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Metabolic-Adipose-Cardio-Arterial-Renal-Enterohepatic-Neurological connection in arterial hypertension (MACARENHA): positioning for the new approach to prevention, diagnosis, treatment, and follow-up of patients living with arterial hypertension in Mexico

Conexión Metabólica-Adiposa-Cardio-Arterial-Renal-Enterohepática-Neurológica en hipertensión arterial (MACARENHA): posicionamiento para el nuevo enfoque de prevención, diagnóstico, tratamiento y seguimiento de los pacientes que viven con hipertensión arterial en México

Luis Alcocer-Díaz-Barreiro,* Alejandro Alcocer,* Humberto Álvarez-López,* Ana E Ancona-Vadillo,* Neftalí Eduardo Antonio-Villa,* Simón Barquera,* Gabriela Borrayo-Sánchez,* David Cardona-Müller,* Ernesto Cardona-Muñoz,* Emilia Cantoral-Farfán,* José Ángel Cigarroa-López,* Aníbal Cruz-Montalvo,* Adolfo Chávez-Mendoza,* Adolfo Chávez-Negrete,* Guillermo Saturno-Chiu,* Sergio Emmanuel Delgado-Félix,* Enrique Díaz-Díaz,* Miguel Ángel Díaz-Aguilera,* Ernesto Díaz-Domínguez,* Manuel Duarte-Vega,* José Manuel Enciso-Muñoz,* Xavier Escudero-Cañedo,* Guillermo Enrique Ferrari,* Abelardo Flores-Morales,* Héctor Galván-Oseguera,* Rafael García-Fernández,* Rosalba García-Méndez,* Sergio Moisés García-López,* Enrique Gómez-Álvarez,* Vidal José González-Coronado,* Ángel Gracia-Ramírez,* Juan Miguel Heredia-Lavín,* Mauricio López-Meneses,* Karina Lupercio-Mora,* Alejandra Madrid-Miller,* José Antonio Magaña-Serrano,* Dania Heloneyda Martínez-Juárez,* Eduardo Meaney-Mendiolea,* Patricio Ortiz-Fernández,* Silvia Palomo-Piñón,* Juan José Parcero-Valdez,* Fabiola Pazos-Pérez,* Abel Alberto Pavía-López,* Adriana Puente-Barragán,* Ariadna Rechy-Rivera,* Luis Rey-García,* Alejandro Ricalde-Alcocer,* Martin Rosas-Peralta,* Miguel Ángel Santiago-Velázquez,* Marissa Silva,* Rosbel Toledo-Ortiz,* Rodrigo Villaseñor-Hidalgo*

* GREHTA Mexico Group.

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Abbreviations:
ACEi = Angiotensin-Converting Enzyme Inhibitors
ARBs = Angiotensin Receptor Blockers
BBs = Beta-Blockers
BMI = Body Mass Index
CCBs = Calcium Channel Blockers
CETP = Cholesteryl Ester Transfer Protein
CKM = Cardiovascular-Kidney-Metabolic
CVD = cardiovascular disease
CVR = Cardiovascular Risk
DBP = Diastolic BP
GIP = Glucose-Dependent Insulinotropic Polypeptide
GLP-1 = Glucagon-Like Peptide-1
GREHTA = *GRupo de Expertos en HiperTensión Arterial* (Group of Experts on Arterial Hypertension)
HBP = High Blood Pressure
HDL = High-Density Lipoprotein
HMOD = Hypertension-Mediated Organ Damage
LVEF = Left Ventricular Ejection Fraction
MACAREHNA = Metabolic-Adipose-Cardio-Arterial-Renal-Entero-Hepatic-Neurological/Behavioral Connection
MASH = Metabolic Dysfunction-Associated Steatohepatitis
MASLD = Metabolic Dysfunction-Associated Steatotic Liver Disease
MRAs = Mineralocorticoid Receptor Antagonists
NAFLD = Nonalcoholic Fatty Liver Disease
POMC = Pro-opiomelanocortin
RSAHT = Randomized Sequence Antihypertensive Escalation
RSD = Renal Sympathetic Denervation
SBP = Systolic BP
T2DM = Type 2 Diabetes
TNF-α = Tumor Necrosis Factor-Alpha
TOD = Target Organ Damage

INTRODUCTION

High blood pressure (HBP) is one of the most common cardiovascular risk factors and a primary contributor to the development of cardiovascular complications, which are the leading cause of death in Mexico and around the world. Systemic HBP is a nosological entity resulting from multiple pathophysiological mechanisms. Its onset, development, progression, damage, and systemic complications define the need to study it with a holistic approach. While HBP per se generates structural and functional damage in the micro and macrocirculation, its damage to various target organs in turn triggers feedback mechanisms that perpetuate or accelerate the harmful behavior of increased pressure values themselves.[1,2]

For this reason, the GREHTA group, a consortium of experts in arterial hypertension, convened to develop a position on the diagnosis, prevention, treatment, and follow-up of patients with HBP in the context of the metabolic-adipose-cardio-arterial-renal-enterohepatic-neurological/behavioral connection (MACAREHNA) that arises in these patients.

Why a Mexican position on the role of HBP in the MACARENHA connection?

Along with HBP, other significant conditions such as dyslipidemia, dysglycemia, kidney damage, cerebrovascular disease, dementia, and liver disease, among others, frequently occur in the same patient, and the relationship between them is a synchronous interaction effect between separate entities, which nevertheless share common pathophysiological roots. The first attempt to evaluate these entities as distinct components of the same process, was the development of the concept of Metabolic Syndrome coined in 1977 by Herman Haller, and later popularized in 1988 by Gerald M. Reaven, who used the term about to signal the association between obesity, diabetes mellitus, elevated blood lipids, high uric acid levels, and hepatic steatosis as a result primarily of insulin resistance and described how the combined presence of these factors increases the risk for atherosclerosis. The pathological interrelationship between the kidney and the heart was named «Cardiorenal Syndrome» in 2004.[3] In 2023, the American Heart Association proposed a broader, multidirectional concept that encompasses the connection between the heart, kidney, and metabolic syndrome, known as Cardiovascular-Kidney-Metabolic (CKM) syndrome.

