ISSN 2683-2828

Cardiovascular and Metabolic Science

Continuation of the Revista Mexicana de Cardiología

2022

High blood pressure: the ambushed serial raider

VOLUME 33, SUPPLEMENT 3
JULY-SEPTEMBER 2022

Indexed under CUIDEN data base (Granada España)
Complete version on internet (indexed and compiled):
Medigraphic, Literatura Biomédica: www.medigraphic.org.mx

PREVENIR ES NUESTRA META

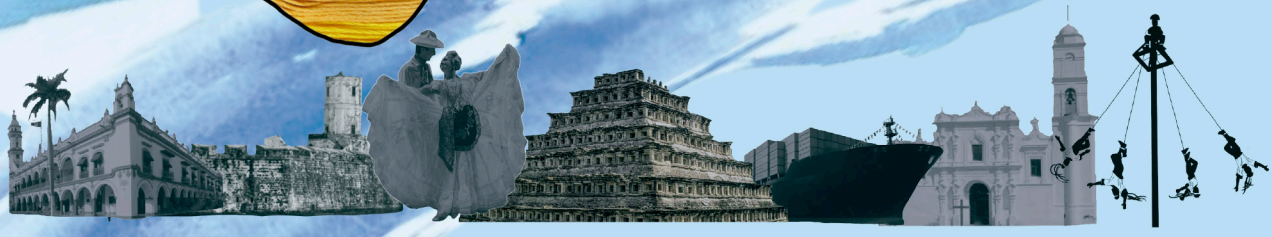
XX Congreso Nacional de Cardiología

SAVE THE DATE

9, 10, 11 y 12 Noviembre 2022

Veracruz

Cardiología Integral Multidisciplinaria



Salones presenciales

Salones virtuales

Desayunos Científicos

Talleres

Simposios

Conferencias Magistrales, Máster

Sesiones del Canal de YouTube para el público en general

Evento dirigido a:
Especialistas en: Cardiología, Medicina interna, Endocrinología, Medicina familiar y general, Enfermería, Fisioterapeutas, Lic. en Nutrición, Estudiantes, Residentes y áreas afines.

Avales en trámite: UNAM / CMC / CONAMEGE / CMIM

Inscripciones: www.ancam.org.mx 55 5636 8002 y 8003

ANCAM México @ancammx @ANCAM_MEXICO @ANCAM_MEXICO2020

Cardiovascular and Metabolic Science

Continuation of the Revista Mexicana de Cardiología

Official communication organ of:

- Asociación Nacional de Cardiólogos de México
- Sociedad de Cardiología Intervencionista de México
- Asociación Nacional de Cardiólogos del Centro Médico La Raza
- Asociación Nacional de Cardiólogos al Servicio de los Trabajadores del Estado
- Asociación Mexicana para la Prevención de la Aterosclerosis y sus Complicaciones
- Alianza por un Corazón Saludable
- Sociedad Mexicana de Cardiología Preventiva
- Sociedad Mexicana de Electrofisiología y Estimulación Cardiaca
- Asociación Médica del Hospital de Cardiología Centro Médico Nacional Siglo XXI

ASOCIACION NACIONAL DE CARDIOLOGOS DE MEXICO

PREVENIR ES NUESTRA META

Asociación Nacional de Cardiólogos de México

Board of Directors 2020-2022

President: Dra. Gabriela Borrayo Sánchez
Vice President: Dr. Arturo Guerra López
Secretary: Dr. Rodolfo Herrera Franco
Assistant Secretary and Social Communication: Dr. Ernesto Díaz Domínguez
Treasure: Dra. Ana Elena Ancona Vadillo
Scientific Committee: Dr. Eduardo Almeida Gutiérrez

Founder President: Dr. Guillermo González Ramírez

SOCiME
Sociedad de Cardiología Intervencionista de México

Board of Directors 2022-2023

President: Dr. Andrés García Rincón
Secretary: Dr. Jorge Emiliano Carrillo Guevara
Assistant Secretary: Dr. Efraín Arizmendi
Treasurers: Dr. Francisco García García and Dr. Narciso de la Torre Jiménez

