, provide a framework and condition the implementation of budgets and coverage.¹⁵

In this project, to be developed within 5 years, we decided to propose PTCA as a priority strategy, and in the cases of thrombolysis, we decided to use tPA (Alteplase), as it is fibrin-specific. The following were considered as indicators of outcomes: pain-to-FMC, window-time (WT), door-to-needle time (DTNT) and door-to-balloon time (DTBT).

We started by the health scenario observed in the population of Alto Valle de RN (2017), activities and actions were prepared, and the necessary resources were estimated (physical, human, financial) approaching this from macro-management.³

The approach of a logical framework was applied (aim, intention, components, activities), with the corresponding matrix and annexes.¹⁶

For the design of a health care network from a community point of view, we took into account the distances according to georeferencing, levels of complexity of the different centers, coverage 12/7 and 24/7, qualified staff available, and according to these data, we established the types of reperfusion recommended, with PTCA as priority strategy.

Interviews were carried out with all ER physicians from different centers, following a guide of questions. The answers and commentaries were useful at the time of outlining the project; for the analysis of those involved, a work breakfast was carried out with the chiefs of the corresponding areas of the Hospital General Roca (Category 6 Hospital).

DEFINITIONS

Pain-to-FMC: time elapsed since the onset of symptoms suggestive of ischemia and FMC, expressed in minutes.

- **WT:** time interval in minutes, from the onset of symptoms until infusion is started or until TCA is started.
- **DTNT:** time interval in minutes since arrival at the institution and the onset of infusion.
- **DTBT:** time interval in minutes since arrival at the institution until balloon insufflation.

VALUES AND DIMENSIONS TO OBSERVE

Effectiveness: benefit obtained in direct relation with need (clinical results). For the same ER service, it is possible to observe variability in clinical effectiveness according to days/providers (competences: attitude, abilities, knowledge, adherence to protocols).^{17,18}

Acceptance-satisfaction: patients perceive how they are received/treated; for patients captive of the ER service of hospital of Alto Valle, it is important to know what vision they have or what credit do they give to a given institution.

Equity: same need, same offer; it is a measure of equality for the population. It would be achieved through an improvement in accessibility.

Efficacy: related to the cost of interventions with the products provided.

RESULTS

The population estimated of the province of RN is 718,646 inhabitants according with the INDEC (*National Institute of Statistics and Surveys*) data, projections prepared based on the 2010 National Population, Homes and Dwellings Survey; 49.8% live in Alto Valle, 357,230 inhabitants, 34.6% have hospital coverage. According to the investigation made in Alto Valle de RN, it was detected that it is unlikely for reperfusion to be applied early in patients with STEACS and for the maximum number of these patients to be treated according to their incidence. The TWs observed were prolonged, with a median of 200 minutes (IQR: 120-480) or a median of 336±290, and only 26 patients were treated in 2017, representing 15 total YPLL; taking into account the population and the incidence of AMI, 50.5 YPLL were not recorded due to lack of treatment of patients in 2017.³

TABLA 1.

Listado de efectores categorizados por Nivel según FAC

Centro	Población	Cantidad de camas	Categoría
Hospital Area Programa General Roca	87.815	140	Nivel B
Hospital Area Programa Villa Regina	36.550	60	Nivel B
Hospital Area Programa Allen	26.277	57	Nivel B
Hospital Area Programa Ingeniero Huerdo	7.974	26	Nivel C
Hospital Area Programa Cervantes	4.023	2	Nivel C
Hospital Area Programa Chichinales	5.040	5	Nivel C
Hospital Area Programa El Cuy	1.627	1	Nivel C
Hospital Area Programa Cipoletti	77.713	92	Nivel B
Hospital Area Programa Cinco Saltos	24.061	41	Nivel B
Hospital Area Programa Catriel	17.600	23	Nivel B
Hospital Area Programa Fernandez Oro	6.185	0	Nivel C
Hospital Area Programa Campo Grande	4.861	7	Nivel C
Clínica Roca	87.815	65	Nivel A2
Sanatorio Juan XXIII	87.815	68	Nivel A1
Fundación Médica	77.713	70	Nivel A1
Policlínico Modelo	77.713	56	Nivel A2

Nota: datos publicados por el MSRN más recomendaciones FAC.

To achieve an improvement in this sanitary scenario, we formulated an early reperfusion project that would improve prehospital/hospital care, implementing a network under the IC protocol.

Categorization of services: public health care services were categorized in Alto Valle de RN, according to FAC recommendations (Table 1).⁷

Level A center: it has intensive care unit (ICU) available, as well as heart surgery, hemodynamics and balloon counterpulsation.

Level A1 center: hemodynamics 7 days per week 7/24 h.

Level A2 center: no hemodynamics 7 days per week and/or 24 h.

Level B center: only ICU.

Level C center: ER or ward admission.

Goals, activities, actions, indicators and expected results were discussed. They are broken down according to the SA proposed and are detailed in Table 2.

Modality of intervention: the project would be presented before the Ministry of Health of Río Negro (MSRN by its acronym in Spanish), provincial authorities of health and directors of the Alto Valle hospitals.

All ER chiefs from hospitals and centers with access to PTCA in Alto Valle and the involved staff will be informed; they will be provided the schedule of activities to fulfill.

The direction of the project would be the responsibility of a cardiologist appointed by the MSRN, and locally, a coordinator appointed by the general director of the project.

Training and work protocols will be organized with cardiologists and chief of ER in each hospital, under the coordination of the corresponding hospital and the person in charge of the project, appointed by the MSRN.

Software system: the main hospitals have a comprehensive management system developed with the Genexus Evolution 2 tools, which allow portability, preventing a dependence on hardware, operative system, development motors and databases. The software operates in a network environment with WEB technology, so as to make access and local database stored data update possible, in a centralized, compatible and operable manner, in TCP/IP network architectures, without sacrificing the safety parameters required. Network support is the internal LAN type, in each station with an internet gateway of low/medium velocity. The CAPS will be connected to a local server.

Analyses will be generated on the information in adequate statistical systems: Epiinfo, Epidat, Epimap and SPSS, among others, and metadata will be generated for suitable indicators.

Work plan:

human, physical and financial resources.

IMPLEMENTATION OF A HEALTH CARE NETWORK

Work in networks constitutes a strategy to bring together and exchange between organizations, programs/projects and/or people associating experiences and knowledge to reach a common goal. The network is the result of this strategy and constitutes an organization and management modality adopted by its members.¹⁹ The main challenge in a network is enhancing geographical and population scope, with support strategies for micro-management, improving nominalization, classification and monitoring processes, strengthening said strategies, consolidating changes, monitoring, evaluating and bringing together different public/private centers and different MSRN areas.

The networks to treat AMI based their operation on two pillars: carrying diagnosis to prehospital timing, along with a coordinated work between centers of different complexity, connected by an efficient Medical Emergency System (SEM by its acronym in Spanish).¹¹

Public hospitals in RN lack the necessary facilities and HR for PTCA in patients with STEACS, as the treatment is only available in a limited number of private centers; emergencies are treated by generalist physicians, and ICUs are polyvalent; fibrinolytic treatment is underused, and referral to private centers for PTCA is observed, with no appropriate control of care timing. It is necessary to redesign the health care network by decreasing total ischemic time

(TIT), limiting the extension of the myocardial lesion and increasing patient treatment.

Once the project with PTCA has been proposed as the main strategy, after diagnosis is made, patients referral should be immediate to the nearest center with hemodynamics service, not stopping by public hospitals or less complex centers, as long as there is a chance to having access to this service in less than 120 minutes since FMC, to obtain higher rates of permeability of ICA, lower rate of recurrent ischemia, reinfarction, and death.^{17,18,19,20,21} ER physicians should diagnose STEACS and activate the IC immediately; 911 should establish an automatic activation system, simultaneous for each member of the team.

The SEM should avoid nearby hospitals with no high complexity, and once in the appropriate medical center, go directly to the hemodynamics laboratory, not going through the ER and/or coronary unit/ICU. If a prehospital diagnosis was not made, the SEM should wait in the ER and immediately refer patients to a center with PTCA available, to be assisted within 120 minutes. In the cases when this time is exceeded, treatment with TBL will be applied (unless contraindicated) and subsequently, patients should be referred to invasive strategy.

A periodical review by a multidisciplinary team on local data, along with immediate feedback by all the staff involved, helps to identify deficiencies in the network, and to

generate initiatives for continuous improvement of care quality. The current guidelines emphasize the importance of quality control measures within regional networks. A useful tool to monitor networks is the national ACS registry, that requires obligatorily reporting to the REFECV integrated to the Argentine Integrated System of Sanitary Information (SISA by its acronym in Spanish) of the National Ministry of Health.

From all parameters that should be recorded, delays in treatment are the most straightforward quality index to audit, and it would allow comparing practices and effects in different regions of the same province and the country to identify figures outside the range. If the quality indicators that are recorded do not reach the recommended reference points, specific interventions should be designed and implemented to approach the system deficiencies.^{22,23}

ESTABLISHING THE IC PROTOCOL

Organizing a sanitary system that would allow care for STEACS according to the recommended protocols constitutes a challenge for Public Health. It requires a very close joint work between health care professionals and the different strata of management, to achieve the implementation of a reperfusion treatment that would improve the course of patients, decrease mortality and readmissions.

TABLE 2.

Project for early reperfusion of STEACS: specific aims, goals, activities and actions

Specific aims	Goals	Activities	Actions	Indicators	Expected results
1. Improving prehospital/hospital care of patients with STEACS by treating more patients and using prehospital/hospital fibrinolysis and/or PTCA as it corresponds in the hospitals of Alto Valle of the province of Río Negro.	• Achieving early reperfusion in STEACS before 120 minutes, 5% within one year, 10% in the second, 25% in the third, 30% in the fourth and 60% in the last year. • Decreasing mortality by STEACS in Alto Valle of the province of Río Negro between 20% and 25% per year until obtaining a reduction of approximately 50% of yearly mortality by the end of the project. • Achieving increasing treating more patients per year following the proportion obtained in the city of Rosario (52%, 150%, 9%, 14% and 28% respectively per year of the project). • Obtaining the necessary HR for the ER services in the hospitals of Alto Valle de Río Negro. • Obtaining 100% of the necessary equipment for a fast diagnosis of STEACS in all ERs of hospitals in Alto Valle de Río Negro. • Obtaining 100% of supplies necessary for a fast diagnosis of STEACS in all ERs of hospitals in Alto Valle de Río Negro within the first 3 months. • Acquiring high complexity ambulances necessary for transfer in all hospitals, two (2) per month, until completing a fleet of 12 ambulances within 6 months. • Achieving building adequacy for ERs in 100% within the first 6 months. • Disseminating and communicating patients and relatives at the time of discharge, as well as the population, about the need to consult quickly when experiencing precordial pain or symptoms compatible with AMI.	• Hiring two cardiologists every 3 months, until completing a total staff of 6, three trained on diagnostic imaging (ultrasound, stress echocardiography, TEE). • Appointing the general director of the Project. • Hiring a nurse per shift within the first 6 months, two nurses within the second semester, until completing a staff in the third semester in hospitals category 5/6. • Hiring an advanced technician in medical emergencies per shift within the first 6 months, two technicians in the second semester, until completing the staff within the third semester in hospitals category 5/6. • Training the staff of physicians, technicians, nurses, drivers, on triage, basic and advanced CPR, management of automated external defibrillators (AED) and administration of TBL. • Buying 100% of supplies and equipment needed for a fast diagnosis of STEACS in all ERs of the hospitals in Alto Valle de Río Negro within the first 3 months. • Buying ambulances of high complexity needed for transfer, for all hospitals, two per month, until completing a fleet of 12 ambulances within 6 months. • Adjusting ERs for the care of patients with STEACS, 100% within the first 6 months.	• Calling exam for physicians specialized in cardiology, nurses, advanced technicians in medical emergencies and coordinators. • Call for tenders to buy supplies and equipment. • Making the Annual Operative Plan to be added to the budget of the subsequent year.	• Number and costs to hire cardiologists, nurses, technicians and coordinators. • Number and costs of equipment and supplies bought. • Number and costs of materials/bills/tickets, to adjust the ERs. • Cost of hiring medical staff. • Cost of hiring technicians and nurses. • Sanitary authorizations for high complexity ambulances. • Technical verifications for vehicles.	• Prehospital/hospital fibrinolysis and/or PTCA is achieved, as it may correspond.

Specific aims	Goals	Activities	Actions	Indicators	Expected results
2. Implementing a regional health care network for the prehospital management of patients with STEACS to administer reperfusion therapy in a fast and efficient way.	- Establishing a main office for coordination, monitoring and feedback to achieve reperfusion in the least time possible in patients with diagnosis of STEACS, 100% within the first 6 months, following a strict protocol of activation of the Infarction Code. - Achieving categorizing centers and services according to the FAC recommendations within the first 6 months. - Achieving referral to private centers with PTCA available, with direct admission to the hemodynamics service, 50% within the first 6 months, 100% within one year. - Achieving the existence of priority beds in private centers for STEACS, 50% within the first 6 months, 100% within one year.	- Organizing the main office of coordination and monitoring, following the strict protocol of activation of the Infarction Code. - Designing an automatic activation system, simultaneous from the operator to the team. - Categorizing centers and services according to the FAC recommendation. - Signing agreements according to the need to georeference and times of arrival with private centers with PTCA available. - Coordinating referral to private centers for PTCA with direct admission to the hemodynamics service. - Defining, organizing and communicating the list of ER physicians from levels A1 and A2 centers to the network for 24/7 coverage. - Establishing the number of priority beds in private centers with capacity for PTCA. - Educating the population to warn the SEM early (call 911) in the case of suspecting a STEACS.	- Centralizing coordination and monitoring according to the IC protocol. - Activating the IC by calling 911 simultaneously to the team on call. - Surveying health care centers according to level of care. - Making agreements with private centers. - Referring to centers with hemodynamics service in cases of STEACS according to geographical distance and time of arrival. - Writing a schedule of ERs. - Save beds for STEACS. - Communicating by different media the significance of calling 911. - Designing leaflets and audiovisual material for the community, and communication campaigns about control of risk factors and cardiovascular prevention. - Designing and installing apps for cell phones for the community, focused on cardiovascular prevention.	- Number of protocols applied by unit of time, by number of patients assisted in the ER. - Percentage of patients admitted with diagnosis of STEACS x hospital. - Percentage of patients that received prehospital thrombolysis. - Percentage of patients that received hospital thrombolysis. - Percentage of patients transferred to other centers for PTCA. - Cost of leaflets and media to disseminate the symptoms of CAD.	- Reperfusion by PTCA is achieved before 120 minutes since FMC. - Reperfusion by prehospital/hospital TBL is achieved before 30 min in cases when it is not possible to apply PTCA in <120 min.
3. Establishing the "Infarction Code" protocol.	- Achieving a record of personal data, origin of patients, history, clinical characteristics, data on infarction and the procedure, arrival-transfer times, time and place of IC activation, times in the different procedures, etc.; 100% within the first 3 months. - Achieving the systematic quantification of times, 100% within the first 3 months. - Reaching a maximum time since FMC until ECG and diagnosis ≤ 10 min, 50% within the first 3 months, 100% within one year. - Reperfuse ICA with PTCA before 120 minutes since FMC, 5% within the first year, 10% within the second, 25% in the third, 30% in the fourth and 60% in the last year. - Reaching a maximum time since diagnosis of STEACS to infusion of thrombolysis in a prehospital/hospital scenario of 10 minutes, 50% within 6 months, 100% within one year, in the case of patients with no access to center with PTCA available before 120 minutes. - Achieving access to PTCA within 60-90 minutes, when thrombolysis did not obtain reperfusion criteria, when there is hemodynamic failure, electrical instability or ischemia worsening, 50% within the first 6 months, 100% within one year. - Achieving coronary angiography and/or subsequent TCA, when indicated, in 2-24 hours after successful thrombolysis, 50% within the first 6 months, 100% within one year. - Achieving the systematic recording of processes and results, 50% within the first year, 100% within the second year. - Achieving the distribution of guidelines and protocols, 100% within the first 3 months. - Achieving HR training, 50% within the first 6 months, 50% within the second semester. - Achieving HR training on IC protocol, 50% within the first 3 months, 50% in the subsequent trimester. - Achieving certification, 50% of the staff within the first 6 months, 50% in the second semester. - Achieving the participation in the National Registry of Cardiovascular Diseases (REFECV), 50% within the first 6 months, 50% within one year. - Achieving the obligatory report of STEACS to the SINAVE, 50% within the first 6 months, 50% within one year.	- Recording the patients' data, their origin, history, clinical characteristics, data on infarction and procedure, arrival-transfer times, time and place of IC activation. - Systematically quantifying all times since the onset of symptoms to the call to the SEM, SEM-FMC, time to ECG, time to reperfusion, DTNT, DTBT. - Coordinating the activities with the other teams in the country working under the IC protocol. - Writing guidelines and manuals about the organization and operation of the program. - Training HR on the IC protocol, basic and advanced CPR, the management of STEACS, triage, precordial pain management protocols, management of complications, transfers, management of technology, etc. - Certifications for HR after training is completed. - Processing and analyzing the information from the third month after starting the project. - Reporting results to the direction of each hospital. - Participating in work protocols and publishing results. - Participating in the National Registry of Cardiovascular Diseases (REFECV) and report STEACS to the SINAVE. - Offering care and transfer from homes to the ER. - Designing the referral and counter-referral (R/CR) system. - Evaluating performance with process and results indicators. - Establishing a control and monitoring system for patients with diagnosis of STEACS at the time of discharge. - Encouraging recording and working along with the statistics departments teams in each hospital.	- Completing worksheets with personal data and characteristics of clinical symptoms. - Recording the times since the onset of symptoms until the 911 call, since the FMC to ECG, since diagnosis to PTCA. - Recording times since diagnosis until infusion of TBL. - Recording of transfers to private centers. - Printing and distributing manuals and guidelines. - Delivering courses and training. - Provide certificates for courses and training. - Write reports for the hospital direction. - Communicating results obtained to the staff and directors. - Sending the obtained data to scientific studies protocol researchers. - Writing papers to be presented in national and international conferences. - Managing passwords for REFECV registries. - Managing statistics departments for mandatory reports. - Communicate data to Vital Statistics of the Ministry of Health of the province. - Improving morbimortality records and upload the data obtained to the software system.	- Proportion of activated IC per hospital. - Percentage of patients who are admitted with diagnosis of STEACS x hospital. - Percentage of patients who received prehospital or hospital thrombolysis. - Percentage of patients who received thrombolysis in less than 30 minutes since the onset of symptoms. - Percentage of patients transferred to to other centers for PTCA. - Percentage of patients who underwent PTCA in less than 120 minutes since the onset of symptoms. - Cost of design, printing and distribution of required guidelines, protocols and documents. - Total cost of PCs, printers, supplies, paper, etc. - Costs of fees of specialists in statistics, computer engineers, graphic designers. - In-hospital rate of mortality by STEACS. - Rate of mortality by STEACS in 30 days. - Rate of mortality by STEACS in 6 months. - Rate of mortality by STEACS in one year. - Percentage of patients who are readmitted within 30 days after discharge with similar diagnosis and/or CHF.	- Achieving in all cases a proper activation of the IC. - Treat all patients with STEACS. - Decreasing mortality by STEACS in Alto Valle de Rio Negro. - Acquiring the maximal knowledge on the management of STEACS. - Communicate to scientific societies, the results obtained with adequate treatments in the management of STEACS. - Decreasing readmissions by CHF. - Decreasing admissions due to stroke. - Decreasing readmissions due to new ischemic events.

The approach should integrate all links, from the information patients have available on CAD and warning symptoms, to training and education of health care staff and transfer of patients, the organization of ER systems, units of interventionism, including management staff and the statistics from the different centers involved; the commitment involves everyone to achieve an increase in accessibility and equity of service.^{7,11,20}

The protocol should be focused on the times impacting the system, organizing them with clear georeferencing, categorizing centers, organizing the SEM and the in-hospital care process from entrance through the ER until the activation of the hemodynamics service and onset of the procedure.

SYSTEMATIZATION AND EVALUATION

The logical framework approach is a tool to facilitate the management process of projects, conceptualization, design, execution and evaluation. It allows to improve their quality and can be used from planning until the ex-post evaluation. It provides a systematized structure for the planning process, facilitates communication of information, relates goals to each other, with the problem to be solved and the activities to be developed, it clarifies functions and responsibilities, it compares the expected results against the real ones (evaluation) and promotes participation (*Figures 1 and 2*).

The methodology of a logical framework includes the analysis of everyone involved since the start of the process, it identifies the actors of the project that may be directly or indirectly related to the problem; it analyzes its dynamics and reactions faced with the project's advancement, it improves planning and the creation of agreement or alliances; it allows to investigate and interpret their needs, expectations and interests; knowing them would benefit the project and its continuity. Each stage of the project may present different dynamics between those involved; detecting them is important to generate corresponding strategies to achieve success (*Tables 3 and 4*).

HEALTH CARE NETWORK RECOMMENDED FOR THE MANAGEMENT OF STEACS IN ALTO VALLE DE RN

The hospitals of the Program Area, dependent from the MSRN are distributed in 6 sanitary zones: Western Alto Valle, Eastern Alto Valle, Mid Valle, Atlantic Zone, Andean Zone and South Zone.

This investigation focused on Alto Valle (Western and Eastern Alto Valle). The specific data on health care centers, type of complexity, number of beds, location, population, recommendations for caring for patients and recommended network are described in *Table 1*.

For the design of a care network from a community point of view, the following aspects were taken into account: georeferencing, levels of complexity of centers, coverage 12/7 and 24/7, qualified staff available and according to these data, the types of reperfusion recommended were established, with PTCA as priority strategy.

Patients with STEACS that established FMC in hospitals from the Eastern zone, with previous activation of the IC protocol, should be referred to Sanatorio Juan XXIII (level A1) or Clínica Roca (level A2). The patients the established FMC in hospitals from the Western zone should be referred to the Fundación Médica (level A1) or Policlínico Modelo of Cipolletti (level A2) to perform early revascularization. Access for the patient should be direct to the hemodynamics service.

The times of arrival both from Catriel (Western zone) and El Cuy (Eastern zone) are in the border to be able to consider PTCA since the FMC within 120 minutes. Patients from these zones should have thrombolytics (Alteplase) as priority treatment (unless contraindicated) and subsequent referral to consider a pharmacoinvasive strategy (*Table 5*).

DISCUSSION

According to the investigation made in Alto Valle de RN (2017), it was detected that it is unlikely for an early reperfusion treatment to be applied in patients with STEACS, and for the maximum amount of patients to be treated according to their incidence. The TW for PTCA was prolonged and only 26 patients were treated, a very low number in comparison to what is expected. Hospitals do not usually use fibrinolytic drugs for the immediate care of infarction, and these patients are referred to undergo PTCA, regardless of the time elapsed since diagnosis.³

Argentina, like other Latin American countries, has a fragmented and segmented health care system, a situation made worse by its territorial judicial organization and by retention and/or transfer process of responsibilities between jurisdictions.²⁴ Formulating a project of early reperfusion is a priority given the evident lack of coordination between social and sanitary policies.