Key messages

1. The importance of CKM syndrome is evident when analyzing mortality in Mexico in 2023. According to INEGI, there were 799,868 deaths that year, of which 399,667, practically half (48.7%), were due to CKM.

2. In the FRIMEX-III study, conducted with 297,370 Mexican participants, 27% had HBP, 50% had hypercholesterolemia, 40% were overweight, and 30% were obese. In these participants, the Body Mass Index (BMI) was found to be linearly correlated with blood pressure, blood glucose, and total cholesterol.[4]
3. The results of the RIHTA Registry published in 2023 by our group, showed in 5590 Mexican patients living with HBP, that the average BMI was 28.8 kg/m^2, waist circumference was 95 cm, fasting glucose was 100 mg/dL, HbA1c was 7.10%, LDL-cholesterol was 110 mg/dL. All these indices exceed the values considered acceptable or desirable. In addition, it was found that 54% of the study subjects were sedentary, and 53% reported anxiety during the previous month. On the other hand, 39% of the participants had diabetes, 83.4% had abdominal obesity, 59.8% had LDL cholesterol levels above 100 mg/dL, 42% had hypoalphalipoproteinemia (low serum HDL-cholesterol), 56.2% had high triglyceride concentrations, and 57.9% were classified as having a high cardiovascular risk.[5]
4. These data suggest a relationship far beyond a coincidence by chance, and allow us to affirm that the problem of arterial hypertension is part of a much broader connection than that described as CKM, so we propose the term MACARENHA Connection to describe this relationship, in a more didactic way, in which we include a greater number of components: Metabolic-Adipose-Cardio-Arterial-Renal-Entero/hepatic-Neurological, in the context of AH (Arterial Hypertension) *(Figure 1)*.
5. Comprehensive diagnosis and management of the MACARENHA Connection are crucial for improving population health and reducing the healthcare burden in Mexico resulting from its outcomes. Moving beyond the simple diagnosis of hypertension to a holistic approach that addresses the interconnected nature of MACARENHA has paramount importance for effective prevention and treatment. Public health initiatives and policy changes aimed at addressing the socioeconomic and environmental determinants of health are necessary to mitigate the impact of the MACARENHA Connection on the population.

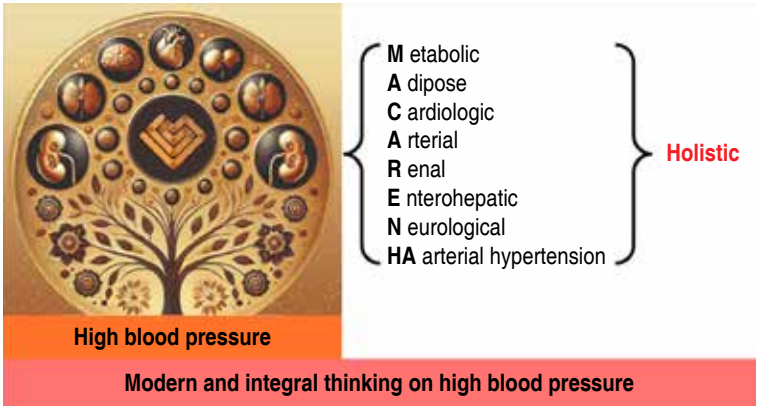

Figure 1: What is MACARENHA? The explanation of the acronym MACARENHA (see text).

How to address cut-off points in the diagnosis of MACARENHA?

The pathophysiological mechanisms underlying the MACAREHNA Connection are multiple and closely interconnected. Thus, the activation of one neurohormonal system leads to the activation of another and sometimes potentiates its harmful effect. Therefore, although the parameter used to define high blood pressure is based on a continuous variable (blood pressure) for which a cut-off point is determined, and a similar approach applies to diabetes and dyslipidemia (glucose and lipid concentrations), they must certainly be analyzed in a broader context.

1. Treating a patient with a blood pressure of 138/86 mmHg in the absence of other factors will not be the same as treating another one with the same blood pressure level but with dysglycemia or hypercholesterolemia. In the former, their cardiovascular risk may be low, and they may not require pharmacological treatment. However, suppose the patient is at high or very high risk due to the presence of other comorbidities (diabetes and/or

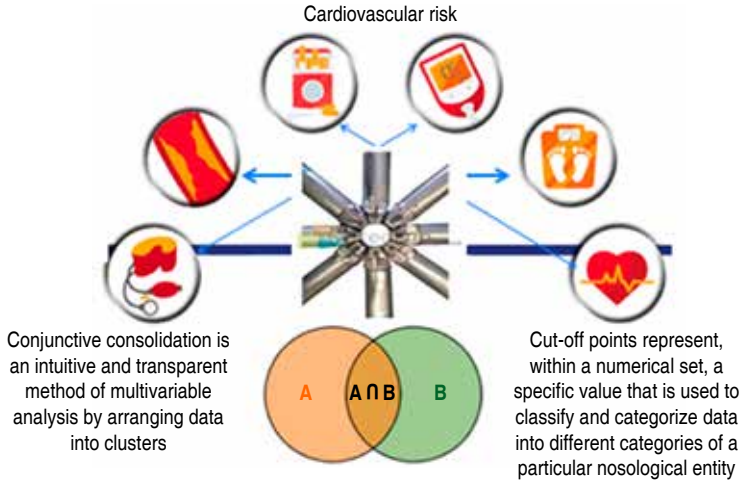

Figure 2: Conjunctive consolidation model. A conjunctive consolidation model emphasizes the importance of analyzing diagnostic cut-off points within the broader context of the patient and their comorbidities.

dyslipidemia, for example) or target organ damage. In that case, they will undoubtedly require pharmacological treatment.[6,7]

2. This cutoff point situation also applies to the goals to be achieved. For example, in dyslipidemia, the target LDL-C value is 100 mg/dL for very low-risk patients, 70 mg/dL for intermediate-risk subjects, and 55 mg/dL or less for high- and very high-risk individuals. Generally, it can be said that the higher the risk, the stricter the control of risk factors becomes *(Figure 2)*.[8]

What is the pathophysiological connection in MACARENHA?