ANCCMR

Asociación Nacional de Cardiólogos del Centro Médico La Raza

Board of Directors 2022-2023

President: Dr. Carlos Obeth Ferreyra Solorio
Secretary: Dr. Eliseo García Rangel
Treasurer: Dr. Narciso de la Torre Jiménez
Founder President: Dr. Marco Antonio Ramos Corrales

ANCISSSTE

Board of Directors 2021-2023

President: Dr. José Alfredo Merino Rajme
Secretary: Dr. Jorge Antonio Lara Vargas
Treasurer: Dra. Luz Dinora Sandoval Castillo
Assistant Secretary: Dr. Ricardo Gutiérrez Leal

Cardiovascular and Metabolic Science (continuation of Revista Mexicana de Cardiología), is the official organ of following medical societies and associations: Asociación Nacional de Cardiólogos de México (ANCAM), Sociedad de Cardiología Intervencionista de México (SOCIME), Asociación Nacional de Cardiólogos del Centro Médico La Raza (ANCCMR), Asociación Nacional de Cardiólogos al Servicio de los Trabajadores del Estado (ANCISSSTE), Asociación Mexicana para la Prevención de la Aterosclerosis y sus Complicaciones (AMPAC), Sociedad Mexicana de Electrofisiología y Estimulación Cardiaca (SOMEEC), Asociación Médica del Hospital de Cardiología Centro Médico Nacional Siglo XXI A.C., Sociedad Mexicana de Cardiología Preventiva, and Alianza por un Corazón Saludable. Address: Magdalena 135, Col. del Valle Norte, Benito Juárez, CP 03103. revistamexicanadecardiologia@medigraphic.com, revmexcardiol@gmail.com.
Cardiovascular and Metabolic Science publishes quarterly, one volume per year. Copyright reservation 04-2019-022717130200-102. Freely distributed with title Certificate No. 3575 and Content Certificate No. 3875. ISSN: 2683-2828. Print run: 2,000 copies. Postage paid, periodic publication permit authorized by SEPOMEX, number PP09-1877. Characteristics 220441116. The partial or total reproduction of the content of this number can be done with prior authorization of the publisher and mention of the source. **The concepts published in the articles are the entire responsibility of the authors. Cardiovascular and Metabolic Science** is registered in the following indexes: Medigraphic, Literatura Biomédica, Sistema Regional de Información en Línea para Revistas Científicas de América Latina, El Caribe, España y Portugal (LATINDEX, by its Spanish abbreviation), Literatura Latinoamericana en Ciencias de la Salud (LILACS), Periódica-UNAM, Biblioteca Virtual en Salud, Brasil (BVS), and University of Salamanca Library, Spain.
Electronic address: **www.medigraphic.com/cms/** E-mail addresses: **revmexcardiol@gmail.com**
Editorial coordination: Dr. José Rosales Jiménez and Marco Antonio Espinoza Lorenzana. Editorial design: Diego Lozano Saavedra.
Art, design, typesetting, pre-press and printing by **Graphimedic, SA de CV.** Tel: 55 8589-8527 to 32. E-mail: emyc@medigraphic.com. ***Printed in Mexico.***

CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

CONTENTS / CONTENIDO

High blood pressure: the ambushed raider

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105180

Preamble

Preámbulo

Guest editors: José Manuel Enciso-Muñoz, MD,* Enrique Díaz-y-Díaz, MD,‡ Héctor Galván-Oseguera, MD,§ Silvia Palomo-Piñón, MD, PhD¶

The following text is not intended to be a consensus document, nor a clinical-therapeutic guide, but rather a set of reflections and positions on specific problems and concepts of high blood pressure (HBP), one of the clinical entities with the greatest impact on the development of lethal or disabling cardiovascular complications. The members of GREHTA (Spanish acronym of ***GR****upo de* ***E****xpertos en* ***H****iper****T****ensión* ***A****rterial de México*, Mexican Group of Experts on Arterial Hypertension) are committed to participate decisively in the plural fight against cardiovascular diseases, the leading causes of mortality in our population, hand in hand and with the support of the sister cardiovascular societies, headed by ANCAM, from whose current president, Dra. Gabriela Borrayo, we have received invaluable help and solidarity. Doubtlessly, HBP is a major risk factor for many catastrophic, even lethal outcomes. Science and technology are moving so fast in our times, that concepts, paradigms, techniques, and therapeutic measures evolve so rapidly that regular revisions and updates are necessary to provide medical service providers with a broad and solid conceptual platform.