Policy is defined as the set of values and aims supported by a specific community to organize and maintain its social, economic and cultural life.²⁵ Formulating policies is establishing priorities, understanding the set of actions and omissions (deliberate decisions to do or not to do) manifested in actions by the State in relation to issues that are of interest for sectors or actors of civilian society. Policies can be offered or demanded; they are instruments to solve problems and reduce inequality; according to their scope, level of aggregation or disaggregation, they are called plans, programs or projects.²⁶

An intervention project is the smallest unit of resource assignment by which a program is realized within a policy.²⁷ It is the planning and realization of a set of activities addressed to solving a problem. Projects require first, formulating a problem and designing the technically feasible alternatives to solve it. The alternatives emerge in general from the theory available or from ex-post evaluations of analogous projects.²⁸

Reduction in mortality and YPLL by STEACS is a priority; to achieve it, we propose the implementation of a health care network for STEACS. A network means the development, within a geographical area, of a coordinated and coo-

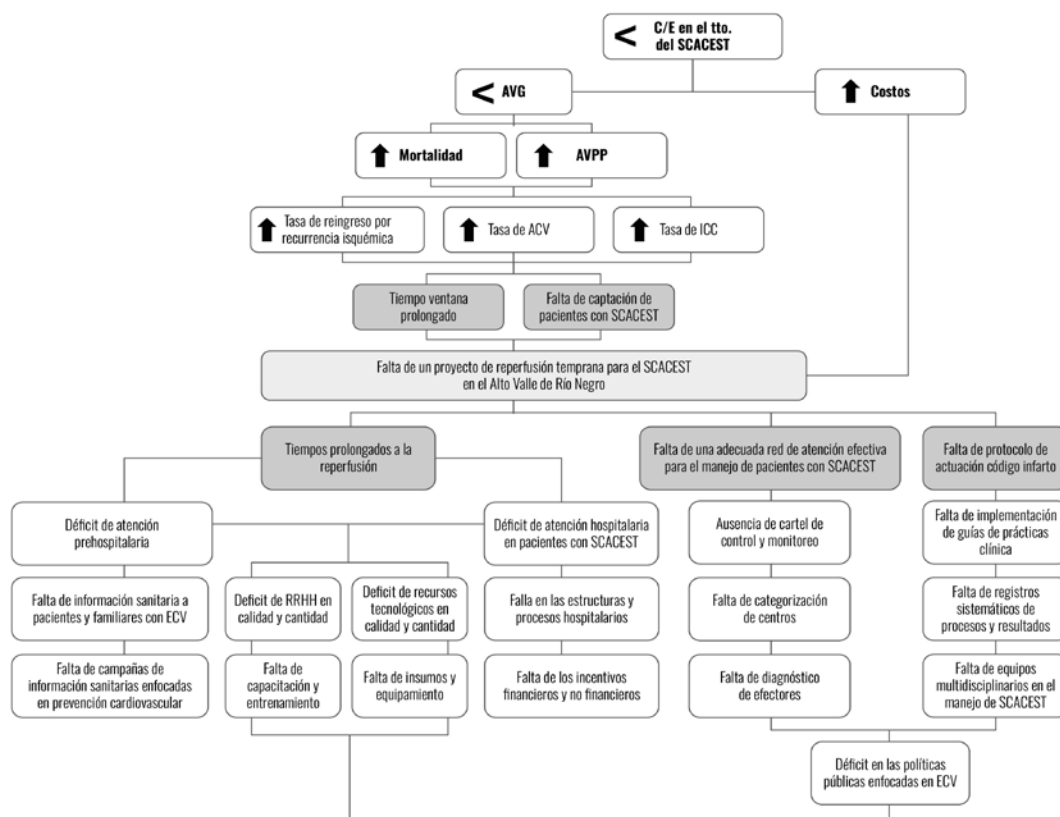


FIGURE 1.
Problem tree analysis

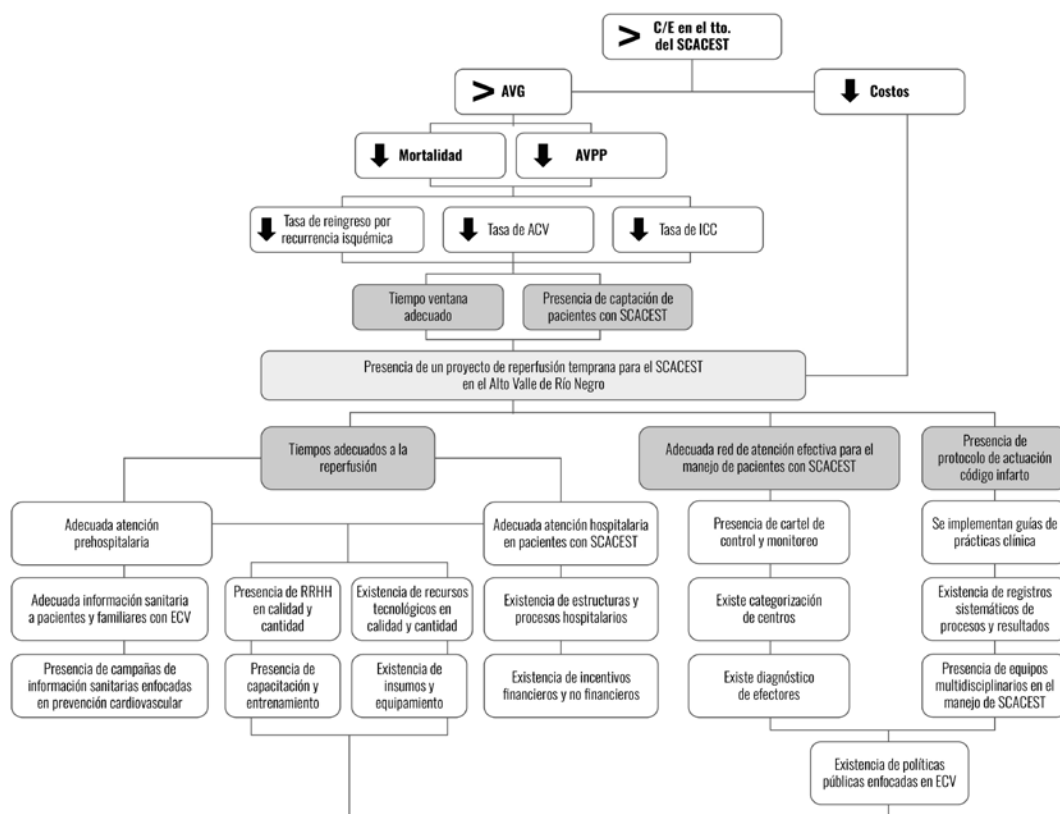


FIGURE 2.
Objective tree analysis

perative health care system by which, according to agreements between health care institutions/teams and based on the needs of the population, the aim is to treat patients with STEACS, improve quality of care, use the required technology to a maximum, and have trained and qualified staff. General success will depend on the performance of each organization, the support from the respective directions and agencies, of an organizational culture addressed to minimizing the delays of the system, along with a continuous improvement of quality.^{29,30}

Using health care networks for AMI is increasing both in Europe and Latin America. In Argentina, the experience of the city of Rosario and the El Cruce Hospital Network in Buenos Aires, achieved increasing the proportion of patients that received TBL within the recommended DTNT, with a tendency to reduction in DTBT, associated to an increase in reperfusion of 28.5% and a significant reduction in times.^{10,31} The centers in Argentina that participated in the SSL Initiative also showed improvements.³²

The results of health care networks in Mexico enabled

TABLE 3.
Analysis of the parties involved

Groups	Interests	Perceived problems	Potentials	Relationships
1. Health care authorities	- Decreasing preventable mortality by one of the main health care problems at a known cost. - Leaving an original health care project established (as the legacy of management). - Strengthening the capacity to lead of the Ministry of Health.	- Lack of systematic prioritization. - Lack of public policies focused on CAD. - Poor sanitary results. - Lack of adequate health care recordings.	- Capacity to lead. - Management. - Financial resources.	- Lack of budget. - Regulation of the Area. - Outdated program. - System fragmentation and segmentation.
2. Cardiologists	- Decreasing preventable mortality by ACS. - Obtaining in-hospital mortality records within 6 months and one year. - Improving diagnoses, control and monitoring of coronary patients. - Leading an original and relevant project. - Obtaining provable achievements (prestige).	- Lack of cardiologists or related specialists. - Lack of adequate protocols and training. - Lack of financial/ non-financial incentives.	- Support and goodwill to participate and improve. - Specific knowledge on the topic.	- Outdated regulations of the program for the Area. - Lack of knowledge on financial and economic topics. - Lack of motivation. - Conflicts with other areas. - System fragmentation and segmentation.
3. Nurses	- Improving quality of care in the FMC. - Improving training, communication and organization between the different services. - Improving ACS recordings. - Obtaining provable achievements (prestige).	- Lack of protocols and training. - Absence of coordination and internal communication. - Lack of financial/ non-financial incentives.	- Support and goodwill to participate and improve. - Capacity to generate and participate in registries. - Qualified HR.	- Law regulating nursing that does not include the presence of Advanced Emergency Degree. - Outdated regulation for the program for the Area. - Conflicts with Advanced Emergency Technicians. - Non-financial resources, political pressures. - Union conflicts.
4. Intensive care units	- Decreasing preventable mortality by ACS. - Obtaining records of in-hospital mortality and morbidity. - Participating in an original and relevant project. - Improving coordination with different services. - Obtaining provable achievements (prestige).	- Lack of coordination with the different services. - Absence of management control. - Lack of financial/ non-financial incentives.	- Support and goodwill to participate and improve. - Qualified HR.	- Outdated regulations for the program of the Area. - Conflict with other areas or specialties. - Lack of motivation. - System fragmentation and segmentation.
5. Physicians on call	- Improving quality of care in FMC. - Improving training, communication and organization between the different services. - Participating as the main link in the Infarction Code protocol. - Improving ACS records. - Obtaining provable achievements (prestige). - Training in R/CR.	- Absence of coordination and internal communication. - Refusal to use TBL. - Lack of protocols and training. - Lack of financial/ non-financial incentives.	- Support and goodwill to participate and improve. - Qualified HR.	- Outdated regulations for the program of the Area. - Conflict with other areas or specialties. - Lack of motivation. - Non-financial resources, political pressure.
6. Drivers	- Increasing financial income x on call shift and transfers. - Participating in an original and relevant protocol. - Prestige.	- Refusal to accept emergency medicine technicians (EMT). - Lack of adequate protocols and training. - Lack of financial/ non-financial incentives. - Poorly maintained vehicles	- HR present in all centers. - Support and goodwill to participate and improve. - Workforce.	- Conflict due to Law on nursing/ EMT Law. - Lack of motivation. - Non-financial resources. - Union conflicts.
7. Private centers	- Increasing the number of services. - Greater use and chance to improve the established capacity (complexity). - Breaking current commercial biases. - Participating in an original and relevant project. - Obtaining provable achievements (prestige).	- Lack of adequate agreements for high complexity services. - Lack of coordination between centers. - Lack of adequate protocols and training. - Lack of qualified HR for 24/7 coverage. - Lack of stents bank.	- Financial resources - Influences. - Presence of high complexity. - HR qualified in high complexity.	- Single service agreement, resistance to breaking exclusivity agreements. - Competition between A1 and A2 centers. - Conflict with level B or C centers that assume an impediment for their future growth or development. - System fragmentation and segmentation. - Political pressure.

TABLE 4.
Logical framework

	Objectives	Indicators	Means of verification	Assumptions
1. Aim	Contributing to improving cardiovascular morbimortality by STEACS in Alto Valle de Río Negro.	- Mortality rate - LYG	Registry of Vital Statistics of the Ministry of Health of the province of Río Negro.	- Updated records of the Ministry of Health of Río Negro. - Support for the hospitals of Alto Valle de Río Negro.
2. Purpose	Implementing early reperfusion treatment in patients with ST-segment elevation acute coronary syndrome (STEACS) in the public field of Alto Valle de Río Negro.	- Rate of in-hospital mortality by STEACS. - Mortality within 30 days by STEACS. - Mortality within 6 months by STEACS. - Mortality within one year by STEACS. - Percentage of patients readmitted within 30 days after discharge with similar diagnosis and/or CHF	- Registry of Vital Statistics of the Ministry of Health of Río Negro. - Records in ER log books. - Records in clinical histories. - REFECV registry.	- Good will to collaborate by the staff of hospitals in Alto Valle de Río Negro. - Mystique and motivation in the health care teams of ER areas of the hospitals in Alto Valle de Río Negro. - Organizational culture that would foster and maintain the emphasis to minimize delays in the system.
3. Components	- C.1: Improving prehospital/hospital care for patients with STEACS by use of prehospital/hospital fibrinolysis and/or PTCA, as it corresponds to hospitals of Alto Valle de Río Negro. - C.2: implementing a regional health care network for the prehospital management of patients with STEACS to administer reperfusion therapy rapidly and efficiently. - C.3: establishing the "Infarction Code" protocol.	- C.1: number of selected cardiologists, nurses, technicians and coordinators. - Number of human resources trained in basic and advanced CPR, triage, handling of AED, management of STEACS and administration of TBL. - Number and costs of equipment and supplies bought. - Number and costs of materials to make ERs suitable. - C.2: number of protocols applied by unit of time, by number of patients assisted in the ER. - Percentage of patients who are admitted with diagnosis of STEACS x hospital. - Percentage of patients who received prehospital thrombolysis. - Percentage of patients transferred for PTCA. - Number of categorized centers. - C.3: proportion of IC activated per hospital. - Number of distributed printed and digital guidelines for the management of the IC. - Percentages of patients added to the REFECV and reported to the SINAVE	- C.1: number of contracts of cardiologists, nurses and EMTs. - List of attendees in training courses. - List of participating professionals and interconsultants. - Billing and tickets for supplies, equipment and upgrade of ERs. - Technical verifications for vehicles. - C.2: reports of Project monitoring. - List of transfers. - Information uploaded to the computer system. - C.3: records of activated IC. - Information uploaded to the computer system. - Guidelines and protocols documented and delivered.	- Health care staff learns about transmitted contents. - The Management Unit is created to allow reaching the indicators successfully, managing the human, material and financial resources of the project. - The actors commit with the activities stated in the project. - There is a budget to add medical, technical and nursing staff. - There is a budget to buy adequate supplies and technology. - There is a budget and an agreement to establish incentives. - The proposal is accepted in the community.
4. Activities	- C.1: 1.a. /1. b./1. c. hiring specialists in cardiology, nursing, EMT. 2. 3. Performing training activities for HR on the management of cardiovascular emergency/IC management and protocol for STEACS in patients who consult to the ER. 4.Performing training activities for HR on the handling of equipment for ECG transmission for an early diagnosis. 5. 6. 7. Performing training activities for HR on triage, basic and advanced CPR, handling of AED and administration of TBL. 8 a. Buying equipment and supplies for the management of STEACS in the ER: ECG devices, defibrillators, oximeter, vital signs monitors, automated analyzers, etc. 8.b. Buying the required high complexity ambulances. - C.2: 9-Establishing a main office for coordination, monitoring and feedback for a rapid access to reperfusion along with the telephone exchange service of the province (911- infarction code). 9 a. Appointing a coordinator for the IC in Alto Valle and relevant substitutes. 9 b. Establishing a single phone number in every hospital for the activation of the IC. 9 c. Categorizing private centers and services. 9 d. Design of the R/CR system. 9 e. Making posters with flowcharts about R/CR. 9 f. Design of the circuit the R/CR records should follow. 9 g. Accessing the network of private services under a new agreement modality for PTCA. 9 h. Establishing the number of priority beds in private centers with PTCA available. 9 i. Educating the population to call the SEM early (call 911). - C.3: 10. Record personal data, origin, history, clinical data, type of AMI, procedures. 11. Quantifying systematically all times since the onset of symptoms. 12. Coordinating activities with the rest of the teams of the country working with IC protocol. 13. Write and distribute clinical practice guidelines manuals and IC procedures. 14. Carrying out training activities for HR for a rapid external and internal transfer of these patients.	- C.1: number of selected cardiologists, nurses, technicians and coordinators. - Number and cost of training activities for HR. - List of materials and supplies bought (sphygmomanometers, oximeters, photography paper, ECG paper, reports printed, envelopes, phones, etc.). - Number and costs of ECGs, X-rays, ultrasounds and cardiac enzymes tests made. - Number of health care authorizations for high complexity ambulances. - Number of technical verifications for vehicles. - C.2: Agreements with coordinators. - Number and costs of PCs, printers, supplies, paper, etc. - List of categorized centers. - C.3: number and cost of design, printing and distribution of required guidelines, protocols and documents. - Number and costs of training activities. - Number and costs of leaflets and media to disseminate CAD symptoms. - Number and costs of hiring specialists in statistics, computer engineers, graphic designers. - Cost of incentives. - Number of reports to SINAVE. - Number of patients admitted to the REFECV.	- C.1: list of hired staff. - Worksheets with salaries. - List of attendees to the different training activities. - Bills and delivery notes. - Record of cardiological, radiological and laboratory tests made. - Records of ER logbooks and clinical histories. - Registry of lists of R/CR. - Meeting minutes. - Accounting records. - C.2: list of hired staff. - Worksheets of salaries. - Bills and delivery notes. - C.3: bills and delivery notes. - List of attendees to the different training activities. - Quality controls with indicators of process and results. - Bills and delivery notes. - List of distributed guidelines and manuals. - List of hired staff. - Worksheets of salaries. - Records for SINAVE and REFECV.	- Enough consensus is reached on procedures. - There is financing to hire medical, technical and nursing staff, statistics staff, computer engineers, graph designers. - There is financing for the necessary equipment and materials for training. - There is consensus and financing to buy equipment and supplies for the ER. - There are resources for the design of the R/CR system. - There are resources to comply with agreed incentives according to results. - There are resources for the design of dissemination campaigns on the importance of consulting early. - Local media guarantees wide dissemination of proposals. - All activities have financing and political support. - The statistics departments take on the commitment to improve records. - Scientific organizations actively participate in the dissemination of proposals.

an increase in reperfusion of STEACS from 34.9% to 71.4%. The group without reperfusion decreased from 65.2% to 28.6%, thanks to an increase in TBL use (25.5% vs 40.1%), and PTCA increased from 9.4% to 31.3%.³ In-hospital mortality decreased from 21.1% to 9.4%. Similar results were obtained in Chile and in Brazil.^{34,35}

Europe had significant results with regional networks for the treatment of AMI, increasing the number of procedures per million inhabitants, and decreasing mortality.^{36,37}

An efficient organization shortens the times of transfer and yields better results in morbimortality, as proven in the AIR-AMI, DANAMI and PRAGUE trials.^{38,39,40,41}

From the investigation made, the need to establish a health care network emerges, integrating the public and private subsectors, and the services to improve prehospital/hospital management of patients with STEACS in Alto Valle de RN.

CONCLUSIONS

A critical socio-sanitary problem has been detected: in the public sector of Alto Valle de RN, there is no early reperfusion made in patients with STEACS, which leads to a high preventable morbimortality. This requires immediate, collective actions, brought together by the different actors to achieve the treatment of STEACS.

In this study, we formulated a project for early reperfusion with prehospital/hospital thrombolysis and PTCA for Alto Valle, with IC protocol. The project would allow achieving LYG and increase the number of patients treated, achieving more accessibility and equity.

This study attempts to prove that, from a scientific and technical point of view, it is possible to contribute with political leaders to achieve results in health care.

The implementation of a project of these characteristics requires a joint effort between health care professionals from different specialties, health care management with competences in health care organization, and essentially, political support. Without this joint collaboration, the creation, operation, maintenance and evaluation of the project is not possible.

LOCATIONS WHERE THE STUDY TOOK PLACE:

Public hospitals of Alto Valle de Río Negro:

Eastern zone:

1. Hospital General Roca
2. Hospital Ingeniero Huergo
3. Hospital Allen
4. Hospital Villa Regina
5. Hospital El Cuy
6. Hospital Cervantes
7. Hospital Chichinales

Western zone:

8. Hospital Cipolletti
9. Hospital Cinco Saltos
10. Hospital Campo Grande
11. Hospital Catriel
12. Hospital Fernández Oro

Private institutions:

1. Clínica Roca
2. Sanatorio Juan XXIII
3. Policlínico Modelo de Cipolletti

Fundación Médica de Río Negro y Neuquén.

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TABLE 5.

Coverage area according to networks

Zona Sanitaria	Hospital Derivador	Latitud	Longitud	distancia (km) a receptor Fundación Médica / Policlínico Modelo	Latitud	Longitud	Tiempo Estimado (en minutos)	distancia (km) a receptor Sanatorio Juan XXIII / Clínica Roca	Latitud	Longitud	Tiempo Estimado (en minutos)
1era Zona Sanitaria Este	Chichinales	39°06'51.62" S	66°56'28.71" O	99	-38.937389°	-68.001254°	97	58,6	-39.029876°	-67.570344°	56
	Regina	39° 6'7.22"S	67° 5'3.71"O	86	-38.937389°	-68.001254°	88	47	-39.029876°	-67.570344°	47
	Huergo	39° 4'32.54"S	67°14'32.46"O	70,6	-38.937389°	-68.001254°	72	32	-39.029876°	-67.570344°	32
	Cervantes	39° 3'6.72"S	67°23'33.40"O	58	-38.937389°	-68.001254°	62	19	-39.029876°	-67.570344°	26
	G. Roca	-39.021591°	-67.572917°	45,1	-38.937389°	-68.001254°	30	1,6	-39.029876°	-67.570344°	6
	El Cuy	39°55'37.89" S	68°20'28.45" O	162	-38.937389°	-68.001254°	140	130	-39.029876°	-67.570344°	103
	Allen	38°58'53.71"S	67°49'6.97"O	17,7	-38.937389°	-68.001254°	30	27,6	-39.029876°	-67.570344°	30
1era Zona Sanitaria Oeste	Cipolletti	38°55'30.32"S	67°58'42.21"O	3,1	-38.937389°	-68.001254°	9	43	-39.029876°	-67.570344°	53
	Cinco Saltos	38°49'35.54"S	68° 4'1.92"O	15	-38.937389°	-68.001254°	18	60	-39.029876°	-67.570344°	80
	Catriel	37°52'39.00"S	67°47'38.74"O	133	-38.937389°	-68.001254°	102	178	-39.029876°	-67.570344°	274
	Fernández Oro	38°57'00.00" S	67°55'00.02" O	9.4	-38.937389°	-68.001254°	19	37.2	-39.029876°	-67.570344°	40
	Campo Grande	[-38.682483°]	-68.212006°	36.5	-38.937389°	-68.001254°	36	84,5	-39.029876°	-67.570344°	88

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Original Investigation Reports

Criteria of the Dutch Clinical Network and genetic testing in familial hyperlipidemia in a group of Colombian patients

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ABSTRACT

Introduction: hyperlipidemia is a group of diseases, both hereditary and acquired, characterized by elevated levels of lipids in the human body, especially prevalent in the western hemisphere.

Methods: this study seeks to identify patients with familial hyperlipidemia using the criteria of the Dutch Clinical Network applied to the subsidized population of Bucaramanga, Colombia, and evaluate their individual profiles.

Results: the prevalence of heterozygous familial hypercholesterolemia (HeFH) is estimated to be 1 in 200 to 500 people, while the prevalence of homozygous familial hypercholesterolemia (HoFH) is 1 in 300,000 to 600,000 people. In Bucaramanga, it is projected that 240,000 people could have HeFH and from 160 to 300 cases of HoFH.

Conclusions: despite the estimates, the real prevalence of the disease in Colombia is unknown, which justifies carrying out this study to obtain more precise data on familial hyperlipidemia in the region.

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic disorder manifested by persistently elevated LDL cholesterol (LDL-C) levels from an early age, which significantly increases the risk of premature atherosclerotic cardiovascular disease^{1,2,3}. Its heterozygous form is estimated to affect approximately 1 in 200 to 500 individuals, and its homozygous form affects 1 in 300,000 to 600,000 individuals, although these data may vary by region and ethnic origin^{4,5}.

FH is primarily transmitted in an autosomal dominant manner and is associated with mutations in the LDLR, APOB, and PCSK9 genes, which alter LDL-C metabolism^{2,6}. These mutations lead to a reduction in hepatic cholesterol uptake, elevating its plasma levels and accelerating the process of atherosclerosis^{1,2,6}. The homozygous form of the disease, although less common, is associated with cardiovascular disease in children due to the almost complete absence of functional LDL receptors^{3,6}.

Most cases of FH remain undiagnosed, limiting the timely implementation of preventive measures^{3,4,7}. Studies conducted in European and North American populations have reported prevalences of 1 in 217 in Denmark, 1 in 150 in Quebec, and up to 1 in 70 in Afrikaners in South Africa^{5,6,7}.

These differences highlight the importance of conducting local studies that consider the genetic and epidemiological characteristics of each region.

To improve identification, diagnostic tools such as the Dutch Clinical Network (DLCN) criteria have been proposed, which integrate personal and family history, LDL-C levels, physical signs, and genetic findings^{2,8}. These criteria have demonstrated adequate sensitivity and specificity compared to molecular diagnosis, considered the gold standard².

In Colombia, the true prevalence of FH is unknown, and the application of standardized clinical criteria has been limited, especially in vulnerable populations such as those receiving subsidized healthcare. Bucaramanga, a mid-sized city in northeastern Colombia, has a population base that allows for the implementation of active screening strategies for FH^{9,10}.

The **objective** of this study was to identify patients with suspected familial hypercholesterolemia in a population of the subsidized healthcare system in Bucaramanga by applying the Dutch Clinical Network criteria and to evaluate their clinical, epidemiological, and genetic characteristics.