Pathophysiology of aggregated cardiometabolic risk factors. In the context of the Mexican population, the aggregation of these cardiometabolic conditions is a consequence of abdominal obesity, which affects most of the adult population and a considerable segment of adolescents and school- and preschool-aged children. The imbalance between caloric intake and energy expenditure causes the expansion of fatty tissue beyond its physiological storage capacity. This has two consequences: On the one hand, fat is deposited in other types of tissues (for example, the myocardium, skeletal muscle, and kidney), a phenomenon we have termed lipothesaurosis (excessive lipid storage), which causes lipotoxicity and damage to the areas where it occurs.[9]

Key messages

1. These structural pathological changes in adipose tissue establish the insulin resistance syndrome associated with reactive hyperinsulinism as long as pancreatic β cells remain capable of secreting insulin. Although the main cardiovascular and cardiometabolic syndromes, such as hypertension, dyslipidemia, and dysglycemia (diabetes and prediabetes), can be caused by many other factors, including inherited pathogenetic phenotypes, obesity itself, directly or in conjunction with genetic traits, is the central etiopathogenic phenomenon in most cases.[10,11]
2. Abdominal obesity, alone or accompanied by a hypertensive heritage, can be the origin of hypertension through intra- and extrarenal compression. Intraparenchymal fat compressing the vasa recta causes increased sodium reabsorption in the loop of Henle. Thus, the *macula densa* detects low fluid osmolality in the distal convoluted tubule and sends a signal to the juxtaglomerular cells, activating the renin-angiotensin-aldosterone axis.[12]
3. Angiotensin II is a potent vasoconstrictor and inducer of arteriolar hypertrophy, effects that increase peripheral arterial resistance and blood pressure. On the other hand, leptin, an adipohormone generated primarily in adipose tissue whose plasma concentration increases in obese individuals, among numerous different effects, acts on the arcuate nucleus of the hypothalamus and activates neurons of the pro-opiomelanocortin (POMC) system, which in turn stimulates the action of the sympathetic nervous system, some of whose adrenergic mediators are also potent vasoconstrictors and inducers of cardiovascular hypertrophy. Furthermore, the binomial insulin resistance/hyperinsulinism is the cause of a profound disorder of lipid metabolism. As a result of insulin resistance, stored fat is mobilized to the liver, and the capacity

of several insulin-sensitive lipolytic enzymes decreases.[13]

4. Macrophages remove cholesterol from tissues, depositing it on immature HDL until they mature, thereby storing lipids through a process known as lipidation. Once engorged, liver scavenger receptors remove mature HDL from the circulation, eliminating or reprocessing their contents. A serum cholesteryl ester transfer protein (CETP) provides an indirect pathway, serving as a bridge for triglyceride-rich lipoproteins to exchange this lipid for cholesterol with high-density lipoprotein (HDL) particles. Vascular and hepatic lipases rapidly attack these cholesterol-poor, TG-rich HDL, which are structurally unstable and easily lose their apolipoprotein Apo A-I.[14]
5. Dysglycemia, the other major atherogenic risk factor, is also a consequence of the insulin resistance/hyperinsulinism complex. Between 85 and 90% of patients with type 2 diabetes (T2DM) are overweight or obese. However, only about 30% of people who are obese or overweight have diabetes, indicating that, in addition to obesity, other, predominantly hereditary, factors are responsible for the development of diabetes.
6. The two entities, obesity and diabetes, are so closely related that the term «diabesity» was coined to highlight the clinical, epidemiological, and pathophysiological shared complexity of both conditions. The mechanisms of insulin resistance secondary to obesity are numerous, including systemic inflammation and nitroxidation of biomolecules, the effect of adipocytokines such as tumor necrosis factor-alpha (TNF-α), which impair insulin receptor signaling, and dysfunction of both the endoplasmic reticulum and mitochondria, among others.[15]
7. One consequence of the insulin resistance/hyperinsulinism binomial is a condition formerly known as nonalcoholic fatty liver disease (NAFLD), and recently renamed as metabolic dysfunction-associated steatotic liver disease (MASLD), which includes a broad spectrum of conditions ranging from a relatively benign and even hepatoprotective condition, steatosis, to increasingly severe conditions such as metabolic dysfunction-associated steatohepatitis (MASH), with or without fibrosis, to irreversible and fatal conditions such as cirrhosis and hepatoma.[13]
8. A final player in this mosaic of pathophysiologically intertwined metabolic and cardiovascular conditions is the intestine, which involves two leading actors: the gastrointestinal hormones and the gut microbiota. Among the former, glucagon-like peptide-1 (GLP-1), a so-called incretin hormone, is secreted by L cells in the intestine in response to the ingestion of food. The hormone intervenes in the energetic and carbohydrate metabolism, inhibiting the pancreatic secretion of glucagon, which promotes glycogenolysis and gluconeogenesis. Another gastrointestinal hormone, the glucose-dependent insulinotropic polypeptide (GIP), increases the release of glucagon and promotes the storage of fat. The «incretin effect» (which refers to the release of two to three times more insulin when a dose of glucose is ingested compared to when the same amount is infused parenterally) is primarily caused by the insulinotropic peptides. Furthermore, GLP-1 regulates appetite, reduces gastrointestinal motility, and enhances myocardial function, as well as various neuronal processes, including neuroprotection, among other effects.[15,16]
9. The other intestinal agent is microbiota, the community formed by the conglomerate of bacteria, viruses, fungi, and archaea in the intestinal tract. It is estimated that there are between 500 and 1,000 different bacterial species in the intestine, resulting in a total population of approximately 10^{14} organisms. Therefore, 1-3% of body weight is contributed by the mass of microorganisms, mainly anaerobic bacteria. The microbiota contributes to overall and metabolic health when there is a virtuous balance between various species, primarily grouped into the Gram-negative *Bacteroidetes* and Gram-positive *Firmicutes* (Table 1).[17-19]

How to estimate cardiovascular risk in hypertensive patients with MACARENHA?