This was the purpose of having asked several distinguished members of our group to write these specific texts on interesting topics, some of them controversial, of the HBP.

We thank the authors of the documents for their commitment and the time dedicated to the writing of these texts. As freedom of speech and thinking are pillars of civilized life, the guest editors respected the ideas of the authors, who are entirely responsible for the concepts expressed freely in their texts. We also want to recognize the editorial freedom that the Editorial Committee and its main Editors gave us in the elaboration of this text. And at the end, but no at last, we would like to express our gratitude to our publishing house Medigraphic and its personnel, for their professionalism and patience.

Correspondence:
José Manuel Enciso-Muñoz, MD
E-mail: jmenciso2@hotmail.com

* Presidente AMPAC, Miembro GREHTA.
‡ Jefe de la División de Cardiología del Hospital de Cardiología CMNSXXI, Miembro GREHTA.
§ Jefe de hospitalización del 2do. piso, Hospital de Cardiología CMNSXXI, Miembro GREHTA.
¶ Presidenta GREHTA.

How to cite: Enciso-Muñoz JM, Díaz-y-Díaz E, Galván-Oseguera H, Palomo-Piñón S. Preamble. Cardiovasc Metab Sci. 2022; 33 (s3): s172. https://dx.doi.org/10.35366/105180

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105181

High blood pressure: the ambushed raider. Introductory remarks

La hipertensión: el asaltante emboscado. Observaciones introductorias

Eduardo Meaney, MD, PhD*

Everything changed for humanity when nomad tribal life, based on hunting and gathering activities, was abandoned and food was acquired through agriculture and livestock once human communities settled in villages and cities and gave rise to civilized life. A dialectical contradiction arose when our genetic inheritance and lifestyle imposed by civilization clashed abruptly. From this phenomenon came out the so-called «diseases of civilization»,[1] infrequent ailments during the Stone Age, that in modern times are the most crucial factors of death and disability around the world.[2]

Systemic high blood pressure (HBP, also known with the somehow physically inappropriate name of «systemic arterial hypertension» or simply «hypertension», terms that despite any critical view are deeply rooted in the medical and popular imaginary and language) is doubtlessly a very clear example of these maladies, which are the result of the interaction between the expression of certain genes and environment. HBP is beyond any doubt the most frequent cardiovascular risk factor.[2] Frequently associated with other major risk factors like dyslipidemia, tobacco consumption and diabetes, HBP is behind the appearance of acute and chronic vascular syndromes (in the brain, coronary bed, and peripheral systemic arteries), left ventricular hypertrophy, systolic and diastolic ventricular dysfunction, overt heart failure, valvular heart disease, kidney damage, arrythmias (as atrial fibrillation), some eye diseases, and vascular dementia, among others.[2,3]

This text, focused on every important aspect of HBP, has been written by a pleiad of talented and diligent physicians for whom HBP is one of the most relevant cardiovascular problems, given its clinical, epidemiological, and socioeconomic importance. Without putting aside scientific rigor and depth, the chapters of this text were written to assist the practice of those medical colleagues who, day after day, conduct the task of discovering and treating HBP, on the front line of medical care.

Frequently, not only in Mexico but worldwide, remarkable HBP pathophysiological, structural, clinical, and therapeutic facts are ignored or downplayed by many health care providers. The result has been a failure in early diagnosis and inadequate treatment and control rates, with ominous clinical consequences. We have repeatedly said that the path of prevention necessarily passes through awareness and information. GRETHA is aware that only when the joint efforts of our group and sister medical societies and academies, the majority of clinical practitioners, the state health and social security institutions, the pharmaceutical and food industries, the citizen organizations, and the entire civil society be able to generate and consolidate a powerful alliance and unite their efforts in just a bundle of wills and actions, the flagellum of HBP and other cardiovascular risk factors will be contained, diminishing their serious complications.