METHODS

The present is an observational study that sought to identify the presence of FH based on the Dutch Clinic Network criteria. Patients aged 18-95 years who had a record of cardiometabolic risk variables including lipid profile and others were included in the study. Patients that did not have the variables as well as secondary causes of hyperlipidemia, such as hypothyroidism, nephrotic syndrome, cholestasis, and treatment with specific drugs (steroids, immunosuppressors, etc.) were excluded. The population that met the inclusion and exclusion criteria consisted of all health centers in the city of Bucaramanga, Santander, Colombia.

Socioeconomic level was classified according to the official Colombian stratification system, which groups the population into six levels based on the characteristics of their housing and surroundings. For this study, the classification was obtained from administrative health records, and strata 1, 2, and 3 were included, representing low to middle-low socioeconomic status.

Familial Hyperlipidemia

To establish the clinical diagnosis of familial hyperlipidemia in the index case, the criteria of the Dutch Lipid Clinic Network (DLCN) are currently used in several countries. These criteria are based on a punctuation system according to personal and familial history of certain variables. Clinical diagnosis is certain when the score is ≥ 8 and likely when it is ≥ 6 . The accuracy of the clinical criteria has been compared with the genetic diagnosis, which is the gold standard, with the DLCN criteria having the best overall sensitivity and specificity¹⁰.

They should only be used for diagnosis of FH over the age of 18 years and never in their family members. To detect FH, an opportunistic search should be performed in patients with premature CVD and those with personal and/or family history of hypercholesterolemia and/or premature CVD¹¹.

Criteria for clinical suspicion of familial hypercholesterolemia¹².

1. Individual with LDL-c > 250 mg/dl and at least one of the following criteria
 - a. Family member < 18 years with LDL-c > 150 mg/dl
 - b. Family member > 18 years with LDL-c > 190 mg/dl
 - c. Presence of premature coronary heart disease in the index case and/or a first degree relative
 - d. Presence of xanthomas in the index case and/or a first degree relative
2. If there is no family data available, familial hypercholesterolemia should be suspected in people with LDL-c > 300 mg/dl.

Genetic test

Genetic testing for familial hyperlipidemia was performed using a kit from the Longwood Company (Lipid in Code®) and processed by molecular engineering DNA analysis using an Ion GeneStudio S5 Series device. The 7 genes

involved in the following were analyzed: Familial hypercholesterolemia: LDLR, APOB, PCSK9, APOE and STAP1 genes, Autosomal recessive hypercholesterolemia: LDLRAP1 gene, Lysosomal acid lipase deficiency: LIPA gene.

Statistical analysis

The quantitative variables are presented as a median $\pm$ standard deviation or median (interquartile range) according to their distribution, and qualitative variables as percentages with confidence intervals (CI) of 95%. Student's t test was performed to evaluate the differences between two variables. All statistical analyses of the database results were performed using the Statistical Package for the Social Sciences (SPSS for Windows, v.20.1; Chicago, IL) and Microsoft Excel was used to tabulate the corresponding databases.

Ethical considerations

The ethical aspects of this research study were conducted based on the criteria of the Belmont Report, adjusted to its principles of respect to the person, benevolence, and justice and, the Helsinki declaration of the World Medical Association of 1964. Likewise, this work will be subjected to the national legislation and its code of medical ethics of 1985 (currently in force) in its title V, chapter 4, regarding research on human beings. The highest of standards were maintained that permitted the protection of the participant's privacy and physical integrity.

By means of informed consent, the objectives of this investigation were explained, in the same manner, the procedures performed, and their inherent risks and complications were explained in detail using clear and understandable language. The study was evaluated and approved by the ethics committee with the highest of standards.

RESULTS

Initially, we present the results of the epidemiological characterization after reviewing the statistics of the population of the cardiovascular risk programme of the subsidized population in Bucaramanga, Santander. **Table 1** presents the sociodemographic characteristics of the included population.

Table 2 depicts the principal comorbidities found in the population included in this study.

Table 3 shows the data corresponding to adherence, degree of control and mean lipid profile, renal function and glucose values of the patients included in the study.

After characterization of all the patients, the criteria for suspected familial hyperlipidemia of the Dutch Lipid Clinic Network were applied.

Genetic testing revealed various mutations: duplication of exons 13-15 with p.Asp47Asn and p.Ser326Cys in the LDLR gene; mutations p.Glu204* and Ile268Met in the APOE gene; and multiple substitutions in the PCSK9 gene, including T>A at nucleotide 621 and T>C at nucleotide 780. Among the patients, 15 were heterozygous, 2 were homozygous, 2 were compound heterozygous, and 1 was double heterozygous. Some PCSK9 mutations were of uncertain

significance, with limited prior documentation in the literature (Table 4).

These findings support the utility of systematic screening using DLCN criteria in high-risk populations, and reveal a significant genetic burden of familial hyperlipidemia that remains underdiagnosed. The integration of genetic testing allowed for the identification of clinically relevant mutations, reinforcing the importance of targeted strategies in primary care for early detection and risk reduction.

DISCUSSION

As seen in Table 1, the majority of the total population were female (68.8%), which is consistent with prior national reports of higher healthcare-seeking behavior among women¹⁰. Additionally, most participants were single (85.7%), a finding previously associated with limited social support and potentially worse adherence to chronic disease management¹¹.

Regarding comorbidities in the overall sample (Table 2), hypertension (81.4%) and non-insulin dependent diabetes mellitus (28.2%) were the most common, followed by hypercholesterolemia and chronic kidney disease (both 24.3%). These findings are similar to those reported in studies from similar populations in Latin America and globally^{12,13,14}.

As shown in Table 3, adherence to treatment was high (91%) and overall control of metabolic indicators was achieved in 70.2% of cases, similar to previous reports^{15,16}. However, these figures must be interpreted with caution, as they reflect the entire cohort and not specifically the subset of patients with suspected familial hypercholesterolemia (FH).

TABLA 1. Características sociodemográficas de la población incluida

Variable	Valores		
Sexo	Mujeres	7256	68,8%
	Hombres	3285	31,2%
Edad promedio	65,67 años		
Estado civil	Casados	435	4,1%
	Otros	599	5,7%
	Separados	88	0,8%
	Solteros	9033	85,7%
	Unión civil	147	1,4%
	Viudos	110	1,0%
	Sin información	125	1,2%
Estrato socioeconómico	Estrato 1 (n: 5952) Estrato 2 (n: 3845) Estrato 3 (n: 744) 24 / 10541		
Evaluación psicológica			
Evaluación nutricional	3841 / 10541		
Evaluación odontológica	2150 / 10541		

When focusing on the 20 patients who met the DLCN criteria for suspected FH (Table 4), the clinical profile was markedly different. This subgroup had a higher cardiovascular burden: 90% had very high cardiovascular risk and 70% had documented coronary artery disease, consistent with patterns described in other FH populations^{17,18}. Hypertension, diabetes, and chronic kidney disease were also frequent comorbidities.

Interestingly, while adherence to lipid-lowering therapy was high (90%), only 30% of these high-risk patients achieved adequate LDL-C control. This therapeutic gap is well-documented in FH cohorts and is often due to both genetic resistance to standard therapies and delayed diagnosis^{3,4,13}.

Genetic analysis revealed mutations primarily in LDLR, along with variants in APOE and PCSK9, the latter often of uncertain significance. These findings align with the global literature, where LDLR mutations account for more than 80% of genetically confirmed FH cases^{1,2}. The identification of compound and double heterozygous mutations also highlights the phenotypic and genetic complexity of FH.

Taken together, these results reinforce the clinical utility of DLCN criteria in identifying suspected FH cases within primary care, especially in underserved health systems. The integration of targeted genetic testing not only confirmed diagnoses but also uncovered clinically actionable mutations, contributing to the growing body of data on FH in Latin American populations. Furthermore, our findings support expanding systematic screening strategies and cascade testing to improve early detection and cardiovascular prevention.

TABLA 2. Comorbilidades principales de los pacientes incluidos en el estudio

Variable	Valores n (%)
Hipertensión	8580 (81,4%)
Diabetes mellitus no insulino dependiente	2971 (28,2%)
Diabetes mellitus insulino dependiente	833 (7,9%)
Insuficiencia renal	2560 (24,3%)
Hipercolesterolemia	2560 (24,3%)
Enfermedad pulmonar obstructiva crónica	833 (7,9%)
Cáncer	21 (0,05%)

TABLA 3. Adherencia, grado de control y perfil lipídico promedio, función renal y valores de glucosa de los pacientes incluidos en el estudio

Variable	Valores n (%)
Adherencia	9592 (91%)
Control	7380 (70,2%)
Promedio de colesterol total	168,353 mg/dL
Promedio HDL	42,735 mg/dL
Promedio LDL	111,919 mg/dL
Promedio función renal	194,906 mg/dL
Promedio triglicéridos	194,906 mg/dL

Future research should evaluate the cost-effectiveness of implementing routine FH screening in primary care settings using clinical algorithms and genetic tools. Such studies are necessary to validate the approach at a larger scale and determine its long-term impact on morbidity and mortality.

CONCLUSIONS

Familial hyperlipidemia (FH) remains significantly underdiagnosed and undertreated in clinical practice, particularly in low- and middle-income countries. This study identified patients with clinical suspicion of FH in a subsidized health population in Bucaramanga using the Dutch Lipid Clinic Network (DLCN) criteria, revealing a high burden of cardiovascular disease and a low rate of LDL-C control despite adequate treatment adherence. Genetic testing confirmed pathogenic variants—especially in the LDLR gene—reinforcing the role of molecular analysis as a complement to clinical screening.

These findings support the integration of standardized diagnostic tools and genetic testing into primary care, especially in resource-limited settings where specialized lipid clinics are not widely available. Primary care physicians are

fundamental in the early recognition of red flags such as persistent hypercholesterolemia or premature cardiovascular events. However, gaps in knowledge and diagnostic capacity remain a barrier to early detection.

To address this challenge, educational programs, improved biochemical screening protocols, and support from multidisciplinary teams—including clinical geneticists—are needed¹⁹. Public awareness campaigns are also essential, particularly for families with a history of early cardiovascular disease or elevated LDL-C.

Future research should explore the broader implementation of systematic FH screening and its effect on cardiovascular outcomes. Advances in genomic technologies and their accessibility may further improve detection, risk stratification, and eventually, the development of personalized therapeutic strategies²⁰. Characterizing the genetic and clinical profile of FH within the Colombian population remains a key priority for national health institutions.

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TABLA 4.

Características clínicas y genéticas de pacientes con sospecha de hiperlipidemia familiar

Categoría	Variables	Valores n (%)
Demografía	Mujeres	17 (85%)
	Hombres	3 (15%)
	Rango de edad	46–88 años
Riesgo cardiovascular	Riesgo estimado muy alto	18 (90%)
	Riesgo estimado alto	2 (10%)
Comorbilidades	Hipertensión	17 (85%)
	Enfermedad coronaria	14 (70%)
	Diabetes mellitus	6 (30%)
	Patología cerebrovascular	4 (20%)
	Insuficiencia renal	4 (20%)
Indicadores terapéuticos	Adherencia a terapia hipolipemiente	18 (90%)
	Logro de control de c-LDL (<100 mg/dL)	6 (30%)
Hallazgos genéticos	Mutaciones LDLR	Variantes patogénicas (por ej., duplicación de exón 13–15, p.Asp47Asn, p.Ser326Cys); observado frecuentemente en casos de genética alterada.
	Mutaciones APOE	Mutaciones como p.Glu204* y Ile268Met; detectados en una minoría de pacientes.
	Variantes PCSK9	Sustituciones que incluyen nt. 621 T>A y nt. 780 T>C; principalmente clasificados

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Original Investigation Reports

Exploring the Association between Clinical Factors and Aortic Morphometry Using Neural Networks.

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ABSTRACT

Introduction: aortic morphometry varies across its segments and may reflect diverse clinical influences.

Objective: to identify which segments of the aorta show the greatest association with clinical variables using neural networks.

Materials and methods: an analytical and cross-sectional study was conducted with 801 adults from the Harvard Dataverse repository (2018–2019) who underwent non-contrast chest CT. Aortic diameters from the sinus of Valsalva to the abdominal aorta, measured using artificial intelligence, were assessed, along with 20 clinical variables. A multilayer neural network was applied as a nonlinear statistical analysis tool.

Results: in the performance analysis of the neural network model, the diameter with the lowest relative error was that of the middle descending aorta, whose relative error was 0.356 in the testing phase, obtaining a coefficient of determination of 0.613, indicating that the model explains 61.3% of the variability in diameter. Its most influential variables were age (importance of 0.168), creatinine (0.106), AST (0.082), and potassium (0.071). The mean square error was 0.324 in the training phase and 0.356 in the testing phase.

Conclusions: the neural network model reveals a stronger nonlinear association between clinical variables and the diameter of the mid-descending aorta, highlighting its sensitivity to hemodynamic and metabolic influences and reinforcing its value as a structural marker in cardiovascular disease assessment.

INTRODUCTION

The aorta is a complex vascular structure and the main blood vessel of the human body, in charge of carrying oxygenated blood from the left ventricle of the heart to organs and tissues.¹ Anatomically, it is divided into several segments: the ascending aorta, the aortic arch, the descending thoracic aorta and the abdominal aorta. Each of these segments presents particular structural characteristics and fulfills specific functions within systemic circulation.² Its morphometry varies over these segments owing to biomechanical, hemodynamic and ageing factors, which may reflect both physiological and pathological processes influenced by clinical, metabolic, liver, kidney and cardiovascular factors.^{3,4} Although it is known that such factors affect vascular health in general, it is not clear which aortic segments present a stronger association with these clinical variables.

Understanding these relationships may provide useful information to characterize segmental vascular remodeling, and potentially contribute to the design of clinical strategies for individualized evaluation and monitoring.

Particularly, learning which aortic segments display a greater sensitivity or correspondence with clinical data may help to prioritize diagnostic resources and to focus surveillance in areas more vulnerable to systemic changes.

In this regard, the goal of this investigation was identifying which segments of the aorta show a greater association with clinical variables using tomographic morphometric measurements. With this purpose, artificial neural network models were used, of the multilayer perceptron type, not with the goal of making a straight clinical prediction, but as an advanced statistical tool to explore complex and nonlinear association patterns between clinical variables and tomographic measurements of the aortic diameter. Through these methodologies, the degree of association between the different segments of the aorta and a common set of clinical variables are compared, with the aim of identifying what regions present a closer and more consistent relationship.

This exploration may contribute novel evidence on the segmental differences in vascular response to clinical factors, and paves the way for new pathophysiological questions on the differential structural vulnerability of the aorta in different clinical scenarios.

MATERIALS AND METHODS

Design and population

Analytical and cross-sectional study on a secondary database, available at the Harvard Dataverse repository. This database included adults with and without comorbidities, who underwent non-contrast chest CT and an evaluation on arterial elasticity by an arteriosclerosis detector, between March 2018 and October 2019.

The population was made up by 801 adults of 18 years or older, all evaluated by chest CT. According to the authors of the original database, the participants did not present significant arterial alterations or diseases that may seriously compromise arterial structure. The following were ruled out: those with history of revascularization or aortic valve replacement, stent placement, genetic syndromes linked to aneurysms or aortic dissections (such as Marfan or Turner syndromes), relevant congenital anomalies of the aortic branches, inflammatory diseases with aortic compromise, acute arterial syndromes (as dissection or intramural hematoma), aortic aneurysms, conditions of hypovolemia or severe hemodynamic instability, advanced heart failure with reduced ejection fraction, and patients in hemodialysis. All available data in the repository were used, so no sampling or randomization techniques were applied.

Variables and measurements

Aortic diameters (quantitative values expressed in millimeters) were analyzed, following an anatomical order from proximal to distal: sinus of Valsalva, sinotubular junction, mid ascending aorta, proximal and mid portions of the aortic arch, proximal descending thoracic aorta, mid descending aorta, aorta at the level of the diaphragm and the abdominal portion in the celiac axis origin. According to the authors of the database, these diameters were obtained by an automated system based on AI, designed for organ segmentation from CT imaging.⁵

To model mid descending aorta diameter prediction, multiple independent variables were considered. These included demographic characteristics such as age (in years) and gender (0 = females, 1 = males); metabolic and biochemical parameters such as AST (U/L), creatinine (mg/dL), BMI (kg/m²), phosphorus (mg/dL), calcium (mg/dL), DBP and SBP (mmHg), triglycerides (mg/dL), ALT (U/L) and total cholesterol (mg/dL); as well as arterial stiffness index (M.CAVI, dimensionless). Also, clinical history was added, including chronic lung disease, osteoporosis, hypertension, diabetes mellitus and ischemic heart disease, all classified as present or absent. Finally, habits like smoking and alcohol consumption were considered, categorized as 0 for absence and 1 for presence. These variables were se-

lected for their potential relevance on aortic diameter variation, considering both physiological and pathological aspects.

Statistical analysis

For the development of the prediction model for aortic segment diameter, a neural network of the multilayer perceptron (MLP) type was used. It is an automatic learning model made up of several layers of nodes or "neurons", where each neuron is connected to those of the following layer, allowing to capture nonlinear relationships between clinical variables and aortic diameters.⁶ This type of neural network is capable of learning complex relationships between input and output variables, by a process of supervised training.⁷ The network was trained with 544 cases (68.20%) and was validated with 254 cases (31.80%).

During the analysis of the neural network model performance, relative errors in the prediction of aortic segment diameters were evaluated, both in the training and in the testing phases. These relative errors, estimated as the percentage difference between the predicted values and the real values, allow to estimate the accuracy of the model, regardless of the data scale.

Next, we carried out an independent analysis of the mid descending aorta segment, because of its better performance in prediction. In this analysis, we observed the nonlinear relationships between variables and mid descending aorta diameter. The estimated coefficients in the hidden layers reflected how each covariate influences on intermediary activations, which are combined to generate the final prediction. The covariate relationships with the mid descending aorta diameters were evaluated in terms of relative significance of each one, which enabled the identification of the most influential factors in aortic morphology.

Data analysis and processing, including using the neural network of the multilayer perceptron type, was made by the SPSS 25TM software.

Ethical considerations

The database used in this study comes from the open access repository of the Harvard Dataverse, which is available under the Creative Commons Zero (CC0) license, which enables its free use. As we worked with secondary data that were already anonymous, it was not necessary to obtain additional specific ethical permits or authorizations. Likewise, participant data confidentiality was ensured, by following the principles established in the Declaration of Helsinki.

The database is available at the following link:

<https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/C0YY9I>

The database specifications are available at the following link:

<https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/C0YY9I>

RESULTS

In the descriptive analysis, the participants presented a wide clinical and biological variability. The average age was 57.97 years, with a range from 18 to 95. High levels of dispersion were observed in BMI, blood pressure, biomarkers (AST, ALT, creatinine and M.CAVI), cholesterol and triglycerides (63.5%) or osteoporosis (83.1%). Only 3.6% reported chronic lung disease. This heterogeneity is key for the clinical associations evaluated (Table 1).

A prediction model was developed by a neural network of the multilayer perceptron type, using 798 valid cases, of whom 68.2% was devoted to training and 31.8% to testing. The network added 20 standardized covariates in the input layer, related to demographic, clinical and biochemical factors. The architecture included a hidden layer with 12 nodes and hyperbolic tangent activation function. The output layer comprised 9 nodes, corresponding to analyzed aortic segments. The dependent variables were standardized and

TABLE 1.
Descriptive statistics and frequency of clinical variables

Descriptive statistics				
Variable (unit)	Minimum	Maximum	Mean	Standard deviation
Age (years)	18	95	57.97	14.14
BMI (kg/m ²)	15.3	40.2	24.55	33.01
SBP (mmHg)	91	223	148.48	20.45
DBP (mmHg)	52	118	79.37	10.28
M.CAVI (arterial stiffness index)	3.215	14.735	818.83	1.42
ALT (U/L)	1	599	27.6	305.21
AST (U/L)	10	444	24.57	21.01
Creatinine (mg/dL)	0.05	6.25	0.8535	0.31499
Calcium (mg/dL)	7.21	234.47	92.22	798.34
Phosphorus (mg/dL)	1.3	7.16	31.9	0.56489
Total cholesterol (mg/dL)	72.97	375.29	1719.27	4322.52
Triglycerides (mg/dL)	36.28	1908.85	1662.69	16873.85
Aortic sinus of Valsalva (mm)	21.4	51.1	35.23	42.53
Sinotubular junction (mm)	23	51.8	32.98	40.45
Mid ascending aorta (mm)	23.5	53.6	37.12	47.31
Proximal aortic arch (mm)	22	44.7	33.15	37.08
Mid aortic arch (mm)	19.3	39.4	30.31	30.83
Descending thoracic aorta (mm)	19.5	40.6	28.6	32.77
Mid descending aorta (mm)	15.9	35.5	25.64	31.94
Aorta in the diaphragm (mm)	15.3	33.5	25.25	25.95
Abdominal aorta(mm)	13	31.7	23.85	25.63
Frequencies				
Variable	Category	Frequency	Porcentaje	
Smoker	No	536	66,9%	
	Yes	265	33,1%	
Alcohol consumption	No	574	71,7%	
	Yes	227	28,3%	
DM (Diabetes Mellitus)	No	509	63,5%	
	Type 1	115	14,4%	
	Type 2	177	22,1%	
Osteoporosis	No	666	83,1%	
	Yes	135	16,9%	
Chronic lung disease	No	772	96,4%	
	Yes	29	3,6%	

TABLE 2.
Summary of case processing and architecture of the neural network model for the prediction of aortic segment diameters

Category	Element	Detail
Case processing	Total of valid cases	798 (100%)
	Cases used for training	544 (68.2%)
	Cases used for testing	254 (31.8%)
	Ruled out cases	3
Neural network model	Type of network	Multilayer perceptron
	Input layer	
	Number of covariates	20
	Variables included	Gender, age, BMI, SBP, DBP, M.CAVI, ALT, AST, smoking, alcohol, HTN, DM, CAD, osteoporosis, chronic lung disease, creatinine, calcium, phosphorus, total cholesterol, triglycerides
	Covariate scaling	Standardized
	Hidden layer	
	Number of hidden layers	1
	Units in the hidden layer	12
	Activation function	Hyperbolic tangent
	Output layer	
	Dependent variables	Aortic sinus of Valsalva, sinotubular junction, mid ascending aorta, proximal aortic arch, mid aortic arch, descending thoracic aorta, mid descending aorta, aorta in the diaphragm, abdominal aorta
	Number of units	9
	Dependent variables scaling	Standardized
	Activation function	Identity
	Error function	Sum of squared errors

the linear activation function was applied with an error criterion based on the sum of squared errors (Table 2).

The analysis of relative errors showed that the model represented the relationship between clinical variables and the mid descending aorta diameter with more accuracy, both in the training phase (0.383) and in the testing phase (0.356). In contrast, the greatest inaccuracies were observed in the aortic sinus of Valsalva and the sinotubular junction. These results indicate a better capacity of the model to capture the relationship in the descending aorta segments (Table 3).

As the neural network showed a higher accuracy in the estimation of the mid descending aorta diameter, a specific analysis was made on this segment. The hidden layers of the model capture nonlinear relationships between clinical covariates and the aortic diameters. In this analysis, the intermediary units of the hidden layers (H(1:1) to H(1:8)) show how the input variables affect the final prediction. The coefficients of the hidden layers indicate that an increase in age is associated to an increase in the mid descending aorta diameter, with significant values of 0.576 in H(1:1) and 0.638 in H(1:8). In contrast, gender shows a more variable relationship, with both negative and positive coefficients, reflecting its varying influence on the processing stages. In brief, the results show how the neural network models the

TABLE 3.
Relative errors in the prediction of aortic diameters by phase of the multilayer perceptron model (training and testing)

Phase	Dependent variable	Relative error
Training	Aortic sinus of Valsalva	0.714
	Sinotubular junction	0.703
	Mid ascending aorta	0.532
	Proximal aortic arch	0.514
	Mid aortic arch	0.531
	Descending thoracic aorta	0.551
	Mid descending aorta	0.383
	Aorta in the diaphragm	0.544
	Abdominal aorta	0.573
Testing	Aortic sinus of Valsalva	0.798
	Sinotubular junction	0.716
	Mid ascending aorta	0.521
	Proximal aortic arch	0.584
	Mid aortic arch	0.630
	Descending thoracic aorta	0.596
	Mid descending aorta	0.356
	Aorta in the diaphragm	0.515
	Abdominal aorta	0.587
	Función de error	Suma de cuadrados

complex nonlinear relationships between clinical variables and the aortic morphology, with special emphasis on the mid descending aorta (*Table 4*).