Cardiovascular risk (CVR) represents the calculated probability that a patient will

Table 1: Predictive algorithms to specific features of MACARENHA.

Factor to evaluate	Algorithm	Construct variables	Description
Visceral adiposity and incidence of T2DM	METS-IR	Serum glucose, HDL-c, BMI, Triglycerides	Non-insulin-based fasting scale for assessing insulin sensitivity validated against the euglycemic-hyperinsulinemic clamp (EHC)
VAT	METS-VF	METS-IR, gender, waist circumference, height, age	Scale in patients with Metabolic Syndrome predicting the incidence of T2DM and HBP, independently of BMI, in primary care
MASLD	FLI, MRE, or THE	GGT, BMI, waist circumference, and triglycerides	Requires validation
Mood	Beck Depression Questionnaire	Symptoms and signs of depression and anxiety	A simplified, self-applied, 21-item scale with four response options that considers the patient's condition over the past two weeks

BMI = body mass index. FLI = fatty liver index. GGT = gamma-glutamyl transferase. HBP = high blood pressure. HDL = high-density lipoprotein. MASLD = metabolic dysfunction-associated steatotic liver disease. METS-IR = metabolic score for insulin resistance. METS-VF = metabolic score for visceral fat. MRE = magnetic resonance elastography. T2DM = type 2 diabetes mellitus. THE = transient hepatic elastography. VAT = visceral adipose tissue.

experience a cardiovascular (CV) event that causes disability or death. This probability is based on the evaluation of factors and/or health conditions that independently contribute a value to this mathematical calculation; these algorithms have been validated in large patient cohorts.

Key messages

1. Real-life epidemiological studies, such as those from the National Registry of Arterial Hypertension (RIHTA) in Mexico, have shown that more than 40% of patients with HBP had an average of 5-6 traditional risk factors, which promote target organ damage (TOD) and cardiovascular disease, with increased frequency in younger adults. Using traditional CV risk calculators such as SCORE 2 and Globorisk, RIHTA showed that 57.9% (95% CI: 56.6-59.2) of patients were at high CV risk. Furthermore, more than half had a high prevalence of cardiometabolic risk factors, whose negative contribution to CV health is well documented.[5,20]
2. Promote and maintain political will to make CVR assessment mandatory in the context of the MACARENHA acronym at all levels of healthcare. To this end, GREHTA presents the proposal in this document and undertakes to disseminate it continuously.
3. Promote and maintain political willingness to make CVR assessment mandatory in the context of the MACARENHA acronym at all levels of healthcare. To this end, GREHTA presents the proposal in this document and undertakes to divulge it permanently.

What is the role of clinical judgment in the risk stratification of MACARENHA?

1. Clinical judgment refers to a healthcare professional's ability to integrate information obtained from the medical history, physical examination, and the results of paraclinical studies, enabling them to establish a diagnostic probability and prescribe appropriate treatment. In other words, it is the whole exercise of the scientific method applied to clinical practice. In the context of MACARENHA, the external habitus, targeted questioning, and a comprehensive physical examination enable the use of logic and reasoning to resolve in favor of the patient.
2. All physicians need to exercise clinical judgment, but this requires the following: 1) Being familiar with the constant advances in

knowledge; 2) To have the time and space to analyze the problem; 3) Having access to equipment and auxiliary studies for precise diagnosis; 4) Being able to seek guidance from a colleague with greater experience and clinical practice. In our setting, several of these premises are limited. The acronym MACARENHA describes the general concept of the problem and provides a clinical guideline helpful for consultation at any level of medical care.[21]

3. Continuing medical education is crucial for enhancing the quality of outpatient care. Although in Mexico and many regions of the world this activity is an individual responsibility, access to the academic environment through medical societies, academies, and colleges is partially accessible and not mandatory in our country. Furthermore, the unfortunate phenomenon of a lack of therapeutic resources undermines physicians' motivation and initiative in learning about and implementing therapeutic advances. GREHTA has the academic structure to support this initiative, which aims to raise awareness and provide training.
4. MACARENHA is an acronym developed by GREHTA that is added to the approved cardiovascular risk stratification. In addition to the contribution of traditional factors, the presence of established cardiovascular disease (CVD), as well as patient characteristics, there are also metabolic, liver, and mood alterations whose contribution to cardiovascular risk is recognized but not integrated into the mathematical algorithms that determine the probability of experiencing a fatal cardiovascular event. In our environment, evaluating these additional aspects in a systematic, clinical, and accessible manner represents an opportunity for early therapeutic intervention.

How to use the therapeutic approach in MACARENHA?