* Professor and Researcher, Superior School of Medicine, National Polytechnic Institute. Mexico City, Member of GREHTA.

How to cite: Meaney E. High blood pressure: the ambushed raider. Introductory remarks. Cardiovasc Metab Sci. 2022; 33 (s3): s173-s178. https://dx.doi.org/10.35366/105181

What are the reasons for considering HBP one of the most important disease factors? To begin with, HBP is remarkably prevalent in modern communities.[4] Secondly, as it was stated above, HBP is armed with a set of mechanisms of vascular damage,[5] leading to lethal or incapacitating parenchymal lesions in vital organs. HBP prevalence increases with age, or it can even appear *de novo*, in elderly subjects who were not hypertensive during most of their adulthood. In Mexico, one out of two elders[6] is hypertensive, and a vast proportion of them show the modality of isolated or predominant systolic hypertension. It has been solidly established that as people of modern societies age fatally occur some structural changes in the elastic arteries (atherosclerosis, calcification, and extracellular matrix dystrophy), which are responsible of a faulty arterial distensibility.[7-9] These changes lead to the generation of early reflection waves that augment the peak of systolic pressure, rising also differential or pulse pressure. The increase of cyclic hemodynamic stress is responsible for left ventricular and vascular hypertrophy, the fracture of vulnerable atherosclerotic plaques, and the rupture of the Charcot-Bouchard brain microaneurysms. Age itself is not the cause of the increase of BP in elderly subjects. Different studies on tribal people that still live under the norms of hunters o fishers-gatherers communities show that HBP seldom occur in them, including the elders.[10] On the contrary, it seems that is the unhealthy lifestyle of civilized societies the responsible of the occurrence of this and other «civilization diseases».

Paradoxically, while blood pressure (BP) level and HBP prevalence have diminished in recent decades in most of the western and Asia Pacific highly industrialized nations, both parameters have risen in East, South and Southeast Asia, Oceania, sub-Saharan Africa, and Central and Eastern Europe countries.[4,11] In general, prevalence reduction has been moderate in most of industrialized nations, but in a great proportion of low and middle-income countries it has increased or remained unchanged.[12] Conflicting conclusions about the BP levels and HBP prevalence in the Caribbean and Latin America nations, including Mexico, arise from the paucity of reliable reports, or uncertainty of data collected from epidemiological surveys.[13] For example, in our country, several governmental probabilistic national surveys show striking differences of HBP prevalence in Mexicans aged 20 years or more, since the beginning of this century. The ENSA 2000 (National Health Survey in the year 2000),[14] as the 2006[15] and 2012[16] versions of the ENSANUTs (National Health and Nutrition Survey) estimated a very consistent HBP prevalence of 30.7%, 30.8%, and 30.0%, respectively. But the so-called ENSANUT MC (National Health and Nutrition Survey «Halfway»)[17] carried out in the middle of the previous federal administration found (with a different measure methodology), a prevalence of just 25.5%. ENSANUT 2018-2019[18] only reported the percentage of respondents who knew they had HBP (about 18.4%), datum that alone lacks certainty and credibility. Finally, the so-called ENSANUT 2018 100K,[19] in population who live in towns under 100,000 inhabitants, found, using the cutoff values of 140/90 mmHg (ciphers accepted by NOM-030-SSA2-2009,[20] the national norm on hypertension, of mandatory observance in Mexico) a total prevalence of 31.6%. But when they used the newer cutoffs of 130/80 mmHg, proposed by the American Heart Association/American College of Cardiology and other associations[21] (that have not been accepted by cardiologic and hypertension societies of everywhere,[22,23] including, some medical organizations of the United States, stating certain methodological shortcomings and conflict of interest[24]), a stratospheric prevalence rose to 49.2%. The worst of all is that the same group of epidemiologists, using identical data from ENSANUT 2006, produced documents showing different results. The official version of that survey, inform a combined gender prevalence of 30.0%, while in a paper published in 2010, the reported prevalence was estimated in 43.2%.[25]