The analysis of the importance of the variables for the mid descending aorta diameter revealed that age was the most influential one (0.168, 100%). Other significant variables were AST (0.092, 54.7%), creatinine (0.084, 49.9%), BMI (0.068, 40.2%) and phosphorus (0.063, 37.5%). Metabolic kidney health factors showed a significant relationship with aortic diameter. Variables such as DBP (0.059, 35.2%) and triglycerides (0.057, 33.8%) were also relevant, just as ALT (0.055, 32.8%). With less impact, there were M.CAVI (0.043, 25.5%) and chronic lung disease (0.040, 24.0%). The variables with less relevance were osteoporosis, smoking, HTN, alcohol consumption, DM and CAD. In summary, age and renal health presented a higher influence on aortic diameter, while the other conditions had a lesser impact (*Table 5*).

The dispersion graph between the values observed and predicted for the mid descending aorta diameter shows a moderate relationship, with an R2 determination coefficient of 0.613. In the graph, the observed values are represented in the X axis, and the predicted values in the Y axis. Most points are grouped close to the identity line, indicating that

the multilayer perceptron model captures a significant part of variability in aortic diameters. However, the dispersion of some points reflects deviations and an error margin in predictions. This pattern suggests that the model explains 61.3% of diameter variability, but still presents an error margin of 38.7%, indicating the need to optimize the model accuracy in future analysis (*Figure 1*).

DISCUSSION

The results obtained in this study show that the clinical variables, such as blood pressure, calcium and phosphorus levels, and the presence of dyslipidemia had a significant association with the mid descending aorta diameter; while this relationship was not observed with the same strength in other aortic segments. This finding is particularly relevant, as it suggests that the clinical behavior of certain systemic conditions (such as hypertension and metabolic alterations) may have a specific impact on this portion of the aorta, and not necessarily on the proximal or distal segments with the same intensity.

The mid descending aorta is in a transition area between the ascending aorta, which has a more elastic structure, and less exposed to direct systolic pressure, and the abdominal aorta, which has a stiffer behavior.^{8,9} This location may ex-

TABLE 4.
Estimation of parameters in the regression model for the prediction of mid descending aorta diameter

Predictor	(H(1:1))	1(H(1:2))	1(H(1:3))	1(H(1:4))	1(H(1:5))	(H(1:6))	(H(1:7))	(H(1:8))	Mid descending aorta
Bias	-0.325	-0.411	-0.160	-0.167	-0.119	0.190	0.409	0.483	-0.058
Gender	-0.289	-0.156	0.179	0.501	0.058	0.151	-0.266	-0.266	-0.266
Age	0.576	-0.274	0.075	-0.065	-0.200	0.419	-0.232	0.638	0.638
BMI	0.269	-0.144	0.331	-0.040	0.180	0.045	0.183	-0.036	-0.036
SBP	0.457	0.157	0.045	0.409	-0.281	-0.283	0.209	0.104	0.104
DBP	-0.291	-0.325	-0.263	-0.518	0.149	-0.189	-0.511	0.578	0.578
M.CAVI	-0.195	0.292	0.556	0.035	-0.520	0.226	0.422	0.129	0.129
ALT	-0.573	-0.009	0.120	-0.305	-0.234	-0.207	-0.476	-0.052	-0.052
AST	0.230	0.463	0.204	-0.028	-0.118	0.251	-0.092	0.047	0.047
Smoking	0.419	0.075	-0.420	-0.299	-0.395	-0.430	-0.293	-0.262	-0.262
Alcohol	-0.223	-0.260	0.363	-0.334	0.233	-0.480	0.016	0.108	0.108
HTN	-0.136	0.049	0.332	0.157	-0.470	-0.024	0.060	0.190	0.190
DM	0.103	-0.245	0.196	0.349	-0.015	0.370	-0.215	0.009	0.009
CAD	-0.001	0.128	-0.117	-0.456	0.104	-0.283	-0.504	0.146	0.146
Osteoporosis	-0.462	-0.370	0.235	-0.164	-0.284	-0.027	-0.088	0.121	0.121
Chronic lung disease	0.483	0.515	0.186	-0.276	-0.003	0.406	0.284	-0.282	-0.282
Creatinine	0.325	-0.420	0.051	0.048	-0.354	-0.164	0.165	-0.007	-0.007
Calcium	0.292	0.438	0.033	0.319	0.151	-0.056	0.058	-0.099	-0.099
Phosphorus	-0.224	0.343	-0.377	0.366	0.027	0.025	0.072	0.359	0.359
Total cholesterol	-0.164	-0.245	0.276	0.264	0.096	0.236	0.018	-0.238	-0.238
Triglycerides	0.360	-0.431	-0.089	0.421	0.185	-0.468	-0.374	-0.176	-0.176

plain why this segment is more susceptible to hemodynamic and metabolic alterations. An elevated systolic BP and changes in elasticity of the aorta can be more evident in the mid descending aorta, as this segment receives the heart pulsation forces directly, but could be more affected by the vascular tone modifications caused by comorbidities, such as hypertension and dyslipidemia.⁹

The mid descending aorta is a critical site for the manifestation of dysfunctions in arterial elasticity due to the aortic stiffness associated with chronic hypertension and an imbalance in the lipid and mineral metabolism.¹⁰ Dyslipidemia can promote the formation of atherosclerotic plaques in this segment, and an increase in the calcium levels in blood may induce aortic calcification, processes that may affect more intensely the mid descending aorta.^{9,11,12} These metabolic factors, along with stiffness induced by hypertension, may contribute to the loss of distensibility in this part of the aorta, which makes it more vulnerable to structural and functional alterations.

Furthermore, the metabolic factors such as elevated calcium and phosphorus levels, as in the case of patients with chronic kidney disease, may affect the composition of the aortic wall; particularly in the region of the mid descending aorta, favoring calcification and endothelial dysfunction.¹³

TABLE 5.
Significance of independent variables in the prediction of mid descending aorta diameter

Variable	Significance	Normalized significance
Age	0.168	100%
AST	0.092	54.7%
Creatinine	0.084	49.9%
BMI	0.068	40.2%
Phosphorus	0.063	37.5%
Calcium	0.061	36.1%
DBP	0.059	35.2%
Triglycerides	0.057	33.8%
ALT	0.055	32.8%
SBP	0.053	31.7%
Total cholesterol	0.050	29.5%
M.CAVI	0.043	25.5%
Chronic lung disease	0.040	24.0%
Gender	0.035	20.7%
Osteoporosis	0.018	10.7%
Smoking	0.013	7.4%
HTN	0.013	8.0%
Alcohol consumption	0.010	5.9%
DM	0.010	5.9%
CAD	0.008	5.0%

This would explain why this segment shows a greater association with the clinical variables observed, in comparison with other more proximal or distal segments of the aorta, that may be less sensitive to these factors.

The dispersion graph between the observed and estimated values of the mid descending aorta diameter, generated by a multilayer perceptron model, showed a moderate relationship, with an R2 determination coefficient of 0.613, indicating that the model explains approximately 61.3% of aortic diameter variability. This moderate performance could be attributed to multiple physiological, clinical and methodological factors, as aortic morphology is the result of complex processes such as vascular ageing, arterial remodeling, aortic wall stiffness, oxidative stress and chronic inflammation, which are mediated by genetic, metabolic and hemodynamic components, that are not always reflected in routine clinical variables.^{14,15}

This result has significant clinical implications, as the mid descending aorta could be a sensitive marker of vascular alterations in individuals with metabolic and cardiovascular diseases, particularly in those with uncontrolled hypertension or dyslipidemia. Physicians may focus on this aortic segment as a priority target to monitor structural changes in patients in high risk, as in those with established cardiovascular disease or those in risk of aortic aneurysms. In this regard, this finding also contributes to the anatomical and physiological understanding of the mid descending aorta, by highlighting its role as a vascular area susceptible to hemodynamic and metabolic influences, reinforcing its relevance as a structural marker in the study of cardiovascular diseases.

In this scenario, physicians can use the identified clinical variables, such as blood pressure, calcium and phosphorus levels, and dyslipidemia to estimate the risk of aortic alterations in this segment, which enables making more informed decisions on additional tests or preventive interventions.

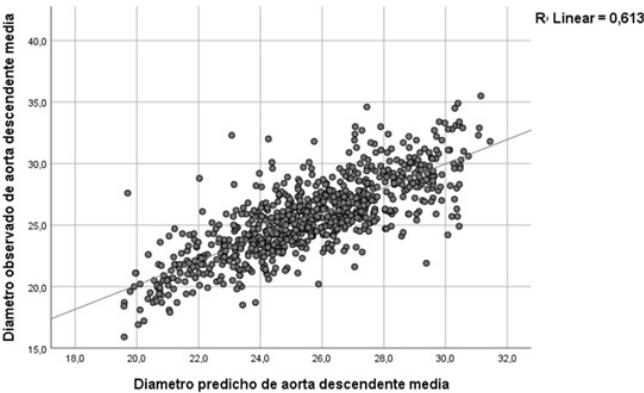


FIGURE 1.
Dispersion graph with coefficient of determination between values observed for the mid descending aorta diameter, obtained by non-contrast CT and predicted values for the mid descending aorta obtained by multilayer perceptron

Moreover, the developed model could be implemented as a clinical support tool for an early identification of patients in risk of aortic diseases, optimizing care and reducing the need for invasive testing in its initial stages, which favors a more efficient and customized care.

The main limitations of this study include a cross-sectional design, which does not enable establishing causal relationships; and the lack of longitudinal follow-up, which prevents observing the course of aortic diameter over time. Furthermore, the study does not consider confounding factors such as genetics or lifestyle, and the evaluation of aortic diameter by CT mediated by AI could present technical biases. Finally, the sample may not be representative for the general population, limiting the generalization of results.

To conclude, the results of the multilayer neural network suggest that clinical variables and cardiovascular risk factors present a nonlinear association with the diameter of the mid descending aorta. This association becomes evident in the adequate predictive capacity of the model for said segment (lower relative error in both phases of the model), as well as in the influence observed of these variables on the activations of the hidden layers and the output layer. Likewise, although this is not a causal or inferential analysis, the results reinforce the usefulness of neural networks to model complex clinical relationships affecting aortic morphology. It is advised to reproduce this research in more extensive cohorts.

We suggest performing longitudinal studies that would enable evaluating aortic diameter changes over time and establishing causal relationships. Likewise, we recommend, for future studies, to include genetic and lifestyle variables, besides validating automated measurements with manual methods. Finally, extending the sample to more diverse populations would improve the generalization of the findings.

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Original Investigation Reports

Bronchial asthma could belong to the group of systemic inflammatory diseases

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ABSTRACT

Introduction: hypertensive cardiovascular disease is a complex, multifactorial, and chronic illness, frequently beginning during childhood or adolescence, that could lead to functional and/or structural organ damage by increase in arterial stiffness and the volume/pressure curve, that in turn can increase the stress into the ventricular-arterial coupling and could produce the appearance of arrhythmias such as atrial fibrillation.

This study **aims** to evaluate patients with bronchial asthma with non-invasive arterial tonometry to determine its possible similarity with systemic inflammatory diseases and also the capability of presenting brief episodes of atrial fibrillation.

Materials and Methods: this was a retrospective, cross-sectional study of 435 patients, of whom 93 were chronic asthmatics and the rest had systemic inflammatory diseases such as psoriasis, rheumatoid arthritis, celiac disease, Sjögren's syndrome and Crohn's disease, ulcerative colitis, endometriosis, and polycystic ovary syndrome. General and anthropological data, blood pressure, and central hemodynamic parameters were recorded using noninvasive arterial tonometry. Episodes of atrial fibrillation were recorded during 24-hour ambulatory electrocardiographic Holter monitoring.

Results: statistically comparing the data of asthmatics with all systemic inflammatory diseases and in both sexes separately, no significant differences were observed.

Conclusions: According to these observations, bronchial asthma presents a similarity with systemic inflammatory diseases due to damage to the arterial wall and the presence of brief phases of atrial fibrillation.

INTRODUCTION

Although Rudolph Virchow defined atherosclerosis as a chronic inflammatory pathology more than a century ago, decades of clinical investigation were necessary to confirm this remarkable intuition.

Different inflammatory pathways present pro-atherogenic and pro-thrombotic effects that may vary from patient to patient, and according to the different phases of natural history of atherosclerotic cardiovascular disease.¹

There are increasingly more proofs that, besides the traditional risk factors, vascular wall inflammation plays a key role in the pathogenesis of vascular diseases and atherosclerotic and atherothrombotic processes. In spite of optimal control of traditional risk factors, cardiovascular events, even fatal ones, persist in some patients.² Chronic systemic inflammatory diseases are associated with premature atherosclerosis and hypertension.³ The links between the immunological system and atherogenesis are properly established. Atherosclerosis is a systemic inflammation state of low grade, associated with immune system activation in

the presence of classical risk factors. This chronic inflammation of low grade is different from the severe chronic inflammatory state associated with autoimmune diseases (for instance, rheumatoid arthritis and psoriasis).⁴ It has been proven that chronic systemic inflammation, as for example in patients with psoriasis, psoriatic arthritis and rheumatoid arthritis can cause accelerated atherosclerosis and is associated with higher cardiovascular risk.^{5,6} Recently, an extensive population study led by Conrad N, et al. confirmed the evidence of an association between autoimmune diseases and cardiovascular risk.⁷

OBJECTIVE

To study patients with bronchial asthma to establish a possible similarity with the more widely known systemic inflammatory diseases, mainly assessing by noninvasive arterial tonometry, measuring central hemodynamic parameters, and also to observe the presence of brief episodes of atrial fibrillation as an important cardiovascular complication.

MATERIALS AND METHODS

To develop this retrospective and cross-sectional study, there were 435 patients registered; 328 were females (75.4%) and 107 were males (24.6%), of whom 93 (21.4%) were chronic asthmatic patients: 66 females (20.1%) and 27 males (25.2%). The age range is between 19 and 88 years, with an average age of 46.4 years, both genders. Gender, anthropological, blood pressure and heart rate data were recorded, as well as central hemodynamic parameters recorded with noninvasive arterial tonometry, and the prevalence of each of the systemic inflammatory diseases in total, separately, and bronchial asthma.

The measurements of blood pressure were made according to standard methods with ERKA sphygmomanometers (N° 7102869 – 18031068). The presence of brief episodes of atrial fibrillation were recorded during 24 h Holter ambulatory monitoring (Spacelabs Healthcare Ltd, USA. Evo N° 001877 - 014012).

Noninvasive arterial tonometry

Central hemodynamic parameters were measured by the SphygmoCor device, model PVX (AtCor-Medical, Australia). Noninvasive arterial tonometry is a valid instrument, using a high-fidelity technique, with software adequate for generalized transfer functions use for pulse wave analysis made on the radial artery, to estimate aortic augmentation index as a substitute measure for arterial stiffness. Central aortic pressure, end of systole pressure, mean blood pressure, pulse pressure and augmentation pressure were measured and expressed in mmHg. Likewise, the augmentation index was measured (AIx) adjusted to 75 beats per minute expressed in percentage (AIx@HR75), with a fidelity index of >85%, being the most commonly used index to measure pressure wave reflections. AIx and pulse wave velocity are closely correlated, in a significant and positive way ($r=0.29$, $p<0.005$). The differences in AIx were estimated between the values observed in regard to normal maximal levels, according to established protocols, according to gender and age.

Statistical analysis

Continuous variables were summarized by descriptive statistics. Data are expressed as mean+standard deviation. Categorical variables were summarized using count of patients and percentages. The differences between the means of central hemodynamic parameters in male and female

patients were compared by Student's t-test for independent samples. Statistical tests were bilateral and alpha level was established in 0.05. Statistical analyses were carried out using the SAS system, version 9.2.

RESULTS

The patients with different systemic inflammatory diseases were 342 (78.6%), such as: psoriasis (125), rheumatoid arthritis (27), celiac disease (13), Sjögren's syndrome (9), Crohn's disease (7), ulcerative colitis (10), endometriosis (10) and polycystic ovary syndrome (141).

In *Table 1*, each of the systemic diseases and asthma are represented, with the number of patients who presented brief episodes of atrial fibrillation recorded in 24 h Holter.

From all systemic diseases between men, there was a predominance of psoriasis (59), and polycystic ovary syndrome between women (141), so the mean age in this gender is lower, while in asthmatic patients, the mean age was similar in both genders.

In most of the groups, body mass index was at the limit between overweight and obesity, except in the celiac disease group being much lower, with this difference maybe being caused by a possible limitation in therapeutic food ingestion by patients because of their base pathology.

Systolic and diastolic blood pressure figures of systemic diseases were in the 120/70 mmHg limit, which is the threshold pointed out as "elevated" blood pressure by the last guidelines on hypertension, observing the most elevated recordings in rheumatoid arthritis.⁸ The criterion applied in this study was that the normal blood pressure level should be the one not producing functional and/or structural alterations on the cardiovascular system (*Table 2*).

Likewise, central hemodynamic parameters, whether between the systemic diseases or in asthma, were always elevated; for instance, central systolic pressure and end systolic pressure exceeding 110 and 100 mmHg, respectively. Also, the augmentation index presented figures above normal levels in all groups and in both genders (*Table 3*).

In a second analysis, the figures of all systemic inflammatory diseases were unified (considering them as a single entity due to their characteristics of producing endothelial damage, and subsequently, arterial stiffness) to be compared with the figures from asthmatic patients, whether by blood pressure, hemodynamic parameters and percentages of brief episodes of atrial fibrillation found in 24 h Holter.

TABLE 1.
Patients with atrial fibrillation according to underlying pathology

AF	Psor	RA	Celiac	End	Sjögren	Crohn	PCOS	UC	Asthma	Total
Women	9	3	1	1	0	0	3	2	6	25
Men	3	1	0		0	1		0	5	10
Total	12	4	1	1	0	1	3	2	11	35

AF: atrial fibrillation; Psor: psoriasis; RA: rheumatoid arthritis; Celiac: celiac disease; End: endometriosis; PCOS: polycystic ovary syndrome; UC: ulcerative colitis.

The mean pressures of asthmatic patients and those of the sample of all patients with systemic inflammatory diseases, in both genders, were higher than the figure of guidelines for hypertension (Table 4).⁸

Once these figures were obtained, they were compared statistically, by contrasting the data from asthmatic patients with all systemic inflammatory diseases, and in both genders separately. No significant difference was observed (Table 5).

DISCUSSION

According to scientific literature, this would be the first study evaluating bronchial asthma as a disease similar to those called chronic systemic inflammatory diseases, such as psoriasis, rheumatoid arthritis, Crohn’s disease, Sjögren’s syndrome, etc., taking central hemodynamic parameters, blood pressure and the presence of brief episodes of atrial fibrillation, as an important complication for hypertension, recorded in 24 h Holter, as reference point.

Several patients in this registry presented two inflammatory pathologies simultaneously, or in different periods of life, as for instance psoriasis and Sjögren’s syndrome, which

led to consider that the base of the disease is a single chronic inflammatory condition, frequently including the arteries. This manifested through the analysis of pulse wave with noninvasive arterial tonometry; so, we can assume that this systemic disease could be a single entity, which according to the response of the target organ where lesions occurred has received a different name in scientific literature.

The relationship in arterial stiffness and the presence of brief phases of atrial fibrillation, as well as its possible prevention, has been expressed in a study with 1500 patients comparing 3 groups of therapy: one group with angiotensin II receptor blockers (ARBs) associated to mineralocorticoid receptor antagonists (MRA), a second group with just ARBs and the third with ARBs associated to hydrochlorothiazide. It was observed that in the first group, lower systolic and diastolic blood pressures were obtained, and that the presence of brief phases of atrial fibrillation were virtually nil, with a statistically significant difference in relation to the other two therapy groups.⁹

TABLE 2.
Anthropometric data, age, blood pressure and heart rate of systemic inflammatory diseases and asthma

Men	n	Age	BMI	WC	SBP	DBP	HR
Asthma	27	52.4	30.2	105.7	139.1	84.6	69.4
Psoriasis	59	53.3	31.7	108.2	134.8	85.3	73.7
Rheumatoid arthritis	6	48.7	35.0	112.0	149.3	99.2	79.5
Celiac disease	5	47.0	27.8	101.0	133.4	83.4	65.0
Crohn	5	43.2	29.0	95.5	125.6	75.4	70.4
Sjögren	1	51.0	31.5	105.0	120.0	82.0	75.0
Ulcerative colitis	4	42.8	28.2	101.5	131.8	88.8	76.8
Women	n	Age	BMI	WC	SBP	DBP	HR
Asthma	66	52.2	30.3	95.7	136.3	82.7	73.9
Psoriasis	66	55.7	31.3	100.0	142.8	84.0	73.5
Rheumatoid arthritis	21	62.2	30.5	97.8	144.5	83.8	66.6
Celiac disease	8	39.3	22.5	83.4	121.9	76.9	74.6
Crohn	2	59.0	33.7	109.0	135.0	82.5	72.5
Sjögren	8	56.9	29.4	93.3	136.3	80.6	62.8
Ulcerative colitis	6	58.8	31.4	99.0	139.7	82.5	72.7
PCOS	141	39.6	30.9	96.8	130.6	83.0	78.4
Endometriosis	10	40.9	26.6	88.0	128.6	77.8	73.6

PCOS: polycystic ovary syndrome; BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate.

TABLE 3.
Central hemodynamic parameters of systemic inflammatory diseases and asthma

Men	CAP	ESP	MBP	PP	AP	AIx	AIx Dif
Asthma	126.3	116.7	103.1	40.8	9.6	19.3	2.9
Psoriasis	123.6	115.1	102.8	37.0	9.0	22.0	4.8
Rheumatoid arthritis	136.0	126.0	116.5	35.3	6.7	18.8	5.0
Celiac disease	123.8	114.2	101.8	39.4	10.4	20.2	5.7
Crohn	113.2	104.4	94.4	34.6	8.0	21.0	9.1
Sjögren	112.0	107.0	95.0	29.0	7.0	24.0	6.5
Ulcerative colitis	121.3	113.8	104.5	31.3	5.8	20.5	8.3
Women	CAP	ESP	MBP	PP	AP	AIx	AIx Dif
Asthma	127.1	116.8	103.0	43.1	13.3	29.0	4.1
Psoriasis	133.0	121.2	106.2	48.0	15.8	31.0	3.6
Rheumatoid arthritis	136.3	124.5	106.2	50.8	19.3	33.9	4.8
Celiac disease	113.4	105.4	90.1	35.4	10.6	26.1	6.8
Crohn	126.0	117.0	101.0	43.0	14.5	33.5	3.5
Sjögren	127.9	116.9	101.0	46.4	17.1	29.6	1.6
Ulcerative colitis	130.3	121.2	104.7	46.0	16.2	34.0	6.8
PCOS	119.8	111.4	100.0	35.3	9.2	25.5	5.5
Endometriosis	117.1	108.6	96.0	38.3	9.4	22.8	1.2

PCOS: polycystic ovary syndrome; CAP: central aortic pressure; ESP: end-systolic pressure; MBP: mean blood pressure; PP: pulse pressure; AP: augmentation pressure; AIx: augmentation index; AIx Dif: AIx difference (difference between the figures observed and normal maximal figures).

Subsequently, in a substudy of the latter study with 500 patients, it was also observed that up to a mean level of 121/73 mmHg of blood pressure measured by sphygmomanometer and an age less than 65 years, treated with the therapeutic association ARBs + MRA, did not present the brief episodes of atrial fibrillation in 24 h Holter monitoring.¹⁰

This observation allows associating arterial wall inflammatory phenomena with the development of hypertension, and one of its most frequent complications such as atrial fibrillation, present in patients with chronic systemic inflammatory diseases and in asthmatic patients.

In regard to systemic diseases, premature atherosclerosis in patients with systemic lupus erythematosus and rheumatoid arthritis has been increasingly observed, which may lead to early coronary death in comparison with the general population.¹¹

Rheumatoid arthritis is the most frequent manifestation of chronic inflammatory polyarthritis, which is present between the third and fifth decade of life, and with an increase

in prevalence of atherosclerotic CAD. This chronic inflammation state has been related with an acceleration of the atherosclerotic process with a rapid increase in the risk of myocardial infarction.¹²

Psoriasis is a chronic inflammatory skin disorder, affecting approximately 1.5-3% of the general population, and seems to be linked to an increase in cardiovascular morbidity and mortality, sharing with atherosclerosis several similar inflammatory mechanisms, with a greater risk of clinical and subclinical CAD.^{13,14} Moreover, it is a well-known independent determinant for myocardial infarction.¹⁵

Coronary flow reserve is often reduced in patients with psoriasis, suggesting a deterioration in preclinical endothelial dysfunction. It was also proven that an increase in intima-media thickness of the common carotid artery in psoriatic arthritis is a marker of early atherosclerosis in the absence of signs and symptoms of cardiovascular compromise and traditional cardiovascular risk factors. This microvascular dysfunction seems to be related with severity, extension and duration of psoriasis.