The goal of hypertension treatment is not only to reduce blood pressure levels, but also to prevent or delay organ damage caused by hypertension and the complex of metabolic, inflammatory, hemodynamic, and structural alterations that damage vital organs and are the cause of cardiovascular morbidity and mortality.[1-3]

1. Non-pharmacological treatment, promoting lifestyle changes, diet, exercise, and optimizing body weight, should be established for all patients living with hypertension.
2. In modern hypertension treatment, the use of drugs that only lower blood pressure cannot be conceived without offering additional benefits of organ protection and improvement of at least one of the most common comorbidities.
3. We must seek beneficial effects in reducing ventricular hypertrophy, preserving vascular and renal function, and improving the metabolic and liver profile.
4. Taking this into account, we agree with the recommendations of most international guidelines. It is essential to initiate antihypertensive treatment with at least two different antihypertensive medications. If control is not achieved, it is recommended to add a third antihypertensive, ideally in a single tablet. If adequate control is not achieved, a fourth antihypertensive should be added. However, it is essential to consider the patient's comorbidities and the specific characteristics of the various antihypertensives when selecting the most suitable ones for each case.
5. Most antihypertensive medications are effective for patients with type 2 diabetes mellitus (T2DM). However, it is worth mentioning that both angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) have a particular benefit in patients with albuminuria. In this regard, ACEi are considered to have more evidence demonstrating a reduction in cardiovascular morbidity and mortality. Similarly, the recently published FIDELIO DKD and FIGARO DKD studies showed the benefits of finerenone on kidney function and the reduction of cardiovascular events in diabetic patients with nephropathy, suggesting that this could be another

medication with added benefits in patients with diabetes. It's worth noting that the use of SGLT2i (sodium-glucose cotransporter-2 inhibitors) has been associated with a modest decrease in blood pressure and a significant reduction in cardiovascular events in this patient group; therefore, their use should also be considered.[1-3,22]

6. Controlling high blood pressure is particularly beneficial in patients with chronic kidney disease, as it reduces both cardiovascular events and mortality. Both ACE inhibitors and ARBs are effective in reducing cardiovascular morbidity and mortality in these patients. Still, the use of ACE inhibitors has been shown to reduce events at a greater rate. Combination therapy with at least two antihypertensives is recommended from the outset in this group of patients: ACE inhibitors or ARBs + BC or diuretics. The use of loop diuretics is often necessary for patients with a glomerular filtration rate of less than 30 mL/min/1.73 m^2. Thiazide-type diuretics such as indapamide and chlorthalidone may be considered for filtration rates up to 15 ml/min/1.73 m^2. In patients with T2DM and kidney disease, finerenone has been shown to reduce cardiovascular morbidity and mortality and the progression of kidney disease and should therefore be considered a therapeutic option. The use of SGLT2i has been linked to a modest reduction in blood pressure; however, it is also associated with a significant decrease in cardiovascular events and the progression of kidney disease in this patient group, making its use a consideration.[23]
7. In patients with a history of ischemic heart disease, the use of a combination of ACEIs/ARBs and beta-blockers is especially beneficial. If patients present with angina, both beta-blockers (BBs) and calcium channel blockers (CCBs) can be considered as treatment options. Therefore, the initial combination for hypertension and ischemic heart disease includes the use of ACEIs/ARBs + BBs. If blood pressure is not controlled, adding beta blockers (BCs) is considered, followed by the use of a thiazide-type diuretic.[23]
8. In patients with heart failure and reduced left ventricular ejection fraction (LVEF), it is considered a priority to initiate antihypertensive treatment with agents that have been shown to improve the prognosis in this group of patients. Therefore, initial therapy for hypertension is considered to include a combination of four blood pressure-lowering medications: ARNi (angiotensin receptor-neprilysin inhibitor), beta blockers (BBs), mineralocorticoid receptor antagonists (MRAs), and SGLT2 inhibitors. In cases of ARNi intolerance, the use of ACEIs is recommended, and if they are intolerant, the use of ARBs is considered.[24]
9. In this condition, adequate blood pressure control is a priority, and it is recommended as in any case of hypertension. However, as with other conditions, it is essential to include drugs in the treatment that have been shown to reduce cardiovascular events and mortality. Therefore, SGLT2 inhibitors and finerenone should be used in conjunction, considering that both have an antihypertensive effect.[25]
10. Benefits of statins: the comprehensive management of hypertensive patients with metabolic and cardiovascular disorders such as diabetes, obesity, dyslipidemia, kidney disease, and fatty liver disease is crucial to reducing cardiovascular risk and improving quality of life. This multidisciplinary approach allows for the treatment of not only hypertension but also comorbidities, thus optimizing the patient's overall health. The use of statins in hypertensive patients with intermediate and high cardiovascular risk has consistently been shown to reduce the incidence of major cardiovascular events and mortality. In this pathology, adequate blood pressure control is a priority, and monitoring is recommended as in any case of hypertension. However, as in all other pathologies, it is essential to incorporate drugs that have been shown to reduce cardiovascular events and mortality in the treatment. Therefore, iSGLT2 and finerenone should be included in parallel with antihypertensive treatment, considering that both have an antihypertensive effect.[26]

11. This clear benefit of statin use in hypertensive patients at intermediate and high risk leads us to recommend their use in most hypertensive patients, except those who should not use statins.

Conclusion. The main objective of pharmacological treatment for hypertension is to reduce the morbidity and mortality associated with it and its related conditions. Therefore, the use of antihypertensive drugs that have demonstrated this benefit is recommended for both hypertension and the conditions that commonly accompany it. Based on the significant evidence available, it is considered that statins should be used concomitantly in most patients with hypertension who also have one or more of the different conditions included in MACAREHNA.

What to do with patients with resistant hypertension?

Use of invasive devices in patients with resistant hypertension (RH)

1. Hypertension is the leading cause of death from ischemic heart disease, cerebrovascular events (both ischemic and hemorrhagic), chronic kidney disease, and others. Despite efforts to detect and control hypertension, less than half of patients diagnosed with hypertension are on treatment goals. Those with RH are among the group of patients with difficulty controlling their hypertension. RH is defined as blood pressure above the target level despite the use of at least three antihypertensive drugs from different classes of substances, including a diuretic in appropriate doses and combinations. Given the significant problem posed by this disease and its difficult control, non-pharmacological therapies have been developed as adjuvants to current treatment to increase control rates and reduce the morbidity and mortality of HBP. Among them, the most studied in the last decade is renal sympathetic denervation. This interventional treatment aims to reduce the sympathetic overstimulation that has been shown to occur in patients with difficult-to-control hypertension.[27]

Is renal sympathetic denervation (RSD) an effective and safe therapy for improving blood pressure in patients with resistant and difficult-to-control hypertension?