According with the best designed and executed ENSANUTs, some non-governmental, academic studies, with huge but non-probabilistic samples have shown that the prevalence of HBP in adult Mexicans goes from 25 to 35%, which has not changed in the last 20 years.[6,26,27] As other cardiovascular risk

factors, HBP has a mosaic-type geographical distribution along our territory, with a northern-southern gradient, according to which, some northern federative states have the highest prevalence rates of HBP, in contrast with some of the southernmost states that show the lowest values. These differences probably signal the effect on BP of the westernized lifestyle adopted by the urbanized acculturated population living in the more developed and industrialized federative states *(Figure 1)*.[15]

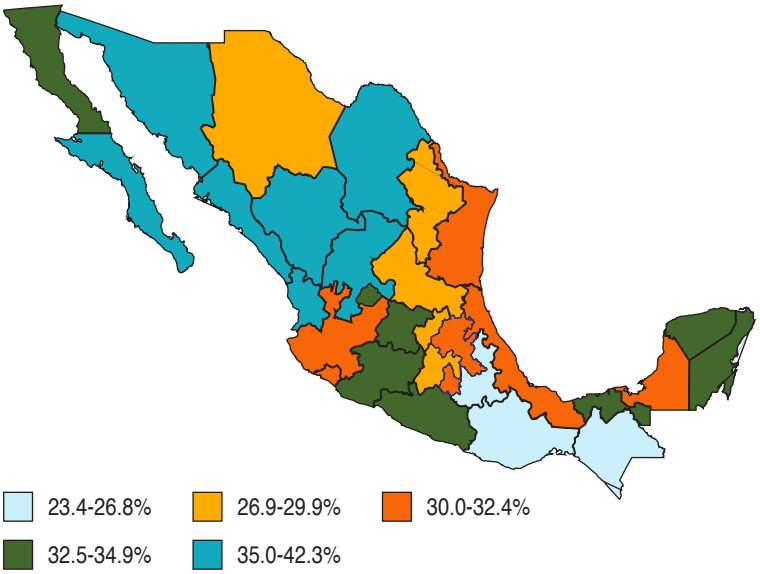


Figure 1: Geographical distribution of the prevalence of HBP in Mexico. Data from ENSANUT 2006.[15]

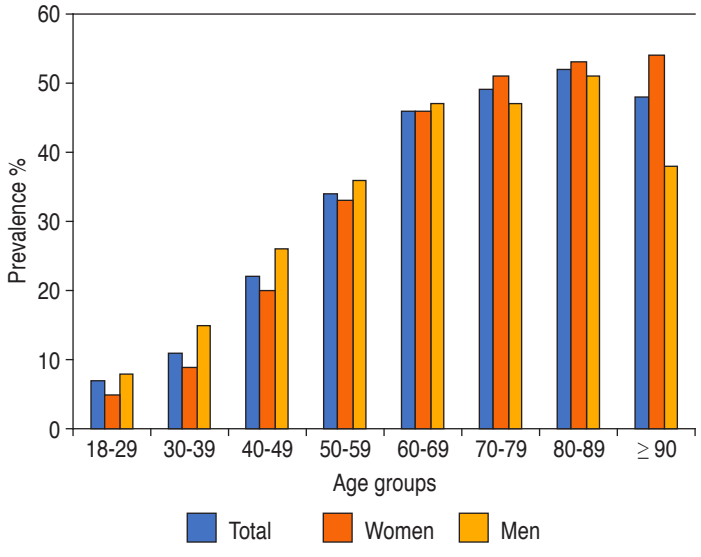


Figure 2: Prevalence of HBP in Mexico, according with age and gender. Modified of Meaney E et al.[6]

As it is well known, prevalence of HBP increases with age. Data from the FRIMEX *(Figure 2)* study[6] show that while prevalence is very low at young ages, it increases every decade, from 8-10% in the youngest, to 34% in the age group of 50-59 years, to a maximum of 52% in octogenarians. In nonagenarians, prevalence falls to less than 50%, maybe because, hypertensive men, are already dead. In those orders of ideas, prevalence is greater in men than in women up to the age of 59 years. Both genders have the same prevalence in the 60-69 years group, but from the age of 70 years women are a little more hypertensive than men, probably because hypertensive men die more than women.