TABLE 4.

Central hemodynamic parameters, systolic and diastolic pressure figures, and the percentage of brief phases of atrial fibrillation observed between asthmatic patients and in systemic inflammatory diseases

Asthma	n	Age	AIx	CAP	ESP	MBP	PP	AP	SBP	DBP	AF	%
Total	93	52.2	3.8	127.8	117.7	103.7	42.9	12.4	138.1	83.8	11	11.8
δ		17.1	8.1	20.6	16.8	13.1	16.6	8.5	20.6	10.5		
Women	66	52.2	4.1	127.1	116.8	103.0	43.1	13.3	136.3	82.7	6	9.1
δ		17.4	8.6	20.7	17.5	14.1	15.0	7.8	20.8	11.0		
Men	27	52.4	2.9	126.3	116.7	103.1	40.8	9.6	139.1	84.6	5	18.5
δ		16.7	7.0	20.7	15.5	10.5	20.1	10.0	20.7	9.4		
SID	n	Age	AIx	CAP	ESP	MBP	PP	AP	SBP	DBP	AF	%
Total	342	46.4	5.0	122.4	113.3	100.6	38.4	10.9	132.7	82.6	24	7.0
δ		15.8	7.6	19.3	16.8	13.6	14.9	7.6	20.2	10.5		
Women	262	45.2	4.8	122.4	113.0	100.0	39.6	11.8	132.5	81.6	19	7.3
δ		16.3	7.4	20.2	17.4	13.6	15.9	7.9	20.8	9.9		
Men	80	51.4	5.3	123.6	115.0	103.2	36.5	8.6	134.9	85.9	5	6.3
δ		13.2	8.4	16.4	14.8	13.3	10.8	5.6	18.0	12.0		

SID: systemic inflammatory diseases; AIx: augmentation index; CAP: central aortic pressure; ESP: end-systolic pressure; MBP: mean blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; AF: atrial fibrillation.

TABLE 5.

P values between central hemodynamic parameters, systolic and diastolic pressures, and the percentages of patients with brief episodes of atrial fibrillation.

	SBP	DBP	CAP	ESP	MBP	PP	AP	AIx	AF	Total AF
Women	0.2	0.5	0.1	0.1	0.1	0.1	0.2	0.5	0.2	0,2
Men	0.4	0.6	0.5	0.6	0.9	0.3	0.6	0.1	0.1	

SBP: systolic blood pressure; DBP: diastolic blood pressure; CAP: central aortic pressure; ESP: end-systolic pressure; MBP: mean blood pressure; PP: pulse pressure; AP: augmentation pressure; AIx: augmentation index; AF: atrial fibrillation.

Polycystic ovary syndrome (PCOS) affects between 6 and 16% of women, with a marked ethnical variation in a reproductive age, frequently associated to hyperandrogenism, with a high prevalence of dyslipidemia, obesity, glucose intolerance, resistance to insulin and diabetes mellitus.¹⁶

Diagnosis is based, most commonly, in the Rotterdam criteria, requiring 2 to 3 data: oligoovulation or anovulation, clinical or biochemical evidence of hyperandrogenism and polycystic ovaries in ultrasound.¹⁷ Also, endothelial dysfunction has been described in these women. In spite of presenting cardiometabolic changes, the American Heart Association has not established PCOS as a factor increasing the risk of atherosclerotic cardiovascular disease.¹⁸ However, other authors have observed that women with PCOS present a significantly higher risk of cardiovascular disease.¹⁹

Endometriosis belongs to a complex interaction between endocrine, immunological, inflammatory and pro-angiogenic processes, and was also defined as an estrogen-dependent inflammatory condition.²⁰ Growing evidence has highlighted a concerning link between endometriosis and cardiovascular disease. Recent guidelines and position statements have provided limited commentaries on the correlation between endometriosis and adverse cardiovascular outcomes, although other studies have proven an association between endometriosis and a greater risk of atherosclerotic cardiovascular disease, particularly CAD and stroke.²¹

Recently, a Danish study of national scope, of the case-control type, has shown that women with endometriosis present a greater risk in the long term, of suffering adverse cardiovascular events in comparison with the general population, such as acute myocardial infarction, ischemic stroke, arrhythmias (including atrial fibrillation and different degrees of blocks) and heart failure.²²

In this study, it was timely to emphasize some investigations that entail a moderate association between bowel inflammation and CAD.

Inflammatory bowel disease, including ulcerative colitis, Crohn's disease and inflammatory bowel disease unclassified, is a chronic inflammatory disorder, affecting mainly the gastrointestinal tract, but that often also presents extra-intestinal manifestations and complications.²³

Some studies have suggested a link between inflammatory bowel disease and cardiovascular diseases, including acute arterial events, venous thromboembolism, hypertension and arrhythmias.^{24,25,26,27}

In Crohn's disease and ulcerative colitis, elevated coagulation factors are observed, such as factor V, factor VIII, fibrinogen and Von Willebrand factor.²⁸

Although thrombocyte and fibrinogen levels increased both in patients with ulcerative colitis and with Crohn's disease, levels of prothrombin times, factor V and factor VIII only increased in ulcerative colitis. On the other hand, plasminogen only increased in Crohn's disease. The difference between control subjects and patients was more marked in those with Crohn's disease in comparison with patients with ulcerative colitis.

Sjögren's syndrome is frequently a secondary phenomenon in patients with lupus, rheumatoid arthritis or scleroderma, or it may present with no other systemic rheumatic disease (primary Sjögren's syndrome). Sjögren's syndrome is associated to lymphocyte infiltration that may present even in kidneys.²⁹

Bronchial asthma is a heterogeneous disease of the respiratory airways, where genetic and environmental factors converge, characterized by inflammation and greater responsiveness to a variety of stimuli. Atopy is the main risk factor of asthma, and non-atopic people have a very low risk of developing asthma.

This observation suggests that other environmental or genetic factors predispose to the development of asthma in atopic individuals.

Asthma is one of the most extended chronic diseases, and it currently affects approximately 300 million people all over the world. In industrialized countries, the prevalence of asthma has increased in the last 30 years, and now it seems to be stabilizing with a prevalence of 10-12% in adults. Respiratory airway mucosa is infiltrated by eosinophils and activated T-lymphocytes, and mastocyte activation is observed in mucosa. The degree of hyperresponsiveness is closely linked to the intensity of inflammation.³⁰

CONCLUSIONS

According to these observations, bronchial asthma presents similarities with systemic inflammatory diseases, whether by damage on the arterial wall, contributing to developing hypertensive cardiovascular disease, or by the presence of one of its most frequent and important complications, namely brief phases of atrial fibrillation that precede its definitive establishment. Patients with bronchial asthma would have a cardiovascular risk similar to patients with systemic diseases.

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Position Statement

Intersocietal document on apolipoprotein B

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ABSTRACT

Apolipoprotein B (ApoB) is the main protein component of atherogenic lipoprotein particles, such as very low density (VLDL), intermediate density (IDL), and low density (LDL) particles. Therefore, the plasma concentration of ApoB allows the total number of atherogenic particles to be estimated. In recent years, various epidemiological and intervention studies have shown that ApoB measurement independently predicts cardiovascular risk, even surpassing conventional lipid parameters such as LDL-bound cholesterol (LDL-C), which remains the main therapeutic target in lipid treatment, with clearly established goals.

The objective of this collaborative effort between prestigious scientific societies is to develop a position paper that addresses, in a clear and practical manner, various aspects related to ApoB measurement by answering ten key questions. The main messages are summarized in the central figure.

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INTRODUCTION

Apolipoprotein B (ApoB) is the main protein component of atherogenic lipoprotein particles, such as those of very low density (VLDL), intermediate density (IDL) and low density (LDL). Therefore, ApoB plasma concentration allows to estimate the total number of atherogenic particles. In recent years, different epidemiological and intervention studies have proven that ApoB measurement predicts cardiovascular risk independently, even exceeding conventional lipid parameters, such as LDL cholesterol (LDL-C), which is still the main therapeutic target in lipid treatment, with clearly established goals.¹

The aim of this collaborative study, carried out by prestigious scientific societies, is developing a position statement

that would approach, in a clear and practical manner, different aspects related to ApoB measurement, by answering ten key questions. The main messages are summarized in the *central figure*.

WHAT SHOULD WE KNOW ABOUT APOB PHYSIOLOGY?

All lipoproteins with atherogenic potential contain one ApoB as a main structural component, which is not exchangeable. In contrast, high-density lipoproteins (HDL), acknowledged for their anti-atherogenic properties, integrate Apolipoprotein A (ApoA) into its membrane.

ApoB-100 is intrinsically associated to VLDL, their remnants (IDL), LDL, as well as ApoB-48 to chylomicrons and

lipoproteins (VLDL); 2) it stimulates ApoB degradation through the ubiquitin-proteasome system, responsible for its intracellular removal; 3) it favors ApoB degradation through the phagolysosomal system, another mechanism of cell degradation.^{5,6}

WHAT ARE THE METHODS AVAILABLE FOR ITS QUANTIFICATION?

Measuring a lipid component, such as the cholesterol of lipoproteins, may be more practical and slightly more economical. However, due to variability in the content of cholesterol between the particles of each lipoprotein family, the standardization of methods to quantify LDL-C or HDL cholesterol (HDL-C) is more complex than the selective measurement of a specific and structurally constant protein molecule, such as ApoB.⁷ Furthermore, ApoB behaves like a robust marker, since it can be measured accurately throughout the range of concentrations, both in normal and pathological conditions, not being affected by the possible pathophysiological variations.

The methods used by clinical laboratories for the measurement of ApoB are completely automatable, and are based on immunoturbidimetric and immunonephelometric techniques. These should meet the standards established by the World Health Organization (WHO) and the International Federation of Clinical Chemistry (IFCC) by using calibrators traceable to international reference materials, currently SP3.⁸ Both methods use specific antibodies like ApoB.

The basis of immunoturbidimetry is the formation of immune complexes with the antibody addressed against the ApoB to be measured. Then, light diffraction is measured in a given angle, which is altered by the immune complexes formed. In the case of immunonephelometry, it could be of "endpoint" when light diffraction is measured in a given angle, altered by the immune complexes formed, or "kinetic" when the dispersed light emission velocity change is measured, according to immune complexes formation velocity.

The equipment necessary to measure ApoB, as well as quality specifications and experience required, are available in a great number of clinical laboratories. Furthermore, several diagnosis companies manufacture assays approved for measurement. The standard methods mentioned are equivalent to other procedures validated and robust, such as nuclear magnetic resonance, whose equipment is addressed to specialized laboratories and that is also used to analyze lipoprotein subfractions.⁹ Since the 1990s, the IFCC has promoted the standardization of ApoB measurement, establishing a temporary reference method based on the measure, by immunonephelometry, of the total protein of LDL previously isolated by ultracentrifugation. In recent years, the IFCC has started evaluating the liquid chromatography-tandem mass spectrometry (LC-MS/MS) as a candidate to a definitive reference method, which would enable a real standardization of ApoB measurement, turning it into the first truly standardized marker of lipopro-

teins.^{7,10} For the time being, different consensus groups, organizers of the External Quality Assessment organizers, the Lipid Standardization Program of the Center for Disease Control and Prevention (CDC) of the US and other clinical chemistry experts have confirmed that the ApoB standardization program developed by the WHO/IFCC meets the necessary requirements to be applied in clinical care.¹⁰

All methods measure total ApoB (ApoB100+ApoB48); however, postprandial contribution of ApoB48 in relation to ApoB100 is minimal and insignificant, except when triglycerides exceed 400 mg/dl, so ApoB can be measured not requiring fasting in most cases. Serum samples can be frozen and then unfrozen for measurement.¹⁰

WHAT IS THE RELATIONSHIP BETWEEN APOB AND CARDIOVASCULAR RISK ACCORDING TO EPIDEMIOLOGICAL STUDIES AND MENDELIAN RANDOMIZATION?

From what was commented earlier, it is reasonable to propose that elevated levels of ApoB are associated to a greater cardiovascular risk. However, although this idea seems logical from common sense, it is necessary to back it up with scientific evidence.

Evidence from population studies shows that high levels of ApoB are associated with an increase in the risk of developing cardiovascular events. Johannesen et al. carried out an analysis on the Copenhagen General Population Study, where they included 53484 women and 41624 men who did not receive statins, and evaluated the relationship between high levels of ApoB and incidence of cardiovascular events.¹¹ After a median follow-up of 9.6 years, they showed a concentration-dependent association between elevated levels of ApoB and the risk of presenting acute myocardial infarction and atherosclerotic cardiovascular disease. This study proved that ApoB presents a significant predictive value beyond LDL-C throughout the concentration spectrum of this lipoprotein, both in men and in women. Before this study, Sniderman et al. published a meta-analysis of observational studies that included 233455 patients, where they proved that ApoB is a better predictor of cardiovascular risk than LDL-C and non-HDL-C.¹² The relative risk ratio for ApoB was 1.43 (95% confidence interval [CI]: 1.35-1.51), in comparison with 1.25 for LDL-C (95% CI: 1.18-1.33) and 1.34 for non-HDL-C (95% CI 1.24-1.44).

In the same line, Mendelian randomization studies have shown that people carriers of genetic variants associated to elevated levels of ApoB present a greater risk of developing cardiovascular events in comparison with those who don't. particularly, an analysis of the UK Biobank showed that ApoB was associated in a multivariate analysis, with nearly double the risk of cardiovascular disease (odds ratio [OR]: 1.92; 95% CI: 1.31-2.81; $p < 0.001$).¹³ On the other hand, another Mendelian randomization study showed that in cases of mismatch between levels of LDL-C and ApoB, the latter correlates more accurately with cardiovascular risk.¹⁴

WHAT IS THE ASSOCIATION BETWEEN APOB LEVELS DURING TREATMENT AND CARDIOVASCULAR RISK ACCORDING TO CLINICAL TRIALS?

As most controlled and randomized clinical trials included patients according to cardiovascular risk and LDL-C, the evidence available specifically on ApoB is more limited. Moreover, these trials generally evaluated therapeutic schemes, not establishing specific aims of ApoB as treatment target. However, the analysis of many of these studies reveals a direct correlation between the ApoB levels reached during treatment and the future incidence of major cardiovascular events.

Multiple clinical trials with statins have shown that the in-treatment value of ApoB has an independent predictive value, regardless of having been observed both in scenarios of primary and secondary prevention.^{15,16} A meta-analysis, including seven randomized clinical studies with statins, showed that a mean reduction of risk of CAD per each decrease in standard deviation (27 mm/dl) in ApoB levels was 24.4%, representing a greater risk reduction in comparison with LDL-C (20.1%) or non-HDL-C (20%).¹⁷ In this analysis, the mean concentration of ApoB per year in the treated group was 85 mg/dl, with a range of values between 71 and 105 mg/dl.

In the IMPROVE-IT study, the addition of ezetimibe to simvastatin, in comparison with just simvastatin, in patients with acute coronary syndrome, was associated to a 15% reduction in the ApoB levels (in-treatment median of 67 mg/dl), and with a 6.4% decrease in the incidence of cardiovascular events combined within 6 years of follow-up.¹⁸ Both in this study and in the FOURIER, which evaluated the effect of evolocumab in comparison with placebo in patients in secondary prevention treated with statins, the level of ApoB reached during treatment was the best predictor of myocardial infarction.¹⁹ Similarly, in the ODYSSEY OUTCOMES trial, that researched the impact of alirocumab in 18000 patients with acute coronary syndrome in comparison with placebo, it was observed that a greater basal level of ApoB was associated with a greater rate of combined cardiovascular events, as well as with greater relative and absolute reduction of events in the group treated with alirocumab.²⁰ Likewise, low levels of ApoB during treatment (<35 mg/dl) were highly predictive of a greater reduction in clinical events. As to in-treatment ApoB levels, values of 38 mg/dl were recorded in FOURIER and of 49 mg/dl in ODYSSEY OUTCOMES, which was associated with a 15% reduction in combined cardiovascular events in both studies, with follow-ups of 2.2 and 2.8 years, respectively. In the REVEAL study, which evaluated the CETP inhibitor, anacetrapib, compared with placebo in patients in secondary prevention treated with statins, a reduction in ApoB of 12 mg/dl (18%) was associated with 9% decrease in the incidence of cardiovascular events.²¹ Similarly, in the REDUCE-IT trial, that used purified eicosapentaenoic acid (EPA), a 10% reduction in ApoB levels was associated with 25% decrease in cardiovascular events.²² On the contrary, in

the STRENGTH study, which used a combination of EPA and docosahexaenoic acid (DHA), there was no significant reduction of ApoB or cardiovascular events observed, reinforcing the coherence of the association between ApoB decrease and cardiovascular risk decrease.²³

A meta-analysis that included 29 clinical studies, with a total of 332912 patients, evaluated whether a reduction of cardiovascular events associated to ApoB decrease depended on the type of drug used.²⁴ Although the magnitude in events reduction was greater in studies with statins, these trials had a weighed mean follow-up longer in comparison with those made with other treatments, such as with PCSK9 inhibitors. A comparative analysis between the FOURIER and the SPIRE studies, that used monoclonal antibodies inhibitors of PCSK9 and the meta-analysis of the CTT group (*Cholesterol Treatment Trialists' Collaboration*), which included the main trials with statins, concluded that a reduction in cardiovascular events, observed with PCSK9 inhibitors, was coherent with the expected reduction during the first two years of treatment with statins.²⁵

In brief, the evidence available is consistent in proving that, regardless of the drug used, ApoB reduction per se is associated with a significant decrease in the risk of future cardiovascular events. Although the results of clinical trials may vary according to the time of exposure to the treatment, the clinical context of patients and the characteristics of the population included, evidence backs robustly that ApoB reduction during treatment constitutes a central therapeutic goal, associated consistently with a decrease in the risk of cardiovascular events.

WHAT IS THE CORRELATION AND AGREEMENT BETWEEN APOB, NON-HDL-C AND LDL-C?

The concepts of agreement and correlation are widely used to assess the association between variables, but, although related, they represent different approaches.²⁶ Correlation focuses on the relationship between the changes observed in two variables; i.e., how one varies according to the other. Instead, agreement focuses on the degree of coincidence between the two measurement or classification methods of a single variable. Thus, while correlation measures association, agreement assesses the degree of agreement between results.

Numerous studies have analyzed the correlation and agreement between the different lipid markers. A study analyzed the lipid profiles of participants with no cardiovascular diseases, belonging to the UK Biobank (n=308182), the Women's Health Study (n=26204) and the Framingham Heart Study (n=2839).²⁷ The analysis showed a good correlation between the different lipid markers. In particular, the correlation between ApoB and LDL-C showed "r" values between 0.80 and 0.96, while the correlation between ApoB and non-HDL-C presented "r" values between 0.85 and 0.96.

It has been well established that there is a mismatch between LDL-C and non-HDL-C for a single value of ApoB.²⁸ A post-hoc analysis on the InPractice data, including pa-

tients with cardiovascular disease, treated with different lipid-lowering schemes, showed that agreement between ApoB and non-HDL-C ranges between 60.6% and 62.4%. Likewise, kappa analysis confirmed a moderate agreement between LDL-C and ApoB levels in all treatment groups, with values ranging between 0.54 and 0.59²⁹.

Data from the United Kingdom indicate that, in spite of the high correlations between ApoB and non-HDL-C (≥ 0.95) at population level (and a slightly lower correlation between ApoB and LDL-C), there is wide variability of ApoB for a given value of non-HDL-C or LDL-C.³⁰ Additionally, using population percentiles of LDL-C, non-HDL-C and ApoB in untreated adults in the National Health and Nutrition Examination Survey (NHANES) 2005-2016, for a non-HDL-C value of 100 mg/dl (approximately in percentile 10-20 of the population), the range of values of ApoB was 52 to 78 mg/dl (approximately from percentile 5 to 30).³⁰ Similarly, for a non-HDL-C value of 160 mg/dl (percentile 70-80), the values of ApoB were between 88 and 112 mg/dl (percentile 40-80). Similar findings were observed when comparing LDL-C with ApoB.

Agreement/mismatch can be defined in multiple ways: mismatch by cutoff points, mismatch by percentiles or mismatch by residuals.³¹ Regardless of the method, agreement and mismatch represent different proportions between parameters compared. Mismatch by cutoff points seems to be the most intuitive and clinically applicable method; the results of these analyses suggest that elevated levels of LDL-C, non-HDL-C or ApoB in individuals not treated with lipid-lowering medication entail a greater risk of cardiovascular disease. Instead, in people that do receive the treatment, elevated levels of non-HDL-C and ApoB seem to indicate residual risk better.

WHO DO APOB, NON-HDL-C AND LDL-C COMPARE AS CARDIOVASCULAR RISK MARKERS?

Although there is a high correlation between ApoB, LDL-C and non-HDL-C levels, different clinical situations may generate mismatches between these values and its predictive capacity for cardiovascular risk.^{30,31} In this scenario, it is important to take into account the following aspects: 1) while ApoB reflects the number of atherogenic particles, the measurement of LDL-C and non-HDL-C quantifies cholesterol mass; and 2) especially in a comparison with LDL-C, which is the main therapeutic goal to reduce cardiovascular risk, its measurement emerges often from the estimation by formulas that, as it is well known, are inaccurate. From a pathophysiological point of view, it could be proposed that if each particle containing ApoB would transport a constant amount of cholesterol, the different lipid markers (ApoB, LDL-C and non-HDL-C) would have a similar predictive value.^{32,33} However, current evidence suggests there is considerable variability in cholesterol content by the ApoB particle. This variability is determined, mainly, by lipid exchange processes between lipoproteins, which depend on multiple factors,

such as for instance, triglyceride concentration.^{34,35} As a result, conditions such as hypertriglyceridemia, obesity and resistance to insulin may generate discrepancies between these measurements, which is translated into an increase in the number of LDL particles (higher ApoB concentration), but with a reduced cholesterol content (lower concentration of LDL-C).³⁵

Different studies have analyzed the differential predictive capacity of these three markers. Considering different cohorts and points of analysis, evidence backs that ApoB concentration is more closely associated with the risk of atherosclerotic cardiovascular disease than LDL-C and non-HDL-C.^{32,36,37,38} However, patients treated with statins constitute a particular population, as these drugs reduce LDL-C preferentially, generating differences in relation to ApoB and non-HDL-C levels.

The results of the Copenhagen General Population Study, that included individuals treated with statins, reinforce this conclusion.³⁹ In cases of mismatch between ApoB and LDL-C figures, cardiovascular risk proved to be more consistently related with ApoB levels. Particularly, participants with ApoB levels above the median and LDL-C below the median presented a higher risk of all-cause mortality. In contrast, those with ApoB below the median and LDL-C above the median showed less risk of mortality. Similar results were observed when analyzing the mismatch between ApoB and non-HDL-C. According to the last Expert Consensus of the National Lipid Association (NLA), when there is mismatch between ApoB and LDL-C, between ApoB and non-HDL-C or between LDL-C and non-HDL-C, ApoB is considered the most reliable predictor for cardiovascular risk.⁴⁰

WHAT IS THE DIAGNOSTIC USEFULNESS OF APOB IN USUAL CLINICAL PRACTICE?

ApoB is an excellent biomarker to optimize cardiovascular risk stratification, particularly in patients with "normal" levels of LDL-C, but high cardiovascular risk.^{40,41} This measurement is particularly useful, as it allows evaluating the risk of cardiovascular disease more accurately in these patients. ApoB is equivalent to quantifying the number of atherogenic lipoproteins, as each particle contains a single ApoB molecule, contributing to a more accurate measurement of atherogenic risk.^{42,43}

Given that each LDL particle contains a specific amount of ApoB, in situations where LDL-C values are similar, but ApoB concentrations vary, LDL particle size and density could be different. This has direct implications on particle atherogenicity, which makes ApoB measurement particularly useful when LDL-C is low or "controlled", conditions where risk could be underestimated. Furthermore, in patients with multiple risk factors, such as hypertriglyceridemia, diabetes, abdominal obesity, resistance to insulin or metabolic syndrome, it is usual to find small and dense LDL particles, which are associated to a greater risk of premature or accelerated atherosclerosis.⁴⁴ For this reason, in

these patients, ApoB measurement provides additional and valuable information for cardiovascular risk stratification. Likewise, ApoB measurement is useful to differentiate between familial hypertriglyceridemia and combined familial hyperlipidemia, as in the former, the value of ApoB is normal, while in the latter it is elevated.^{45,46}

In brief, ApoB is a specific and useful indicator, acting as a supplementary tool for LDL-C measurement. Its measurement allows for a personalized evaluation of cardiovascular risk, associated to lipids and facilitates the establishment of more accurate therapeutic goals, optimizing the strategies to reduce atherosclerotic cardiovascular disease.