2. The first study on RSD was Simplicity HTN-1 with 50 pts with HR, with a reduction in office systolic BP (SBP) of 27 mmHg and diastolic BP (DBP) of 17 mmHg at one year, and with reductions in 88 patients at three years of 32 mmHg in SBP and 14 mmHg in DBP, with no significant adverse events.[11] The Symplicity HTN-2 study included 106 patients with HR who were randomized to RSD (n = 52) or medical treatment (n = 54) with a reduction in office SBP of 32 and DBP of 11 mmHg in the RSD group compared with a reduction of 1/0 mmHg in SBP/DBP in the control group, with no evidence of significant adverse events related to RSD. The Symplicity HTN-3 study included 535 HR pts randomized 2:1 to RSD vs a Sham procedure where the RSD group reduced 14 mmHg and the Sham group 11 mmHg, therefore the difference between groups at six months did not reach the statistical difference of more than 5 mmHg for the efficacy outcome, the primary safety endpoint was met with no significant adverse events in the RSD group. The final 36-month follow-up of this study was published in Lancet in 2022 demonstrating a reduction in office SBP of 26 mmHg in the RSD group vs 5 mmHg in the Sham group ($p < 0.0001$) and a reduction in ABPM of 15.6 mmHg in the RSD group vs 0.3 mmHg in the Sham group ($p < 0.0001$). Since the publication of HTN-3 in 2014, changes have been made to the radiofrequency denervation catheter, transitioning from monopolar to tetrapolar, self-expanding, and coiled devices, such as the Spyral. Additionally, an ultrasound-based catheter, known as the Paradise System, has also been developed. The results of subsequent studies were performed with these technologies. The HTN Spyral Off Med study again demonstrated proof of concept for denervation in 331 patients,

166 in the DSR group and 165 in the control group (Sham). These patients did not receive pharmacological treatment to evaluate the pure response to DSR. The safety and efficacy endpoints were met, with statistical differences in favor of the DSR group. Subsequently, the Spyral HTN ON Med study included patients with difficult-to-control hypertension and BP between 140 and 170 mmHg and randomized them to DSR vs. Sham. At 36 months of follow-up, the differences in ABPM for blood pressure were: the RSD group had a reduction in SBP/DBP of −18.7/−11.9 mm Hg, while the Sham group had a reduction of −8.6/−6 mmHg. These differences were statistically significant (p = 0.0039 for SBP and p = 0.0055 for DBP), with the additional benefit of a 24-hour effect observed through ABPM for RSD compared to the Sham group. Additionally, the Sham group had a greater need for increased antihypertensive medication load than the RSD group. The DENERHTN study analyzed 101 patients with HBP, of which 48 were assigned to the RSD + randomized sequence antihypertensive escalation (RSAHT) group versus the RSAHT group alone. The conclusion was that the RSD group at six months reduced daytime SBP on ABPM by −15.8 mmHg vs. −9.9 mmHg in the SSAHT group alone, a baseline-adjusted difference of −5.9 mm Hg (−11.3 to −0.5; p = 0.0329). The RADIANCE-HTN TRIO study, which utilized ultrasound technology, enrolled 136 patients with hypertension, randomizing 69 to receive RSD and 67 to receive Sham treatment. In this study, RSD reduced SBP by 4.5 mmHg more on ABPM than the control group within six months, representing a statistically significant difference. It is worth noting that the primary safety endpoints have been fully met in all previous studies.[27]

3. RSD is approved as an adjunct to pharmacological therapy to help manage patients with heart rhythm disorders (HR). There is no position from any Latin American society regarding the treatment or the algorithm to follow for determining candidates for it. The proposal is to develop an algorithm for selecting candidate patients by guidelines and algorithms for patients with RH. It is suggested that, if the position is favorable regarding RSD, the steps to follow are to determine:

    a. Which patient should be considered HR?
    b. Objectively and practically rule out pseudo-resistance.
    c. Establish ABPM as a fundamental part of the HR study algorithm.
    d. Prioritize those patients at higher cardiovascular risk, who are most susceptible to adverse events and in whom BP control has an even greater benefit (the fundamental objective of MACAREHNA).
    e. Establish a practical algorithm to rule out secondary hypertension.
    f. Emphasize avoiding therapeutic inertia.
    g. Recommend the establishment of an expert group to determine therapeutic options and consider the patient's decision.
    h. Suggest appropriate pathways for a patient to undergo a safe and effective procedure performed by experienced operators.

4. RSD is a minimally invasive treatment that is safe and effective in significantly reducing SBP and DBP in patients with RH, in conjunction with drug treatment. Its durability, as evidenced by at least 3 years of follow-up, has been proven, and it offers a 24-hour effect. This therapy should be regulated to establish its proper use based on scientific evidence and prevent its abuse.

How would digital health be useful in MACARENHA?