In Mexico, overweight or obesity (O/O) affects more than 70% of our adult population.[26,28] Therefore, HBP is associated in a vast proportion of patients to O/O and more than 50% of them fill the criteria of the so-called metabolic syndrome,[25] whose best denomination would be «dysmetabolic overweight or obesity».

Consequently, in a great proportion of our overweighed or obese hypertensive patients underlies the insulin resistance syndrome, with all its conglomerated damaging factors, as hyperinsulinism, inflammation, and atherogenic dyslipidemia (the association of hypertriglyceridemia, hypoalphalipoproteinemia [low HDL cholesterol], and an increase of small and dense LDL particles).[29] There is evidence signaling that this type of dyslipidemia together with HBP, are the most important causes of myocardial infarction in our society.[30]

The relationship between HBP and insulin resistance in a wide proportion of Mexican hypertensives requires a particular management of the BP disorder in our population. Those antihypertensive drugs that increase insulin resistance, such as high-dose of thiazide diuretics or poorly selective β-blockers, are not recommended as first-line drugs. Contrariwise, as HBP in patients with O/O is commonly associated with an overexpression of the renin-

Table 1: Awareness, treatment, and control in Mexican hypertensives.

Study	Prevalence %	Awareness %	Treated %	Control in treated %	Total control %
ENSA 2000	30.1	39	51	21	5
Lindavista	32.0	68	84	38	20
FRIMEX	26.5	49	74	36	13

Data from references 35 (recalculated), 6 and 26.

angiotensin-aldosterone system (RAAS) and an overactivity of the noradrenergic system, the modulators of the axis (ACE inhibitors and antagonists of the At1 receptors) are highly recommended, as well as third-generation vasodilator β-blockers. Even most important is the recognition that a main mechanism of HBP in obesity is not insulin resistance but the renal compression by extra and intra renal fat that secondarily activates the RAAS.[31] For that reason, the treatment of obesity is mandatory in this kind of patients.

A marker of the quality of medical knowledge and care, as well as the proof of the success or not of preventive public policies in a particular community or nation, is the so-called «law of the halves», coined in the 70s of the past century,[32] which describes the fact that half of the hypertensive patients are not aware that suffers the disease, while half of those who are aware indeed are not treated, and finally, that half of those who are treated are not well-controlled. The consequences are a high rate of morbidity and mortality of HBP. In many countries, the improvement of medical care and social awareness have changed this old *dixit*, to the point that a new paradigm has come out and it is expressed in the so-called «the law of the three-quarters»,[33] according to which, 75% of hypertensive patients should be aware of their ailment, 75% of them would be treated, and other 75% would be controlled. Unfortunately, these goals are still far from being achieved. As HBP is a «silent» (asymptomatic) disease, healthcare providers must diagnose it proactively by the simple rutinary measurement of BP, in every medical examination. Frequent mass screening programs conducted in public spaces, building offices, and factories, also would be helpful, along with sustained campaigns of medical and social education. The low rates of treatment and good control are more complex phenomena, whose explanation is beyond the scope of this introduction. In what situation is Mexico regarding the law of halves? Again, ENSANUTs data are absent or misleading. *Table 1* concentrate estimations done on the rate of awareness, treatment, and control of HBP in several studies and surveys.