Situations where ApoB measurement is particularly useful:

a) Optimizing cardiovascular risk stratification, especially in patients in high or very high risk, presenting “normal” or “controlled” LDL-C figures, according to the established therapeutic targets. In such cases, the presence of elevated ApoB suggests a higher atherogenic residual risk, and it may justify the intensification of therapeutic measures.

b) Improving risk stratification in patients with hypertriglyceridemia, diabetes, obesity, resistance to insulin or metabolic syndrome, where LDL-C estimation by formula is not recommended, while the measured LDL-C value may mask the presence of small and dense particles.

WHAT IS THE IMPACT OF THE MAIN LIPID-LOWERING DRUGS ON APOB LEVELS?

Different lipid-lowering therapies have proven to be efficient in reducing ApoB, contributing to a decrease in cardiovascular risk.

Statins inhibit HMG-CoA reductase, reducing cholesterol synthesis and increasing LDL receptor expression. High-intensity statins can reduce ApoB levels between 30% and 50%.⁴⁷

Ezetimibe inhibits intestinal absorption of cholesterol through the NPC1L1 transporter. When associated with statins, it provides an additional reduction of approximately 20% in ApoB levels.⁴⁸

PCSK9 inhibitors (alirocumab and evolocumab) increase recycling of LDL receptors and facilitate the depuration of particles containing ApoB. These therapies achieve reductions in ApoB of between 45% and 55%.^{19,20}

Similarly, inclisiran, a small interfering RNA (siRNA), inhibits liver synthesis of PCSK9. It is administered twice a year and produces sustained reductions of ApoB of approximately 43%.⁴⁹

Bempedoic acid inhibits ATP citrate lyase, an enzyme acting before HMG-CoA reductase. Whether alone or in combination with ezetimibe, it reduces ApoB levels between 14% and 19%.⁵⁰

Evinacumab is a monoclonal antibody inhibiting ANGPTL3, promoting lipolysis and depuration of lipoproteins containing ApoB. In patients with homozygous familial hypercholesterolemia (HoFH), an average reduction of 40.8% has been observed in ApoB levels.⁵¹ On the other hand, lo-

mitapide, an MTTP inhibitor, prevents the assembly of lipoproteins containing ApoB, achieving reductions of between 29 and 56%.⁵²

Finally, obicetrapib, an oral, selective, new-generation inhibitor of the cholesteryl ester transfer protein (CETP), known for its significant effect on atherogenic lipoproteins beyond increasing HDL-C levels, has been shown to reduce ApoB levels by 26.5% in comparison with placebo, according to a recent meta-analysis.⁵³

A summary of the impact of the different drugs on ApoB levels is presented in [Table 1](#).

WHAT ARE THE CURRENT APOB TARGETS?

One of the first recommendations in favor of using ApoB in the United States (2009) came from the American Association of Clinical Chemists, that backed ApoB measurement as a useful tool for the evaluation and follow-up of patients in risk of cardiovascular disease.⁵⁴

Canadian and European guidelines have recommended ApoB measurement in specific populations for several years now. Since 2012, the Canadian Cardiovascular Society (CCS) guideline for the diagnosis and treatment of dyslipidemia acknowledges using ApoB measurement in people with elevated levels of triglycerides, defined as >1.5 mmol/L (131 mg/dl).⁵⁵ Likewise, since 2026, the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) have recommended considering ApoB measurement, when available, in patients with hypertriglyceridemia.⁵⁶

The 2018 multi-society guideline from the American Heart Association (AHA) and the American College of Cardiology (ACC), prepared in collaboration with different leading medical organizations, established that people with triglycerides levels ≥ 200 mg/dl have a “relative indication” for ApoB measurement.⁵⁷ Additionally, the guideline indicates that an ApoB level >130 mg/dl should be considered a “risk enhancing factor” at the time of evaluating the need to start lipid-lowering therapy. However, performing universal tests for ApoB is not advised in the general population.

In 2019, ESC and EAS recommended the measurement of ApoB as an alternative for LDL-C measurement, and even, possibly, being preferred in comparison with non-HDL-C, as main marker for detection, diagnosis and treatment in individuals with elevated triglycerides, diabetes, obesity, metabolic syndrome or very low levels of LDL-C.⁵⁸ The same guideline pointed out that LDL-C levels can underestimate the risk of atherosclerotic cardiovascular disease, by not reflecting accurately the total concentration of cholesterol transported by LDL, or the total number of lipoproteins containing ApoB. On the other hand, the document defined secondary lipid targets for ApoB of <65 mg/dl, <80 mg/dl and <100 mg/dl in patients in very high, high and moderately high risk, respectively. These correspond to LDL-C targets of <55 mg/dl, <70 mg/dl and <100 mg/dl.

The 2020 guideline from the American Association of Clinical Endocrinologists (AACE) and the American Colle-

TABLE 1.

Impact of the main lipid-lowering drugs on apolipoprotein B levels.

Drug	Percentage reduction	Mechanism of action
High intensity statins	↓ 30–50%	They inhibit HMG-CoA reductase, reducing liver synthesis of ApoB by reducing production of VLDL-C. Moreover, the decrease in liver cholesterol stimulates an increase in liver uptake of LDL particles (containing ApoB) from circulation. ApoB reduction is proportional to the power of the statin used.
Ezetimibe	↓ 20%	It inhibits intestinal absorption of cholesterol (inhibiting the NPC1L1 protein) and, when associated with statins, it exerts a synergic effect on reduction of production of particles containing ApoB.
PCSK9 inhibitors (evolocumab, alirocumab)	↓ 45–55%	Monoclonal antibodies that inhibit PCSK9 in extracellular space. They increase recycling of LDL receptors and facilitate depuration of particles containing ApoB.
Bempedoic acid	↓ 14–19%	It inhibits the ATP citrate lyase, which participates in an early state of the production pathway of cholesterol in liver, just before action by the HMG-CoA reductase (target of statins). It reduces liver synthesis of ApoB by reducing production of VLDL-C. Also, the decrease in liver cholesterol stimulates an increase in liver uptake of LDL particles (containing ApoB) from circulation.
Inclisiran	↓ 43%	Small interfering RNA. It inhibits liver synthesis of PCSK9. It increases recycling of LDL receptors and facilitates depuration of particles containing ApoB.
Evinacumab	↓ 40.8%	It inhibits ANGPTL3, an inhibitor of LPL and EL. It promotes lipolysis and depuration of lipoproteins containing ApoB.
Lomitapide	↓ 29-56%	It inhibits MTTP, preventing assembly of lipoproteins containing ApoB.
Obicetrapib	↓ 26.5%	Oral, selective and new-generation inhibitor of CETP. By interfering in the exchange of cholesterol esters from HDL to LDL and VLDL for triglycerides, it modulates the composition and metabolism of these lipoproteins, decreasing ApoB levels indirectly.

ANGPTL3: angiopoietin-like 3; **ApoB**: apolipoprotein B; **CETP**: cholesteryl ester transfer protein; **HMG-CoA**: 3-hydroxy-3-methylglutaryl coenzyme A; **EL**: endothelial lipase; **LPL**: lipoprotein lipase; **MTTP**: microsomal triglyceride transfer protein; **NPC1L1**: Niemann-Pick C1-like 1.

ge of Endocrinology (ACE) emphasized that ApoB measurement can offer a more accurate evaluation for atherogenicity.⁵⁹ The guideline also acknowledged the value of ApoB in the evaluation of lipid-lowering treatment efficacy, as ApoB levels may remain above the target, even after reaching the target values for LDL-C.

In its most recent 2021 guideline, the CCS recommended using ApoB or non-HDL-C instead of LDL-C as preferred lipid measurement for the screening of patients with triglycerides >1.5 mmol/l (133 mg/dl).⁶⁰ The CCS also suggested a threshold of ApoB ≥70 mg/dl as criterion to intensify lipid-lowering treatment in patients with established atherosclerotic cardiovascular disease. The recent scientific statement by the NLA backed measuring ApoB as a reasonable strategy, not just for initial lipid evaluation, but also in patients that are under lipid-lowering treatment.⁴⁰ According to this document, the thresholds to start or intensify pharmacotherapy for ApoB levels are not as properly established as for LDL-C and non-HDL-C levels. Nevertheless, on the basis of population studies and controlled randomized trials on individuals treated with lipid-lowering drugs, it is suggested that ApoB thresholds for patients with very high, high or intermediate cardiovascular risk are 60, 70 and 90 mg/dl, respectively, to correspond with the current treatment thresholds for LDL-C and non-HDL-C.

A study made in Argentina proved that, in a healthy population, percentile 20 of ApoB was 72 mg/dl.⁶¹ It is rele-

vant to point out that this figure is found among the ApoB targets recommended by the ESC/EAS and NLA guidelines for people with high cardiovascular risk. Furthermore, percentile 10 was less than 60 mg/dl, a level that coincides with the lipid targets given by the same recommendations for a population in very high risk. In contrast, an ApoB value of more than 117 mg/dl was observed in 20% of individuals with a greater concentration of atherogenic particles, which may indicate a threshold of greater vascular risk, even in apparently healthy people.⁶¹

WHAT SHOULD WE KNOW ABOUT HYPOBETALIPOPROTEINEMIA?

Familial hypobetalipoproteinemia (FHBL) is characterized by reduced plasma concentration of LDL-C below percentile 5 for gender and age.⁶² More frequently, the monogenic form in adults results from heterozygote variants of loss of function in ApoB, and less frequently in PCSK9, leading to dominant autosomal disorder. The mutations in the ApoB gene lead to production of truncated ApoB proteins (both of ApoB100 and ApoB48), affecting the liver capacity to export lipoproteins, leading to an accumulation of triglycerides in hepatocytes, increasing the risk of developing liver diseases.⁶³ The ApoB48 mutation affects lipid absorption from the intestine, leading to malabsorption of fat and fat-soluble vitamins, and is associated with gastrointestinal, neuromuscular, ophthalmological and hema-

tological complications. The homozygous or compound heterozygous form (HoFHBL1) is rare, and may cause severe complications and phenotypical manifestations similar to abetalipoproteinemia (ABL), an autosomal recessive disorder caused by mutations in the microsomal transfer protein (MTTP). The heterozygous form (HeFHBL1) is relatively common and, in general, asymptomatic, except for moderate hypolipidemia and a tendency to fatty liver disease.⁶²

In a recent study about FHBL, more than 140 variants of the APOB gene were identified.⁶² The frequency of truncated ApoB in the general population is 1:3000 (HeFHBL1); while the homozygous form or compound heterozygous (HoFHBL1) has an estimated incidence of less than 1:1,000,000. FHBL can also be caused by mutations in the angiopoietin-like protein 3 gene (ANGPTL3), being called FHBL2 in the latter case.

HeFHBL1 is usually asymptomatic, except for low levels of LDL-C and ApoB, which reach approximately one third of normal levels. Patients may present moderate liver dysfunction, and 5-10% develop severe fatty liver disease, with possible complications like cirrhosis and liver cancer. Some rare cases present neurological complications, possibly due to vitamins E and A deficiency. On the contrary, patients with HoFHBL1 have severe clinical forms and present phenotypical characteristics similar to ABL. Among them, we find neuromuscular disorders (due to vitamin E deficit), ophthalmological disorders (due to vitamin A deficit), gastrointestinal disorders (steatorrhea, deficit in growth due to malabsorption syndrome, fatty liver disease that rarely progresses into cirrhosis and hepatocellular carcinoma), anomalies in bone metabolism (due to vitamin D deficit) and hematological anomalies (acanthocytosis in 50% of the erythrocyte population). Severe cases are diagnosed in early childhood, while moderate cases are usually diagnosed in adults during general medical checkups, due to hypolipidemia.⁶²

The diagnosis of FHBL1 is based on the identification of genetic mutations, extremely low levels of LDL-C and ApoB (less than 15 mg/dl) and the presence of clinical symptoms. Differential diagnoses should be considered, such as hypobetalipoproteinemia, secondary to chronic or terminal diseases like cancer, liver disease, hyperthyroidism, malabsorption of fats due to chronic pancreatitis and malnutrition.⁶²

Recently, polygenic forms have been described of hypobetalipoproteinemia associated with a lower risk of liver lesions and fatty liver disease, in comparison with monogenic forms, which are diagnosed by polygenic risk score and are more prevalent in the general population than previously described monogenic mutations.⁶⁴

There is no specific treatment for FHBL. This is focused on supplementation with high doses of fat-soluble vitamins and essential fatty acids, with the aim of preventing or delaying complications. Furthermore, it is important to guarantee an appropriate caloric ingestion and to restrict the ingestion of fats to prevent delays in growth.

Finally, these low cholesterol syndromes have been associated to less risk of developing cardiovascular diseases, which has opened the door to new therapeutic strategies. One example is mipomersen, an antisense oligonucleotide (ASO), which inhibits the production of ApoB100 and is used in patients with HFHo. Another relevant treatment is lomitapide, which inhibits MTTP production and is used both in the treatment of HFHo and in familial chylomicronemia syndrome (FCS).⁶⁵

CONCLUSIONS

ApoB has consolidated as a key lipid marker in the management of dyslipidemic patients, contributing diagnostic and prognostic information with great clinical value. By reflecting directly the number of circulating atherogenic particles, its quantification allows estimating the total atherogenic potential with greater accuracy. This is evident in the excellent correlation between ApoB and LDL-C, although with a moderate agreement between both parameters. Different epidemiological and genetic pieces of evidence, and those coming from clinical studies back its prognostic value in prevention of atherosclerotic cardiovascular disease. Likewise, there are efficient pharmacological tools to reduce its levels. A routine addition of ApoB in the evaluation of cardiovascular risk could optimize stratification and therapeutic approach, particularly in scenarios where LDL-C concentrations may underestimate residual risk. In this context, the acknowledgement and use of ApoB as an emerging therapeutic goal may contribute to decreasing the overall load of cardiovascular disease in a more effective manner.

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Position Statement

Practice guidelines of vascular Doppler Echo 2022 of the Argentine Federation of Cardiology. FAC Peripheral Vascular Disease and Stroke Committee. Upgrade 2025 focalized on atherosclerotic plaque and dolichoarteriopathies.

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Vascular Doppler,
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ABSTRACT

Vascular Doppler ultrasound is now considered worldwide as the first-line non-invasive technique for evaluating all vascular territories of the body, with the advantages of extremely high sensitivity and specificity, as well as positive and negative predictive values. Currently, vascular ultrasound is a subspecialty of significant importance due to its contribution to clinical practice in diagnosis, decision-making, and therapeutic guidance.

This update aims to expand the characterization of atherosclerotic plaques and include the evaluation of a quite common finding: tortuosity, kinking, and coiling.

INTRODUCTION

Doppler vascular ultrasound is now considered the first choice noninvasive technique throughout the world, for the evaluation of all vascular territories of the body, with the advantages of being highly sensitive and specific, as well as its positive and negative predictive values. Currently, vascular echography is a very important subspecialty due to its contribution to clinics for diagnosis, decision-making and therapeutic guidance.

It is operator-dependent. Being an "observer of flow and image" is key for a good vascular echography specialist, because flows and images "speak", and provide invaluable information that enables a great diagnostic approach.

To study all vascular territories there are other excellent techniques, such as multislice CT, magnetic resonance angiography, PET scan, capillaroscopy, conventional angiography, etc. The Committee on Peripheral Vascular Diseases and Strokes of FAC presents this update of the Practical Guideline for Doppler Vascular Echocardiograms, published in 2022, to turn it into another tool for cardiologists that have been or are being trained in this exciting and constantly evolving subspecialty, offering practical considerations on the principles and practice of vascular echocardiography. It was centered on the characterization of carotid plaque and dolichoarteriopathies.

Dr. Adrián H. D'Ovidio

CHARACTERIZATION OF CAROTID PLAQUES

This update is addressed to enhancing the characterization of atherosclerotic plaques and adding the evaluation of a very frequent finding such as tortuosities, kinks and coils. The rest of what is written in the 2022 guidelines has not changed, so we suggest to keep taking them into account always.

By making a study on Doppler Echocardiogram of Neck Vessels, it has been suggested already in the guidelines published by the Committee on Peripheral Vascular Diseases and Stroke, and also published in the Journal of the Sociedad de Imágenes (*Imaging Society*) of the Sociedad Interamericana de Cardiología (*Inter-American Society of Cardiology*), to use five steps to organize the evaluation of patients who undergo the study and to prevent key omissions.^{1,2}

The 5 steps are:

1. Presence and number
2. Location and extension
3. Characterization
4. Hemodynamic significance
5. Conclusions.

The first approach is through direct view with 2-dimensional images. Intima-media is characterized by a double

line with defined intima-lumen and media-adventitia interfaces. EIM is the distance between two acoustic interfaces. Atheromatous carotid plaque (CP) is defined as a focal structure extending at least 0.5 mm toward arterial lumen and/or measuring more than 50% of the surrounding EIM and/or presenting an EIM > 1.5 mm.^{3,4,5,6,7,8,9,10,11}

To characterize an atherosclerotic plaque, several classifications have been described and used over the years, based on the different characteristics of plaques.

Characterizing is knowing clearly which are the characteristics of atherosclerotic plaques that make them more or less dangerous, with risk of stroke, and also being able to evaluate its evolution over time.

As a fundamental concept, we should always take into account that atherosclerotic plaques are a “living” element, not an accumulation of fat that developed within a vessel, but a richly vascularized structure, that changes significantly over time, that can become more stable or unstable with the presence or absence of optimal medical treatment (lifestyle and medications).

CHARACTERIZATION

- **Echogenicity:** defined comparing the plaque's echogenicity with those of adjacent structures (blood, muscle, vessel adventitia and bone), and classified into:
 - *Hyperechoic or echolucent:* darker, that is to say, of echogenicity similar to blood and less echogenic than the sternocleidomastoid muscle. Intraplaque echolucent areas correspond mainly to bleeding by neovascularization; the latter is the key culprit for plaque instability.
 - *Isoechoic:* echogenicity close to that of the muscle.
 - *Hyperechoic:* lighter than adjacent muscle.
 - *Calcified:* very echogenic, creating acoustic shadow due to calcium deposits. Echogenicity is comparable to that of bone.
- **Echotexture:** plaque texture is classified into homogeneous or heterogeneous.
 - *Homogeneous:* uniform in low and high echoic levels.
 - *Heterogeneous:* a mixture of high, medium and low echoic levels.
- **Surface:** it is classified into three classes, taking into account the surface toward the vessel lumen into:
 - *Smooth:* irregularities of less than 0.4 mm of depth.
 - *Irregular:* from 0.4 to 2 mm of depth.
 - *Ulcerated:* crater greater than 2 mm of depth and 2 mm of width.
- Area, volume, length and height of plaque.
- Evidence of embolic activity.
- Changes in plaque appearance over time.
- Plaque mobility.
- Color flow and pulsed-wave Doppler (laminar, turbulent, normal and pathological wave morphology).

It is known that the mechanisms by which an atherosclerotic plaque is more “dangerous” in relation to plaque instability are its size (plaque height greater or lesser than 3 mm and plaque area greater or lesser than 0.39 cm²), its vol-

ume, the presence of large lipid core, thin fibrous layer (less than 200 μ m), the presence of neovascularization, related to intraplaque bleeding, the presence of ruptures, ulcerations, thrombosis, etc.

All these characteristics entail the key concept of “plaque vulnerability”, that is related to its characterization and not with hemodynamic significance.

The known mechanisms generating carotid plaque instability are:

- Inflammation
- Oxidative stress
- Endothelial dysfunction
- Intraplaque bleeding (related to neovascularization)
- Lipid metabolism
- Vascular remodeling
- Calcification
- Plaque rupture and ulceration.

The fibrous layer, the thinner it is, the more chances it presents to undergo erosions or just break, generating brain embolisms, ulcerations or plaque thrombosis. It is interesting to take into account that plaques in coronary arteries suffer erosions of its capsule more frequently than carotid arteries. The point of greatest danger of rupture is around 65 μ m, while in the carotid plaques, the point of greatest rupture danger is around 200 μ m. This is related to differences in flow velocity and shear stress, which are much greater in the carotid arteries in regard to coronary arteries. Noninvasive image modalities (ultrasound, CT, MRI) and intravascular techniques (intravascular ultrasound, optical coherence tomography and near-infrared spectroscopy) have played an essential role in characterization and detection of unstable carotid plaques. Structural phenotypes

TABLE 1.
Classical classification (Grey-Weale)⁶

Type	Description
1	Predominantly echolucent with thin fibrous layer
2	Substantially echolucent plaque with small areas of increased echogenicity
3	Predominantly echolucent plaque, with one or more echolucent areas (<25%)
4	Uniformly echogenic

TABLE 2.
European consensus 1997

Type	Description
1	Uniformly echolucent, no need for an echogenic cap to be present
2	Predominantly echolucent and <50% of echogenic material
3	Predominantly echogenic plaque, and <50% of echolucent material
4	Uniformly echogenic
5	Not classifiable (extensive calcification)

TABLE 3.
Classifications of Stary et al. 1995¹⁴ and Cai et al. 2002¹⁵

Conventional classification (Stary et al. 1995) ¹⁴		AHA MRI (Cai et al. 2002) ¹⁵	
Type I	Initial lesion with foam cells	Type I-II	Almost normal myointimal thickness, with no calcification
Type II	Fatty streak	Type III	Diffuse myointimal thickening or small eccentric plaque with no calcification
Type III	Preatheroma (intermediate lesion) with extracellular lipid pool	Type IV-V	Plaque with necrotic lipid core, atheroma with echolucent lipid core, surrounded by fibrous tissue, with possible calcification
Type IV	Atheroma with echolucent lipid core	Type VI	Complex plaque with possible surface defect, with bleeding or thrombus
Type V	Fibroatheroma	Type VII	Calcified plaque
Type VI	Complicated plaque (possible surface lesion, hemorrhage or thrombus)	Type VIII	Fibrotic plaque with no lipid core, with possible small calcifications
Type VII	Calcified plaque		
Type VIII	Fibrotic plaque with no lipid core		

TABLE 4.
Classification of Johry et al.

Grade 0: absence of plaques, myointimal thickness <1.5 mm
Grade I: protruding (focal thickening of vessel wall, myointimal thickness <1.5 mm
Grade II: protruding or diffuse (increased myointimal thickness ≥1.5 mm), plaque thickness 1.5 to 2.4 mm.
Grade III: protruding or diffuse (≥2.5 mm)

TABLE 5.
Plaque-RADS classification (Saba et al. 2024)⁶

RADS-Score 1	Absence of plaques. Normal study.
RADS-Score 2 Plaque height ≤ 3 mm	Myointimal thickening Necrotic core, rich in lipids Calcifications
RADS-Score 3a Plaque height ≥ 3 mm	Thick fibrous layer + necrotic core, rich in lipids
RADS-Score 3b Plaque height ≥ 3 mm	Thin fibrous layer + necrotic core, rich in lipids
RADS-Score 3c Plaque height ≥ 3 mm	Ulcerated plaque
RADS-Score 4a	Intraplaque bleeding
RADS-Score 4b	Plaque rupture
RADS-Score 4c	Endoluminal thrombosis
Complementary characteristics	Calcifications Neovascularization Inflammation Positive remodeling Plaque load Stenosis progression
Modifiers	Calcifications Stents Endarterectomy

of carotid plaque, including its location and amount, affect plaque biomechanics, contributing to the risk of rupture.^{13,14,15,16,17}

Here, we should remember that when we discuss hemodynamic significance, it means the capacity of vessel diameter reduction that this plaque generates to reduce tissue perfusion, being applied to any territory of the organism, and in the specific case of carotid and vertebral plaques, the risk of ischemic stroke.^{1,12,13}

“All hemodynamically significant plaques are vulnerable, but not all vulnerable plaques are hemodynamically significant.”¹

Within classifications, we have classical ones, like the one by Gray et al., about echogenicity of plaques, graded from I through IV, with hypoechoic plaques being the most dangerous and related to stroke.