Cardiovascular diseases are the leading cause of death in Mexico and worldwide. Despite significant advances in pharmacological treatments and invasive procedures for the management of acute myocardial infarction, it remains the leading cause of mortality globally. Furthermore, an increase in the prevalence of other chronic diseases such as heart failure, atrial fibrillation, aortic valve stenosis,

chronic kidney disease, fatty liver disease, and cognitive impairment, among others, has been observed.[28]

1. High blood pressure is frequently associated with multiple cardiometabolic risk factors, such as obesity, diabetes, and dyslipidemia. Together, these factors contribute to multi-organ damage, affecting vital organs such as the heart, brain, liver, and kidneys. The high prevalence of these risk factors, combined with the low control rates observed in most countries, underscores the urgent need to adopt innovative strategies to address this issue. In this context, digital health, new technologies, and artificial intelligence are emerging as key tools to optimize both the diagnosis and comprehensive management of these conditions.
2. To address the problem of controlling high blood pressure and cardiometabolic risk factors in Mexico and Latin America, it is crucial to consider the unique characteristics of the region, including unequal access to health services, the high prevalence of obesity and diabetes, and economic constraints. Specific and tailored solutions are proposed below.
3. Strengthening primary care through the use of digital technologies for mass training, employing a multidisciplinary approach that involves health personnel (physicians, nurses, nutritionists, social workers, psychologists, etc.) to enhance primary prevention, detection, and comprehensive management of hypertension and associated cardiometabolic risk factors via standardized protocols.
4. Promoting digital health through the use of electronic medical records, mobile applications, voice assistants, and portable electronic devices, such as digital sphygmomanometers, glucometers, digital scales, and rhythm strip electrocardiographs, considering indigenous languages and different literacy levels. Train healthcare personnel and patients in the use of digital tools and artificial intelligence to enhance their care and treatment.[28]
5. Education and prevention campaigns: highlight and promote a healthy lifestyle from childhood, focusing on proper nutrition and physical activity. Implement educational programs in schools and textbooks, and increase the use of mass media, including social media and digital platforms, to enhance knowledge and understanding.[28]
6. Promote public policies: health regulations on sugary drinks, ultra-processed foods, and easy labeling. Promote recreational spaces that promote physical activity, such as parks and bike paths.
7. Encourage the use of artificial intelligence and big data: Enhance traditional risk prediction and stratification systems, and implement regional databases, such as the RIHTA (Registro de Hipertensión Arterial), to inform clinical and public health decisions. Develop pharmacogenomics, personalized medicine, and AI-based therapies.
8. Increase international collaboration: A collaborative approach is required among governments, health institutions, academia, industry, and civil society. Furthermore, it is essential to adapt these approaches to local specificities within Mexico and Latin America, prioritizing equity and sustainability.
9. The use of digital health, new information technologies, wearable devices, and artificial intelligence has not only proven to be key tools for improving patient education but also has the potential to significantly increase the diagnosis, monitoring, and follow-up rates of patients with multiple cardiometabolic risk factors and multisystem organ damage. Within the framework of the MACARENHA Connection, these emerging technologies promise to optimize care and clinical outcomes comprehensively *(Figure 3)*.

What would be the preventive approach? MACAREHNA's vision

Primordial Prevention

1. Focused on avoiding the onset of CVRFs before they develop.[29]
   Involves changes in public policies, improvements in the context at the macro

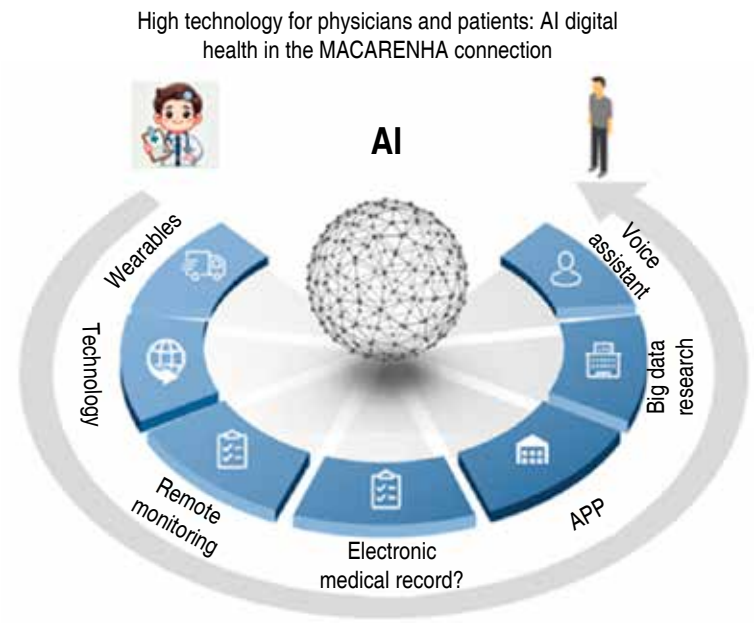

Figure 3: Artificial intelligence in the context of MACARENHA.
AI = artificial intelligence.
MACARENHA = Metabolic-Adipose-Cardio-Arterial-Renal-Entero-Hepatic-Neurological-behavior in Hypertension.

level, encompassing the physical, urban, economic, environmental, and social environments, as well as changes in individual behavior.

a. For example, programs that promote physical activity and healthy eating from childhood.
b. Promotion of Healthy Lifestyles: Promoting regular physical activity and a balanced diet are cornerstones of this initiative.
c. Educational campaigns that increase awareness about CVRFs.
d. Access to Preventive Health Care: Facilitate universal access to health services that promote prevention, periodic health checkups, and campaigns for correct blood pressure measurement.

Primary prevention: intervention in individuals already with CVRF[30]

1. For GREHTA, it is essential to focus on people who already have high blood pressure (disease/risk factor).
2. The goal is to prevent progression to established cardiovascular disease.
3. Key strategies include early detection and diagnosis, appropriate pharmacological management of hypertension and risk factors such as obesity, DM, dyslipidemia, etc.
4. The recently published study «Overweight, Obesity and Age: The Main Determinants of Cardiovascular Risk Aggregation in the Current Mexican Population: The FRIMEX III Study», by Eduardo Meaney et al., establishes that in developed countries, hypertension behaves according to the so-called «law of thirds», in developing countries it behaves like the well-known «law of halves», and that in Mexico, control is only 8%, which is alarming.
   Secondary prevention, according to the WHO, is intended for the early detection of incipient disease (before clinical manifestations appear). It means searching for diseases as early as possible in «apparently healthy» subjects.
5. And the WHO continues: «It includes actions resulting from early diagnosis and timely treatment, particularly for arterial hypertension in its early stages, by conducting periodic check-ups and monitoring the patient, monitoring its progress, and detecting any possible sequelae (target organ damage) promptly. Secondary prevention refers to the strategies and measures implemented to control and manage hypertension in individuals who have already been diagnosed with this condition, to prevent complications and improve quality of life».
6. An unquestionable aspect, starting with primary prevention and predominantly in secondary prevention, is the importance of follow-up in secondary prevention and the suspected diagnosis of hypertension-mediated organ damage (HMOD). Accordingly, in this MACAREHNA connection, we highlight the metabolic involvement (fasting blood glucose, HbA1c, weight control, CRP, thyroid hormone), as well as the effects on the heart, blood vessels, brain, kidney, and liver, among others, proposing basic studies to investigate these effects. Several international societies have already emphasized this comprehensive