The data from ENSANUT 2012 and ENSANUT 2019 K100 have been left out for having clear inconsistencies between the text and some of the tables, and the latter also because it uses estimated data with the new AHA/ACC classification, which contravenes the current official Mexican hypertension norm, of obligatory use in the country.[34,35]

The most important marker in the «law of the halves» estimation is the percentage of the total mass of hypertensive subjects that have controlled BP (< 140/90 mmHg). The uncontrolled segment encompasses those patients unaware of their disease, plus those who knowing it are not treated, and those who despite the treatment are not controlled. The data exposed in *Table 1* point to the incontrovertible fact that in Mexico HBP is not well diagnosed or treated, for countless reasons, the analysis of which is beyond the limits of this text. Even in the Lindavista study cohort, composed by middle-class urban, educated, inhabitants of Mexico City, covered by a somehow generous social security system, just one out of five hypertensive patients

had controlled BP ciphers. The country has not yet reached even the very modest levels originally described by the «law of halves». The modification of these unacceptable low rates of awareness, treatment, and control is a task that the Mexican State, but also the medical community, owe to our people.

REFERENCES

1. Murphy HBM. Diseases of civilization? Psychol Med. 1984; 14: 487-449.
2. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. Hypertension. 2020; 75: 285-292.
3. Fraser-Bell S, Symes R, Vaze A. Hypertensive eye disease: a review. Review Clin Exp Ophthalmol. 2017; 45: 45-53.
4. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nat Rev Cardiol. 2021; 18: 785-802.
5. Touyz RM. Molecular and cellular mechanisms in vascular injury in hypertension: role of angiotensin II. Curr Opin Nephrol Hypertens. 2005; 14 (2): 125-131.
6. Meaney E, Lara-Esqueda A, Ceballos-Reyes GM, Asbun J, Vela A, Martínez-Marroquín Y et al. Cardiovascular risk factors in the urban Mexican population: the FRIMEX study. Public Health. 2007; 121: 378-384.
7. Meaney E, Soltero E, Samaniego V, Alva F, Moguel R, Vela A et al. Vascular dynamics in isolated systolic arterial hypertension. Clin Curdiol. 1995; 18: 721-725.
8. Pinto E. Blood pressure and ageing. Postgrad Med J. 2007; 83: 109-114.
9. Laurent S, Boutouyrie P. Arterial stiffness and hypertension in the elderly. Front Cardiovasc Med. 2020; 7: 544302.
10. Gurven M, Blackwell AD, Rodríguez DE, Stieglitz J, Kaplan H. Does blood pressure inevitably rise with age? Longitudinal evidence among forager-horticulturalists. Hypertension. 2012; 60: 25-33.
11. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet. 2017; 389 (10064): 37-55.
12. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020; 16: 223-237.
13. Ruilope LM, Chagas AC, Brandão AA, Gómez-Berroterán R, Alcalá JJ, Paris JV et al. Hypertension in Latin America: Current perspectives on trends and characteristics. Hipertens Riesgo Vasc. 2017; 34 (1): 50-56.
14. Olaiz G, Rojas R, Barquera S, Shamah T, Aguilar C, Cravioto P et al. Encuesta Nacional de Salud 2000. Tomo 2. La salud de los adultos. Cuernavaca, Morelos, México: Instituto Nacional de Salud Pública; 2003.
15. Olaiz-Fernández G, Rivera-Dommarco J, Shamah-Levy T, Rojas R, Villalpando-Hernández S, Hernández-Avila M et al. Encuesta Nacional de Salud y Nutrición 2006. Cuernavaca, México: Instituto Nacional de Salud Pública; 2006.
16. Gutiérrez JP, Rivera-Dommarco J, Shamah-Levy T, Villalpando-Hernández S, Franco A, Cuevas-Nasu L et al. Encuesta Nacional de Salud y Nutrición 2012. Resultados Nacionales. Cuernavaca, México: Instituto Nacional de Salud Pública; 2012.
17. Hernández Ávila M, Rivera Dommarco J, Shamah Levy T, Cuevas Nasu L, Gómez Acosta LM, Gaona Pineda EB et al. Encuesta Nacional de Salud y Nutrición - MC 2016 (ENSANUT- MC 2016). Cuernavaca, México: Instituto Nacional de Salud Pública; 2020.
18. Shamah-Levy T, Vielma-Orozco E, Heredia-Hernández O, Romero-Martínez M, Mojica-Cuevas J, Cuevas-Nasu L et al. Encuesta Nacional de Salud y Nutrición 2018-19: resultados nacionales. Cuernavaca, México: Instituto Nacional de Salud Pública; 2020.
19. Campos-Nonato I, Hernández-Barrera L, Flores-Coria A, Gómez Álvarez E, Barquera S. Prevalencia, diagnóstico y control de hipertensión arterial en adultos mexicanos en condición de vulnerabilidad. Resultados de la Ensanut 100k. Salud Publica Mex. 2019; 61: 888-897.
20. NOM-030-SSA2-2009, Para la prevención, detección, diagnóstico, tratamiento y control de la hipertensión arterial sistémica. Diario Oficial de la Federación. Lunes 31 de mayo de 2010.
21. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018; 71 (6): e13-e115.
22. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39 (33): 3021-3104.
23. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020; 75: 1334-1357.
24. Miyazaki H. Overdiagnosis or not? 2017 ACC/AHA high blood pressure clinical practice guideline: Consequences of intellectual conflict of interest. J Gen Fam Med. 2018; 19 (4): 123-126.
25. Barquera S, Campos-Nonato I, Hernández-Barrera L, Villalpando C, Rodríguez-Gilabert C, Durazo-Arvizú R et al. Hypertension in Mexican adults: results from the National Health and Nutrition Survey 2006. Salud Pública Méx. 2010; 52 (Suppl 1): S63-S71.
26. Meaney A, Ceballos-Reyes G, Gutiérrez-Salmeán G, Samaniego-Méndez V, Vela-Huerta A, Alcocer L et al. Cardiovascular risk factors in a Mexican middle-class urban population. The Lindavista Study. Baseline data. Arch Cardiol Mex. 2013; 83: 249-256.
27. Fanghanel-Salomón G, Gutiérrez-Salmeán G, Samaniego V, Meaney A, Sánchez-Reyes L, Navarrete U et al. Obesity phenotypes in urban middle-class cohorts; the PRIT-Lindavista merging evidence in México: the OPUS PRIME, study. Nutr Hosp. 2015; 32: 182-188.