There are different forms described in literature to classify carotid plaques based on plaque echogenicity, its homogeneity, myointimal thickness, and whether they protrude or not: Gray-Whale’s classification ([Table 1](#)), the description of atherosclerotic plaques according to European consensus ([Table 2](#)), and the AHA classification ([Table 3](#)).^{6,9,14,15}

Later, within the framework of the Guidelines of the American Society of Echocardiography (ASE), Johry et al. started highlighting the height of the plaque (more or less than 2.5 mm of height) and its rupture, significantly contributing, along with classical classifications, to identify plaques with greater potential for rupture or embolization (plaque vulnerability) ([Table 4](#)).¹⁶

In February 2024, Saba et al. published the RADS-Score classification for atherosclerotic plaques, based on echocardiography tests, MRI and anatomical pathology, which is very important to know, and that his Committee strongly recommends for use, making a position statement, as it is practical and validated. It does not invalidate, naturally, those previously described, which remain useful, but they are included in this new classification ([Table 5](#)) ([Figures 1 through 9](#)).¹⁸

The risk of stroke of type 3 plaques is moderate. The risk of stroke of type 4 plaques of the RADS classification is high.

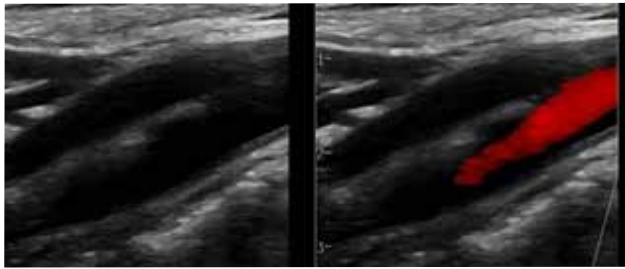


FIGURE 1.
Rads-Score 1, normal study. Absence of atherosclerotic plaques

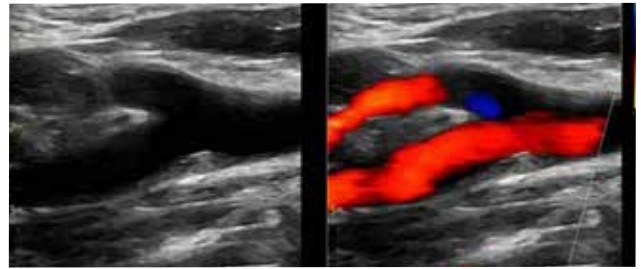


FIGURE 2.
Rads-score 2, myointimal thickening, necrotic core, rich in lipids, calcification

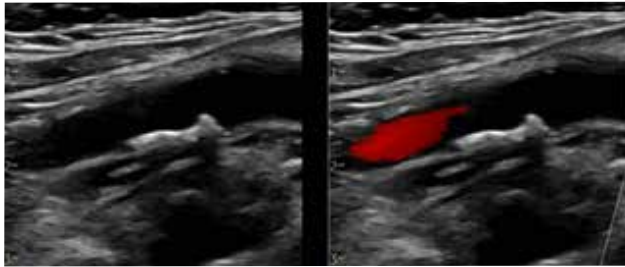


FIGURE 3.
Rads-score 2, myointimal thickening, necrotic core, rich in lipids, calcification

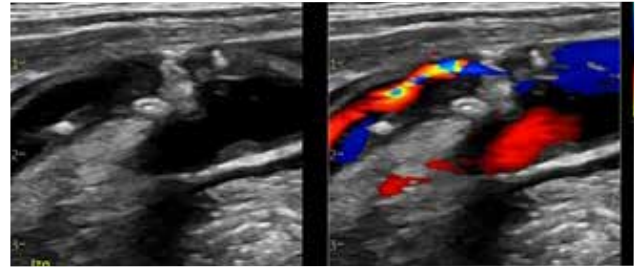


FIGURE 4.
Rads-score 3a (plaque height ≥ 3 mm). Thick fibrous layer + necrotic core, rich in lipids

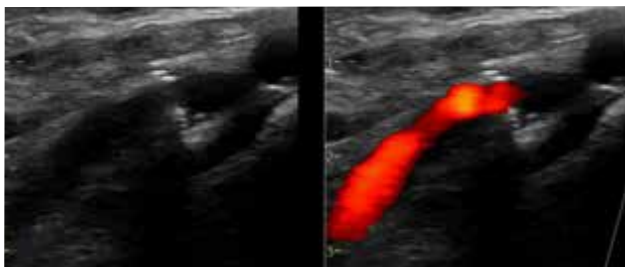


FIGURE 5.
Rads-score 3b (plaque height ≥ 3 mm). Thin fibrous layer + necrotic core, rich in lipids

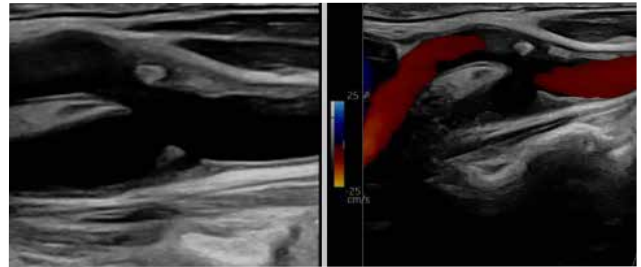


FIGURE 6.
Rads-score 3c (plaque height ≥ 3 mm), ulcerated plaque

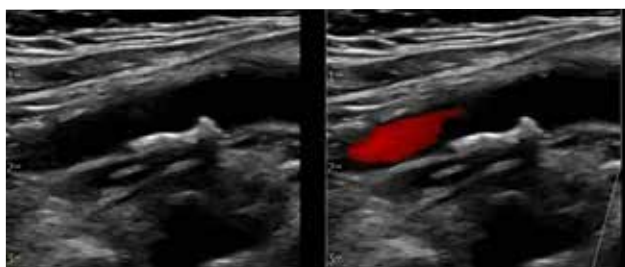


FIGURE 7.
Rads-score 4a, regardless of height. Intraplaque bleeding

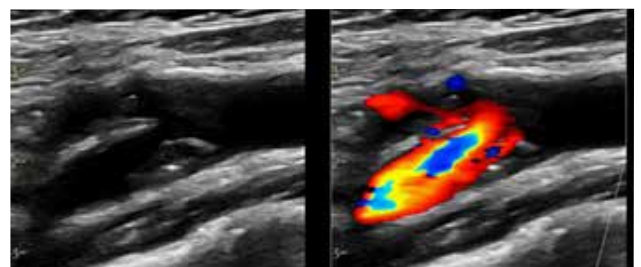


FIGURE 8.
Rads-score 4b, regardless of height. Ruptured fibrous layer

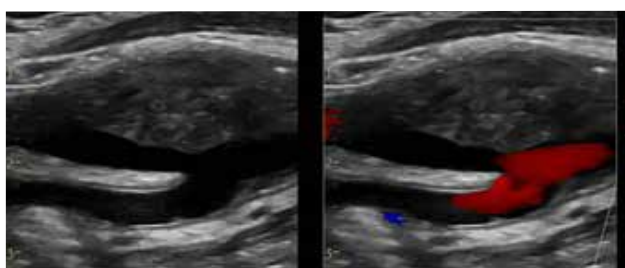


FIGURE 9.
Rads-score 4c, regardless of height. Endoluminal thrombosis

TABLE 6.
Classification of Togay

Tortuosity	Elongation or undulation in S or C in ICA trajectory
Mild kinking	ICA kinking with angle $\geq 60^\circ$
Moderate kinking	ICA kinking with angle $30\text{--}60^\circ$
Severe kinking	ICA kinking with angle $< 30^\circ$
Coiling	Elongation or redundancy of ICA, leading to circular configuration (360°).

This classification has (and this should be included in reports) supplementary characteristics (*Figures 10 through 12*):

- Calcifications
- Neovascularization
- Inflammation
- Positive remodeling
- Plaque load
- Stenosis progression
- “Limited” diagnostic study
- Stents
- Endarterectomy.

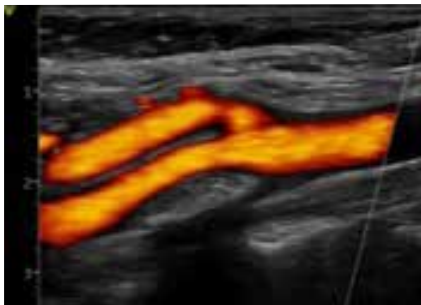


FIGURE 10.
Calcifications

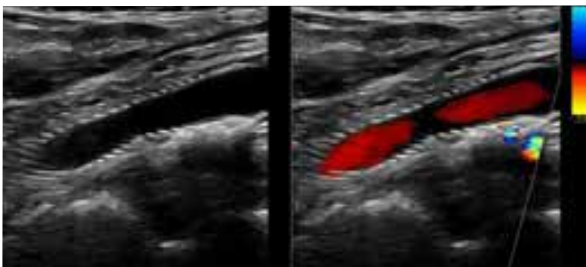


FIGURE 11.
Stent

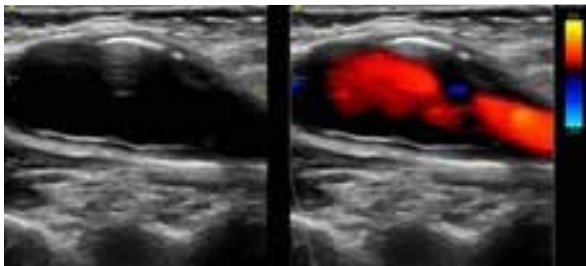


FIGURE 12.
Endarterectomy

This last classification is practical, guiding, it includes the other classifications and gives them value again, it is validated and it allows, with an adequate characterization of plaques, to detect those that present greater risk of stroke for patients. It is a therapy guide, with prognostic value, and for follow-up.^{18,19,20}

CONCLUSIONS

This update of our Guidelines of Practice for Doppler Vascular Echocardiography of the Argentine Federation of Cardiology, focused on the characterization of the carotid plaque, were motivated by the publication of the new Plaque-RADS classification, comprehending all previous classification, and it is practical for daily use, it has a message, it estimates the vulnerability of the plaque, and it allows for a uniform language, it is validated, so a routine use is suggested.

CAROTID DOLICHOARTERIOPATHIES

Introduction

The morphological variations in the trajectory and geometry of carotid vessels are called dolichoarteriopathies (DAP). In literature, there are different synonyms to describe tortuosities, kinks and coilings, such as elongations, undulations, loops, spirals or winding.

The cervical portion of the internal carotid artery has two fixation points, specifically in its bifurcation and at the base of the skull (fibrous ring of the temporal bone). The dolichoarteriopathies of the internal carotid artery may occur if the vessel size is larger than the distance between these two points.²¹

This entity was initially described in the 18th century, in autopsy specimens, until it was related to bleeding complications during otorhinolaryngological surgeries, and in the mid-20th century, it was related to cerebral ischemic events. Since then, the knowledge on this pathology has enhanced, and it has been found to be not rare, but in most cases to be asymptomatic.²²

The common carotid artery (CCA) and the initial portion of the internal carotid artery (ICA) emerge from the third aortic arch. The distal portion of the ICA emerges from the cranial portion of the left dorsal aorta, and these structures make up a “loop”. All these process occur in the embryonic pharynx. In the fifth month of intrauterine life, the carotid arteries are normally bended, and when the fetal neck takes shape, the heart descends into the mediastinum,

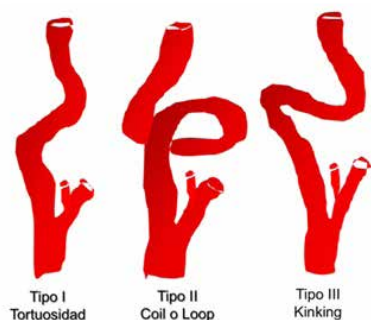


FIGURE 13.
Classification of Weibels and Fields

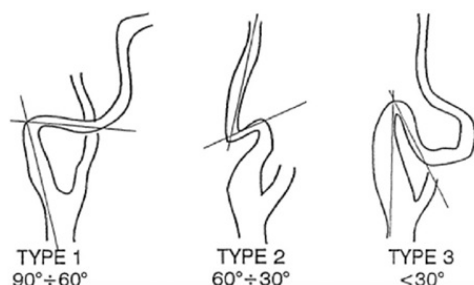


FIGURE 15.
Metz classification

and the supra-aortic vascular structures stretch and become straight. The alterations in cardiac descent or vascular elongation would explain the origin of dolichoarteriopathies (persistence of embryonic anatomy). The proximal portion of the internal carotid artery is drawn from the third aortic arch, and the rest of the artery, from the left dorsal aorta.²³

The prevalence of the general population is 1.3%, in patients with history of TIA it is 20%, and in the patients with arteriographies made due to severe neurological symptoms, the finding of carotid anomalies ranges between 4 and 58%, according to other authors, and up to 30% of cases with Doppler echocardiogram.^{24,25,26}

DAPs are more prevalent in women and elderly patients, particularly in those older than 60 years, and could be both uni and bilateral, affecting the common carotid (CCA), internal (ICA) and external carotid arteries (ECA), but most frequently ICA, particularly from the left side.^{27,28} Tortuosities and kinks are more frequent than coiling, and the most affected artery is the ICA, then the CCA, the ECA, and finally the vertebral one.

CLASSIFICATION

Weibel and Fields (Figure 13)²⁹

Type 1: tortuosity: it is defined as non-rectilinear trajectory of an artery with angles of more than 90°.

Type 2: loop: angulation of an artery in 360° over its transversal axis (circular configuration).

Type 3: kinking: by definition, it is the inflection of two or more segments of one artery with internal angle equal or less than 90° (Figure 14).

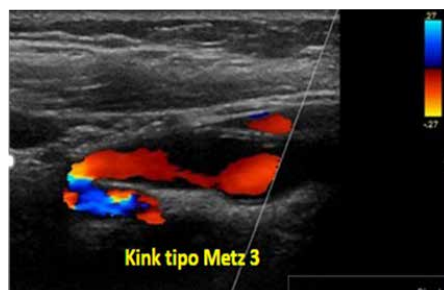


FIGURE 14.
Kink of the Metz 3 type

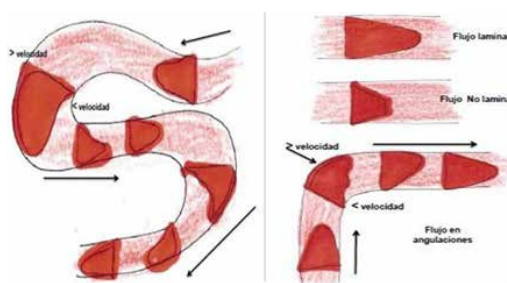


FIGURE 16.
Kink hemodynamics

Metz et al. classified kinking into three grades of severity, depending on the vessel angulation over its axis: grade 1, curvature over its axis between 90° and 60°; grade 2, between 60° and 30°; and grade 3, less than 30° (Figure 15).³⁰

In year 2025, Togay et al. published a classification with the modified criteria proposed by Weibel-Felds and Metz, based on exploration by Duplex color ultrasound (Table 7).³¹

ETIOLOGY

Embryology theory

It is based on these anatomical anomalies being observed by different methods of diagnosis in fetuses, children and teenagers.^{31,32,33,34} Due to persistence of the embryological status of ICA (with kink since intrauterine life) by failed absorption in the third aortic arch, or due to asynchronous development of the carotid arteries and the skeletal system in the process of growth, the arteries would adopt a winding trajectory.^{23,24} In a study made in Argentina with tests made with Doppler echocardiogram, almost the same prevalence of DAP was observed in children and adults.²⁶

Acquired DAP theory

In relation to his, hypertension would produce alterations in the wall, favoring its weakening, with the subsequent kinking of the artery, while other authors proposed the importance of the relationship between arterial ageing and degenerative alterations in artery walls, as elasticity loss along with action by hemodynamic forces would lead to an increase in preexisting elongation or angulation.^{35,36,37,38,39} Also, an association between atheromatosis

and carotid kinks has been described, or with anatomopathological patterns with arterial media thickening by cystic necrosis or hyperplasia, elastic fragmentation and fibrosis; in some cases with histological characteristics of classical abdominal aortic aneurysm (AAA) (thinning of tunica media underlying the atherosclerotic plaque), suggesting a common base of connective tissue alterations underlying both pathologies.^{40,41}

There is a hypothesis that tissue inflammation of aponeurosis in the area surrounding the carotid artery would produce artery retraction.⁴² Others claim that DAP could be due to kyphosis and lordosis that would deviate the carotid axis.²⁴ La Barbera proposed a hypothesis by which extracranial ICA is considered a segment of transition between an elastic vessel (CCA) and a muscular one (intracranial ICA), so the elastic and muscular tissues of the ICA in patients with DAP is substituted by lax connective tissue, configuring a metaplasia of the tunica media.⁴³

Although still controversial, most authors propose that the main cause is the acquired one, associated with atherosclerosis, an advanced age and hypertension.

The pathophysiology of DAP is controversial, and the association with traditional risk factors is not clear, since although correlated, they do not depend on the latter.⁴⁴

In general, it is considered a multifactorial disease, with a genetic predisposition, associated to cardiovascular risk factors, causing arterial wall thickening and significant hemodynamic disorder, which may change blood flow within a vessel and entail an infrequent cause for stroke.⁴⁵

Kinking is a very important cause, as it is not rare, and along with dissections, it represents the most likely cause for cryptogenic stroke.^{46,47}

PATHOPHYSIOLOGY

Hemodynamics of kinks

Tortuous vessels can have an effect over velocities.

A flow that runs through a non-rectilinear circuit, such as in DAP, experiences both centrifugal and viscous forces on the vessel walls, and the result of these forces is a secondary flow in the shape of 2 helicoid vortices (turbulence).

In the case of parabolic flow, the flow in the center of the vessel experiences the highest velocity, and thus develops the greatest strength. These vortices will cause the high-velocity flow to move toward the far wall of the vessel. If the velocities in curvatures exceed 170 cm/sec, we should think that besides the curvature and its turbulence, the presence of significant atheroma could be suspected (*Figure 16*).

Atherosclerotic/thrombotic mechanism

There would be an atherosclerotic or thromboembolic mechanism, as endothelial lesions have been described, mainly microulcerations secondary to flow alterations in the curvature sites, as well as the concomitant presence of atheroma plaque with formation of platelet thrombi and distal embolization. The last point is crucial in the prognosis and management of DAP.⁴⁸ HTN and age would play

a key role with an increase of endoluminal pressure and parietal pressure.

Hemodynamic mechanism

The other pathophysiological mechanism proposed is the hemodynamic one, by which there is an inverse relationship between the kink angle and flow reduction; the more acute, the more severe.

When the kink is very marked (internal angle <90°), neurological ischemic symptoms may occur if there is blood flow reduction because of kink.

It may be triggered with changes in the head and neck, by what is called dynamic obstruction. For example, in supine position or when getting up from bed, and even it has been proven arteriographically and with oculoplethysmography, that rotation maneuvers in the neck could reduce carotid flow.

The hemodynamic mechanism becomes more important the greater the kink. There are experimental studies showing that blood flow can be reduced to less than 40% with 60° kink in ICA, and 60% with 30° kink. The tests made in patients showed a marked increase in pressure drop when the torsion angle was less than 30°. The marked kink induced an average decrease of 15.5% in blood pressure.⁴⁹

Diagnosis and clinical implications

Most DAPs are asymptomatic, but they could be suspected by auscultation of carotid murmurs or the presence of hyperpulsatility in the neck, palpable masses, dysphagia, dysphonia or feeling of cervical foreign element.

DAPs may cause hypoperfusion or cerebral ischemia with hemispheric syndromes (TIA, stroke, amaurosis) leading to encephalopathy, vertigo, diplopia, TIA and infarction.⁴⁸ The prevalence of cerebrovascular symptoms in patients with DAP ranges between 15 and 23%.⁵⁰ They can be exacerbated with movements of the head or neck turning or stretching. Reproduction or demonstration with Doppler echocardiogram of neck vessels, transcranial Doppler ultrasound or angiography is a clear indication of surgery.

The addition of risk factors to the presence of DAP may increase the risk of vascular events.³⁸ Iwai-Takano et al. observed an association between DAP and ageing, HTN and gender, but not with dyslipidemia, diabetes or smoking.⁵¹

Its clinical course seems to be benign, but on occasions is associated to cerebral ischemic phenomena, in isolation or when associated to atherosclerotic lesions of carotid bifurcation, so a better knowledge on its natural evolution would allow improving treatment indications.

In general, it is considered a multifactorial disease, with a genetic predisposition associated with cardiovascular risk factors, which leads to arterial wall thickening, and significant hemodynamic disorder, which may change blood flow within a vessel and entail an infrequent cause of cerebral vascular event.

These anomalous configurations, according to the degree of severity, may significantly reduce blood supply to

the brain, which may overlap to conditions like atherosclerosis, hypertension and ageing, which would produce significant hemodynamic symptoms and alterations.^{52,53}

When there is clinical suspicion that neurological deficit could be the consequence of a morphological alteration in the carotid artery, it is essential to rule out the rest of causes for cerebral pathologies (arrhythmia, orthostatic hypotension, epilepsy, labyrinthine alterations, etc.), mainly if symptoms are not focal. A kink with no atherosclerotic plaque (frequent entity) is a very rare cause of stroke.

In adult patients with cerebrovascular ischemia with symptoms, internal carotid kinks are associated frequently with atheromatosis of the carotid bifurcation. When these two lesions are combined in symptomatic patients, surgical treatment is indicated, during which endarterectomy will be carried out in the atheromatous plaque, and kink correction will be conducted.⁵⁴

Also, kinks without severe plaque but symptomatic by dynamic obstruction have indication of surgery. Surgical techniques consist of resection and reanastomosis of tortuous ICA, or use of patch, reimplantation of ICA, grafts with GSV or prosthesis, or artery pexy to the muscle.

To this date, there are few studies assessing the results of endovascular treatment in carotid kinking, and the recommendations are limited to patients in very high surgical risk and in post-endarterectomy restenosis.⁵⁵

Elongations are relatively frequent in children. It is advised to rule out this type of pathology when neurological location appears, although there is no study recommending surgical intervention in asymptomatic children.⁵⁶

IMAGING DIAGNOSIS

Doppler ultrasonography

To study DAPS, the gold standard seems to be ultrasonography.^{57,58} It is possible to observe focal parietal thickening, and turbulent flow with velocity increase.⁵⁹

Besides, it is useful to evaluate significant concomitant atheromas.

Erroneous diagnoses may arise (carotid artery pseudo-occlusion or "interruption" of its flow) during neck vessel Doppler echocardiogram, as often the vessel does not appear in a single plane. The transducer should be manipulated in different positions and change the steer constantly to observe the vessel trajectory. Occasionally, vessel ascent may appear as not rectilinear in the short axis.

In the echographic presence of DAP, mainly kinking, it is advisable to determine the kinking, based on the mentioned classifications. It is essential to detect the presence of atheromas within the kink, and in case of observing them, velocities should be measured before the kink, within the kink, and in the kink outlet. Togay-Isikay observed in a study on 345 echocardiograms on neck vessels that peak systolic velocity (PSV) is greater in the kink than in the coils and tortuosities, being greater in the kinks, at the origin of ICA than in the kink outlet.³¹ Likewise, they stated that the relatively high PSV, the angle correction of the sample while

the study was made at kink level, it is often not optimal and produces an overestimation of flow velocities.

With Doppler echocardiogram, continuous changes can be observed in the direction of the blood column and in its velocities. PSV in the kink greater than 170 cm/sec support the diagnosis of hemodynamic compromise secondary to ICA kink.

In the presence of coils, it is possible to observe a sign similar to the Yin-Yang of aneurysms.

Other methods

Digital subtraction angiography (DSA), CT angiography, SPECT and MRI

Digital subtraction angiography (DSA) provides hemodynamic data of DAP and their morphology, but cannot determine the pathological changes at the level of the ICA wall.⁵⁰ CT angiography and SPECT allow studying ICA tortuosity morphology with greater definition and alterations secondary to perfusion, and evaluating subtle anomalies, such as microaneurysms. CT 3D reconstructions seem more efficient at the time of classifying the morphological variations of ICA and detecting these anomalies.^{60,61,62,63} MRI is a good choice for DAP diagnosis.⁶⁴

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Clinical Case

Do we know everything about intermediate risk pulmonary embolism? A case report at a high complexity hospital in Medellin 2024.