approach to hypertension management in different ways.[31]

Tertiary Prevention

1. According to the WHO, it refers to actions related to the complete recovery of the clinically manifest disease, through correct diagnosis and treatment, and physical, psychological, and social rehabilitation in cases of disability or sequelae, thus seeking to reduce them *(Figure 4)*.[32,33]

What other ways are there to prevent cardiovascular risk?

Role of influenza vaccination[34-37]

In Mexico, for the last six years (2016-2023), cardiovascular disease has been the leading cause of death, surpassed only by COVID-19 infection in 2022. Other respiratory illnesses, such as seasonal influenza and pneumonia, have also been among the top 10 causes of death in Mexico in recent years, according to the National Institute of Geography and Statistics (INEGI).

Key Messages

1. All patients with high blood pressure must receive an annual influenza vaccination.
2. Include all adults aged 50 years and above in the universal vaccination program with standard doses, regardless of comorbidities.
3. The use of a high-dose differentiated influenza vaccine is recommended for adults over 60 years of age (it will be available in Mexico shortly).
4. According to the latest report from the World Health Organization (WHO) (Global Respiratory Virus Activity Weekly Update No. 503), the activity of seasonal influenza viruses and SARS-CoV-2 remains at inter-epidemic levels in Mexico, even elevated in other countries around the world.
5. According to the WHO, there are estimated to be over 3.5 million cases of seasonal influenza each year, resulting in up to 650,000 deaths annually.
6. We know that diseases such as influenza, pneumonia, and COVID-19 are more than just respiratory illnesses, as they also cause uncontrolled cardiovascular risk factors, including diabetes and high blood pressure, in adults. These infections are directly related to an increase in neurological, renal, and cardiovascular complications such as cerebrovascular events (CVA), encephalopathy, acute kidney failure, acute myocardial infarction (AMI), heart failure, myocarditis, and venous thromboembolism.
7. The mechanisms by which these infections increase the risk in these patients derive from effects generated by the acute respiratory disease, such as hypoxemia (with increased myocardial oxygen demand), increased inflammatory cytokines that cause hypercoagulability, and increased adrenergic activity, which can lead to the rupture of an atheromatous plaque, causing atherothrombosis at the coronary, cerebral, or peripheral levels. In addition, the viruses can lodge directly at the vascular, myocardial, or cerebral levels, causing myocarditis or encephalitis. Undoubtedly, the impacts of vaccination against influenza viruses.
8. COVID-19 and pneumococcus have been beneficial in the global and Mexican population with cardiovascular risk factors. For example, it is estimated that influenza vaccination in older adults reduces cardiovascular death and death from all causes by up to 41%.
9. According to the vaccination guidelines for the 2024-25 winter season in Mexico, the

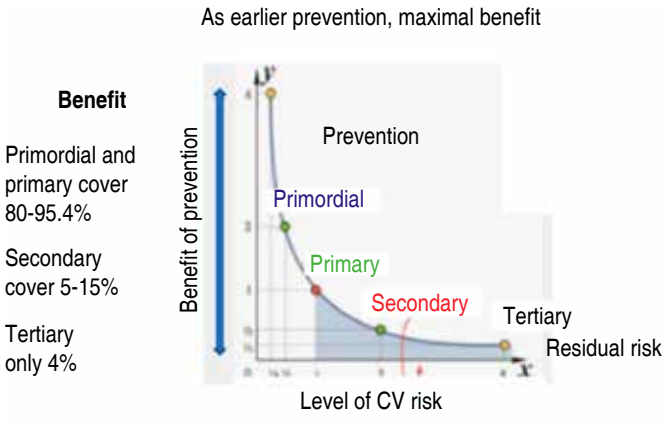

Figure 4: Comprehensive cardiovascular prevention.
CV = cardiovascular.

target population for the pneumococcal vaccine is all adults over 60 years of age, while for influenza, the target population is children from six months to five years of age, adults over 60 years of age, as well as at-risk populations such as pregnant women, healthcare personnel, children, and adults in general with comorbidities such as diabetes, morbid obesity, chronic lung diseases, kidney failure, immunocompromised individuals, and cardiovascular disease. These guidelines also recommend vaccination for COVID-19 in this same group of patients, except for children under five years of age and adults with acquired or congenital chronic cardiovascular diseases that require prolonged use of salicylates. It is not clear whether all patients with essential hypertension are considered comorbid or high-risk patients. Another aspect to consider is that ages with high influenza mortality rates, such as those between 50 and 60 years of age, are not eligible for influenza vaccination in Mexico.

10. All adults over 60 years of age must achieve and maintain 95% pneumococcal vaccination coverage.
11. Vaccination against influenza and other infections, such as COVID-19 and pneumococcus, in patients with hypertension and the MACARENHA connection is essential for preventing complications and reducing morbidity and mortality in these patients in Mexico.

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Correspondence:
Martin Rosas Peralta
Grupo de Expertos en
Hipertensión Arterial. México.
E-mail: martin99.rosas99@gmail.com