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ABSTRACT

Venous thromboembolic diseases such as pulmonary embolism and deep vein thrombosis are the third more prevalent cause of cardiovascular syndrome. Pulmonary embolism has an incidence of 39 to 115 in 100,000 inhabitants annually and a mortality of approximately 300,000 people every year in the United States. Some risk factors of the disease are infections, trauma, lower limb fractures, venous thromboembolic disease and major surgeries. People have symptoms like dyspnea, syncope, chest pain, dizziness and abdominal pain. It is classified according to the risk of the patient into low, low-intermediate, high-intermediate and very high; the last one saved for patients with hemodynamic instability defined by the presence of cardiac arrest, obstructive shock and persistent hypotension. Antithrombotic therapy is the best treatment option, but in very high-risk patients, thrombolytic therapy is an option too.

CLINICAL CASE

Female, 34-year-old patient with history of tibial fracture, who consulted due to syncope, dyspnea, diaphoresis, vomiting and oppressive chest pain; ECG with sinus tachycardia and McGinn-White pattern. Wells score of high risk (9 points). CT angiography of pulmonary arteries leads to diagnosis of acute bilateral pulmonary thromboembolism, with saddle embolism in pulmonary arteries, lobar, segmental and subsegmental arteries (*Figure 1*). Transthoracic echocardiogram showing right ventricular dilatation with basal diameter of 5.5 cm, RV/LV ratio of 2.2, McConnell's sign, TAPSE of 14 mm, dilated RA with a volume of 37 ml/m², tricuspid valve with severe secondary regurgitation with vena contracta width of 0.7 cm and regurgitation of 10 cm², maximum gradient of tricuspid regurgitation of 39 mmHg, and thrombus in right chamber of 2.1 cm x 0.6 cm with area of 1.7 cm² in the right branch of the pulmonary artery. Pulmonary trunk of 2.6 cm, right pulmonary branch of 1.7 cm, left pulmonary branch of 1.5 cm. PASP of 49 mmHg and tricuspid regurgitation velocity estimated in 303 cm/sec. Admission tests with troponin T 47.5 ng/ml (positive), arterial blood gas with hyperlactatemia and lactic acidosis compensated with 2.49 mMol/L lactate. She was classified as in intermediate-high risk according to the 2019 European guidelines criteria on the diagnosis and management for pulmonary thromboembolism, and she was anticoagulated with unfractionated heparin infusion. In spite of the analgesic, anticoagulant and support treatment,

she remained with tachycardia, tachypnea, WHO function class deterioration from I to IV, and progressive increase of lactate in blood. In spite of not meeting the criteria for hemodynamic instability, taking into account the high risk of clinical deterioration and compromise of quality of life, besides the acute right heart compromise evident in transthoracic echocardiogram, a multidisciplinary meeting was conducted, and the choice was made to apply thrombolysis in situ. Seventy-two hours after admission, catheters were

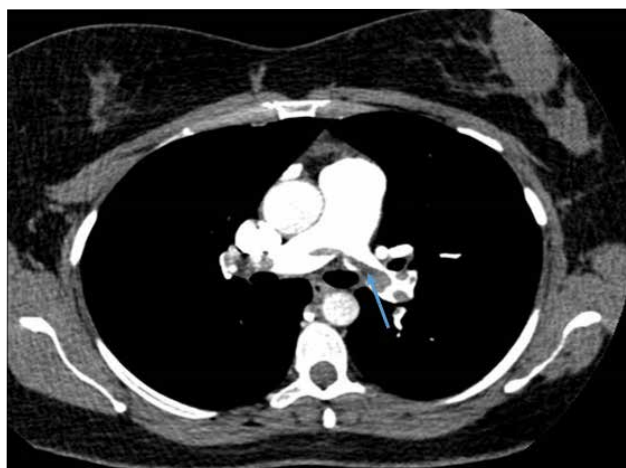


FIGURE 1.
CT angiography of pulmonary arteries

advanced into each pulmonary artery, the location was verified by pulmonary arteriography and in situ infusion was administered of alteplase, at a dose of 1 mg/h for 3 hours and 35 minutes with no complications. Four days after the procedure, control transthoracic echocardiogram was made, showing normal RV size, with basal diameter of 3.5 cm, TAPSE 18 mm, right atrium with 12 cm² area and volume of 13 ml/m², tricuspid valve with mild regurgitation, pulmonary valve with normal morphology and flows by Doppler, pulmonary trunk of 1.7 cm, right pulmonary artery of 1.2 cm, left pulmonary branch of 1.0 cm, PASP 36 mmHg with tricuspid regurgitation velocity of 280 cm/sec. The patient presented adequate clinical course and tolerated supplemental oxygen weaning.

DISCUSSION

Reperfusion therapies, particularly in systemic thrombolysis, is the treatment of choice for high-risk pulmonary embolism. The question has been raised that in patients with intermediate risk, these therapies may entail a bleeding risk exceeding the benefit of the intervention; however, it is known that within the group of patients with intermediate-high risk, they represent a significant mortality in the short term, suggesting the need for a more aggressive treatment.

Catheter-directed thrombolysis is a management strategy by which a slow infusion of a thrombolytic agent is administered into the pulmonary artery through a catheter with multiple holes, which is locally introduced into the thrombus/embolus. The dose of the thrombolytic agent is approximately 25% of the systemic dose, seeking to maintain therapeutic effectiveness with less bleeding risk.

Therapies such as surgical embolectomy or catheter-directed therapy could be management alternatives, but their use is limited due to their low availability.

In the USAT IH-PE study, a multicenter, retrospective and prospective registry carried out in 5 centers in Italy, including 102 patients with pulmonary embolism of intermediate-high and high risk, who were treated by catheter-directed thrombolysis facilitated by ultrasound, from March 2018 to July 2023, the incidence of pulmonary embolism was studied. It was defined as medium pressure of the pulmonary artery ≥ 20 mmHg in rest during right heart catheterization performed in patients presenting PASP ≥ 40 mmHg in echocardiographic follow-up. For secondary outcomes, the following were evaluated: parameters of RV function (TAPSE, RV/LV ratio, pulmonary artery systolic pressure, TAPSE/PASP ratio), in the short and mid-term, all-cause in-hospital mortality, and bleeding associated to the procedure as safety outcome.

From the 102 patients, 86% presented pulmonary embolism of intermediate-high risk, with an average age of 63 years. In 70 of the analyzed patients, an improvement was verified in RV function parameters within 24 hours after thrombolysis, with 44.1% of patients presenting signs of RV insufficiency (TAPSE ≤ 16 mm and/or PASP ≥ 40 mmHg and/or RV/LV > 1), which during the subsequent follow-

up (3-6 months), it was just 5.9%, with an incidence of residual pulmonary hypertension of 1.43%.

Mortality rate during follow-up was 11%, with in-hospital mortality of 3.9% and mortality upon discharge unrelated to pulmonary embolism.

In the KNOCOUT PE study, a prospective cohort including 489 patients from 64 centers, with acute pulmonary embolism of intermediate-high and high risk, treated by catheter-directed thrombolysis facilitated by ultrasound (USCDT), using reduced thrombolytic doses and shorter infusion durations, 94.7% were classified as in intermediate-high risk. The total medium dose of r-tPA administered was 18.1 mg, with a mean duration of infusion of 10.5 hours.

The patients received USCDT performed by an endovascular specialist; the dose and treatment durations were determined according to the criterion of the individual investigator. The follow-up terms were carried out during hospital stay, before discharge and within 3 and 12 months after the treatment. The echocardiographic follow-up was carried out within 3 months for those with initial abnormal echocardiogram after the procedure, with the aim of assessing chronic pulmonary hypertension signs, and within 12 months for all patients. In regard to the analyzed outcomes, 8 major bleeding events occurred within the first 72 hours after the treatment, with a single episode of intracranial bleeding, which represented a rate of major bleeding of 1.6%. Five patients died during the first 30 days after the treatment; all of whom were intermediate-high risk patients. The assessment of echocardiographic changes showed a modification in the RV/LV ratio of 1.35 to 0.98 within the first 24 hours, and of the estimated medium RV systolic pressure from 50.35 mmHg to 35.77 mmHg within 24-48 hours.^{1,2,3,4,5}

In a retrospective cohort conducted in 2022 including 74 patients with diagnosis of pulmonary thromboembolism with intermediate risk, clinical variables were evaluated, in association with adverse outcomes in patients with pulmonary thromboembolism; namely, brain natriuretic peptide, leukocytes and RV/LV ratio, which were all greater in patients with adverse outcomes in comparison to controls. The patients that presented adverse outcomes presented higher rates of syncope, negative T waves in V1-V3, and low arterial oxygen saturation (SaO₂ $< 90\%$) upon admission.⁶

In the PEITHO study, the efficacy and safety of systemic thrombolysis with 50 mg of tenecteplase was evaluated in patients with intermediate-high risk. No statistically significant differences were found related to mortality, and for this reason, it is not a therapy used frequently in our area; however, given the variable behavior of patients, there are no other therapeutic strategies with evidence supporting an improvement in the outcomes of patients.

In a meta-analysis of observational studies and clinical trials, including 12 studies, most used the Ekosonic device for the thrombolytic treatment of patients; where the effectiveness of catheter-directed thrombolysis was compa-

red with systemic anticoagulation, which is the standard management according to the 2019 European guidelines in patients with submassive PTE or of intermediate-high risk. The primary outcome that evaluated this study was in-hospital mortality within 30 days, 90 days and one year. Additionally, secondary significant outcomes were evaluated, such as major bleeding (defined as the presence of intracranial bleeding or any source of bleeding that may produce hemodynamic instability), minor bleeding and blood transfusion. Patients with hemodynamic instability were ruled out. From the 7 studies analyzed, only 1 found a real difference in terms of mortality when the odds ratio was compared with other studies. Possibly, this difference is due to the size of the sample. Additionally, in terms of heterogeneity, this was low among groups. However, a tendency to lower mortality within one year was identified, and to the recovery of RV function in patients who had underwent thrombolysis. When evaluating the secondary outcome of major bleeding, there were no statistically significant differences. It is then believed that the intervention seems to reduce mortality without increasing the risk of major or minor bleeding.⁶

Currently, the PEITHO-3 TRIAL is ongoing; this is a study evaluating the outcomes of efficacy and safety when administering reduced doses of IV alteplase at 0.6 mg/kg in 15-minute infusion, not exceeding the total dose of 50 mg.⁷

Finally, in the HI-PEITHO study, an ongoing study, the usefulness of catheter-directed thrombolysis is being evaluated in comparison with anticoagulation in patients with pulmonary thromboembolism with intermediate-high risk.⁸

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Clinical Case

Endovascular treatment for Type III Endoleak by disconnection of aortic stent graft components

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ABSTRACT

Endovascular repair of abdominal aortic aneurysms (EVAR) has expanded in recent years. Compared to surgical repair, EVAR is associated with lower 30-day morbidity and mortality although it has higher reintervention rates due to the presence of endoleaks during follow-up. We put forward the case of an 81-year-old patient who, four years after EVAR, presented with a type 3 endoleak owing to disconnection between the main body and the proximal cuffs of the endograft. Emergency endovascular treatment was performed via both surgical and percutaneous femoral access. The endograft components were threaded through a catheter and hydrophilic wire, respectively, and then replaced with two Lunderquist wires, achieving acceptable alignment. Finally, a thoracic endograft was implanted with sufficient overlap in the disconnection area, thus sealing the endoleak. The patient progressed without major complications and was discharged 48 hours after the procedure.

INTRODUCTION

Endovascular aneurysm repair (EVAR) is recommended for patients presenting favorable anatomy and a reasonable life expectancy. Also, we should consider the treatment modality preferred for elective abdominal aortic aneurysm (AAA) repair (class IIa recommendation, level B of evidence).¹

EVAR, compared with surgical repair, is associated to less mortality and morbidity within 30 days, and discharge is also faster. However, it is also associated to higher rates of reintervention than conventional surgery, and the presence of endoleaks is the most frequent indication.^{2,3}

The definition of endoleak is the presence of continuous blood flow toward the aneurysm sac outside the endograft. Endoleaks are classified into primary, when they occur during the endograft implant, or secondary, when they manifest during follow-up.

White et al. classified this post-EVAR complication into: 1) endoleak type 1: proximal (1a) or distal (1b): they correspond to a fixation defect of the endograft to the wall due to incomplete opening, tortuosity or angulation; 2) endoleak type 2: they occur when there is retrograde blood flow in the aneurysm sac through an excluded aortic branch, most commonly the inferior mesenteric artery or a lumbar artery; 3) endoleak type 3: from a disconnection of components (3a) or fabric defect (3b); 4) endoleak type 4: defined as secondary to prosthetic material porosity.⁴

Although a rare entity, endoleak type 3 can lead to aneurysm sac increase, enhancing the risk of rupture.

As years pass, endografts have evolved achieving a decrease in the number of complications, including endoleaks, and overcoming anatomical limitations challenging for implantation.

Anatomical fixation in the aortic bifurcation, and a modular proximal cuff for aortic seal, differentiate the AFX endovascular AAA system (Endologix) from many other endoprosthetic products.

This model of endograft has several advantages associated with anatomical fixation; however, some reports showed an increase in endoleaks type 3a (ET3a).⁵

In response, Endologix improved the device material and released new endograft models to the market. Several studies later showed a decrease in ET3a in comparison with first-generation endografts.⁶

However, there is an ongoing discussion in terms of the presence of ET3a in long-term follow-up after EVAR with this type of endografts.

We present the case of a patient carrier of AAA treated by endoprosthesis, in whom component overlapping was lost, leading to structure disconnection during distant follow-up (4 years), originating ET3a. We present the endovascular treatment for said complication, using thoracic branch endoprosthesis.

CLINICAL CASE PRESENTATION

Female, 81-year-old patient. History of hypertension, former smoker. Chronic obstructive pulmonary disease (COPD). Hypothyroidism. Previous medication: losartan 100 mg/day, nebivolol 10 mg/day, spironolactone 100 mg/day, rosuvastatin 10 mg/day, clopidogrel 75 mg/day, T4 100 mcg/day.

AAA started 25 mm below the level of the renal arteries origin. Cylindrical and regularly-shaped neck, of 28 mm, with 45° angle between infrarenal neck axis and aneurysmal lumen axis. Saccular dilatation extends distally 110 mm until iliac bifurcation, reaching a greater diameter at abdominal level, of 98 mm, with mural thrombus.

Due to the high surgical risk, mainly due to COPD, and as she presented favorable anatomy, endoluminal treatment was indicated to exclude AAA. After anatomical evaluations and the endoprosthesis being granted by the medical insurance of the patient, the procedure was scheduled.

In December 2020, EVAR was carried out by placement of bifurcated Endologix AFX2 BEA® endograft, main body 25-80/I13-40, an Endologix VELA® proximal extension of 28-28 mm of diameter x 95 mm of length (A28-28/C95-O20), and a second Endologix VELA® extension of 28-28 mm of diameter x 75 mm of length (A28-28/C75-O20).

The patient coursed without complications. One year later, CT angiography was carried out, ruling out the presence of endoleaks.

Later, she dropped medical controls, being readmitted due to abdominal pain of sudden onset, accompanied by profuse sweating and hypotension in January 2025.

Emergency CT angiography was carried out, showing infrarenal saccular aneurysmatic dilatation of 116 mm of length x 105 mm of cross diameter, with active extravasation compatible with endoleak type 3 by disconnection of components, proximal extensions of the main body (Figure 1A and B).

Abdominal aortogram was carried out. Fluoroscopic imaging showed disconnection of the endograft as the cause for the endoleak (Figure 1C).

Endovascular treatment was applied again. It consisted of surgical access and exposition of right common femoral artery, direct puncture of this artery and placement of 7F introducer under 0.035" guide wire, percutaneous puncture of left common femoral artery and placement of 6F introducer under guide wire 0.035".

By right access, a Cobra 5F hydrophilic catheter was advanced under hydrophilic guide wire. The body of the endograft was ascended through it, and later threaded and ascended through the proximal extensions, then positioning distal guide wire and catheter in the aortic arch. It was exchanged by Lunderquist guide wire, which did not achieve endograft components alignment. For this reason, the maneuver is repeated from the left femoral access threading the components. Subsequently, it was exchanged by marker pigtail catheter, where angiographic test was made (Figure 2A).

Next, it was exchanged by a second Lunderquist guide wire. This maneuver of adding a second guide wire with the stiffness of the Lunderquist one determined for the main body of the endograft to align with the proximal extensions. Thus, a Medtronic Valiant™ thoracic endograft, with Captivia™ release system (36-36/24F, of 107 mm of length), was ascended with good support through the right surgical access. It started to be released, achieving enough overlap in the disconnection area, with the proximal extensions (5 cm) and with the body of the previously implanted bifurcated endoprosthesis (5 m), sealing the endoleak area (Figure 2B).

Next, expansion of the new implanted prosthesis was carried out with an elastomeric balloon (Figure 2C). Finally, control testing was made, not showing any leak (Figure 3).

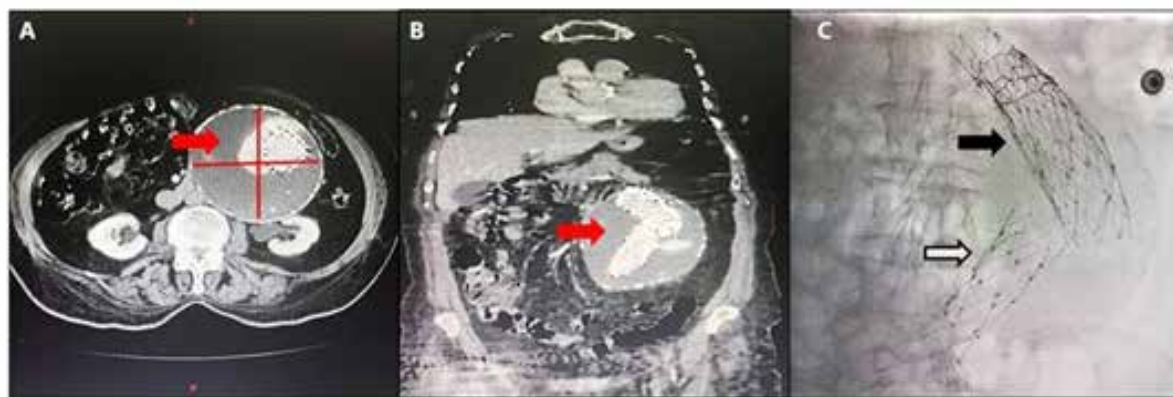
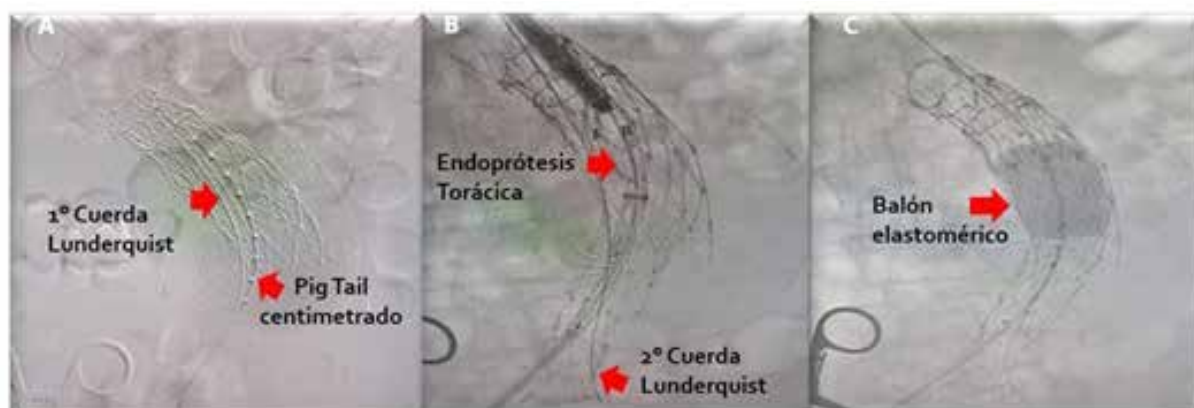
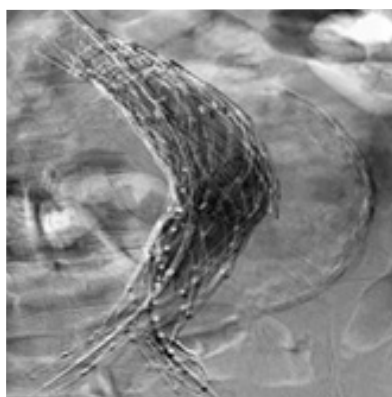


FIGURE 1.

A) and B) Axial and coronal image obtained from emergency CT angiography made 4 years ago post-EVAR. Saccular aneurysmatic dilatation is observed, of 116 mm of length x 105 mm of cross sectional diameter and active extravasation (red arrow) toward the aneurysmatic sac. C) Fluoroscopic image of endograft showing proximal extensions disconnection (black arrow) from the main body (white arrow) of the endograft.

**FIGURE 2.**

Reconnection of endograft components by bilateral femoral access. A) First extra-stiff Lunderquist guide wire by right femoral access. B) Second extra-stiff Lunderquist guide wire by left femoral access and thoracic endoprosthesis being ascended by right femoral access. C) Elastomeric balloon inflation in overlapping area.

**FIGURE 3.**

Final angiographic image after thoracic endoprosthesis implantation to treat endoleak type 3 by disconnection of previously implanted abdominal endograft components, with aneurysmatic sac exclusion being visible.

The patient coursed the postoperative period with no major complications and was discharged 48 hours later.

DISCUSSION

The incidence of endoleak type 3 is low. Clinical trials like the EVAR Over and registries like the EUROSTAR show an incidence of 3 to 4.5%. If the incidence of ET3a is analyzed according to the device used, we observe a higher presentation in first-generation devices compared with the current third-generation ones, recording a 1% incidence with the latter, with the subsequent reduction in post-EVAR reinterventions.^{7,8,9}

An early diagnosis of this post-EVAR complication in follow-up is essential. It has been established that multislice CT with IV contrast is the study of choice to assess the appearance of leaks within the first month after the surgery, to then repeat controls at 6 and 12 months, and then once a year.

The Endologix device has the advantage of passive anatomical fixation in the aortic bifurcation, preventing the distal migration of the main component, and later proximal anchoring is made.

In the follow-up, endoleak type 3 has been detected, both early and late, as a consequence of the design proper of the endograft (fabric fixation with the device only in the superior and inferior ends).¹⁰

The disconnection of the endograft components may occur between the main module (bifurcated body) and a main proximal extension, or between the main body and the iliac extension.¹¹

Several reports show a greater frequency of ET3a with Endologix AFX devices.^{12,13,14,15}

According to the system of notifications of Medical Devices from the US Food and Drug Administration (FDA), and the yearly clinical updates for physicians provided by manufacturers, a line of Endologix AFX endografts (AFX with Strata, AFX with Duraply and AFX2) is associated with a high frequency of endoleaks type 3.¹⁶

The FDA, furthermore, by providing information related with the risk of endoleak type 3 of the Endologix AFX devices from several different information sources, including studies in the real world, published abstracts and peer-reviewed literature, advises health effectors to use other alternatives available for endovascular treatment.¹⁷

The treatment for ET3a could be both conventional or endovascular. The current recommendations refer to endovascular therapy as being first line, and to leave conventional surgery for cases where the first option failed. The treatment for ET3a includes the placement of sheathed stents, sealing the gap between the components as done in our case.^{18,19}

A thoracic device has been chosen to treat ET3a after EVAR. This endograft particularly enabled, once enough alignment is achieved for the components with two extra-stiff Lunderquist guide wires, ensuring a good overlapping

area, 5 cm with the main module and 5 cm with the proximal extension. A report by Russo A et al. has been found in literature, using this type of prosthesis to contain an ET3a.²⁰

The Maleux et al. study shows that 25% of patients treated for this complication presented a new ET3a in follow-up. This fact underscores the significance of a close follow-up for these patients to achieve an early diagnosis and treatment for ET3a.²¹

CONCLUSIONS

Endovascular repair for AAA (EVAR) has expanded. The most frequent complication is the presence of endoleaks. ET3a due to endograft modules disconnection has been observed more frequently with first-generation devices. The resolution of the disconnection of the implanted device components timely was feasible and safe, using an endograft designed for implantation at thoracic level, but due to its characteristics could be used and implanted at abdominal level. A follow-up by imaging tests is relevant to detect this post-EVAR complication early.

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