28. Barquera S, Campos-Nonato I, Hernández-Barrera L, Pedroza A, Rivera-Dommarco JA. Prevalencia de obesidad en adultos mexicanos, 2000-2012. Salud Pública Méx. 2013; 55 (Suppl 2): S151-S160.
29. Grundy SM. Atherogenic dyslipidemia associated with metabolic syndrome and insulin resistance. Clin Cornerstone. 2006; 8 Suppl 1: S21-S27.
30. Estrada García T, Meaney A, López-Hernández D, Meaney E, Sánchez-Hernández O, Rodríguez Arellano E et al. Hypertension and lipid triad are the most important attributable risks for myocardial infarction in a middle class urban Mexican population. Ann Nutr Metabol. 2013; 63: 1343.
31. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res. 2015; 116: 991-1006.
32. Wilber JA, Barrow JG. Hypertension-a community problem. Am J Med. 1972; 52: 653-663.
33. Ismail IM, Nandy S, Adhikari S, Revathi TM, Gupta D, Deeptha M et al. Time to switch to 'rule of three-quarters' from 'rule of halves' in hypertension? A descriptive study from Dakshina Kannada, South India. Cureus. 2021; 13: e13142.
34. Rivera-Dommarco J, Shamah-Levy T, Barrientos-Gutiérrez T, Bautista-Arredondo S, Romero-Martínez M, Pelcastre-Villafuerte B et al. La salud de los mexicanos que habitan en localidades de menos de 100 000 habitantes. Salud Pública Méx. 2019; 61 (6): 709-715.
35. Velázquez Monroy O, Rosas Peralta M, Lara Esqueda A, Pastelín Hernández G, Fause A, Tapia Conyer R. Hipertensión arterial en México: resultados de la Encuesta Nacional de Salud (ENSA) 2000. Arch Cardio Mex. 2020; 72: 71-84.

Correspondence:
Eduardo Meaney, MD, PhD
E-mail: lalitomini1@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105182

Implementation and barriers of high blood pressure guidelines and standards

Implementación y obstáculos de las directrices y normas sobre hipertensión arterial

Arturo Guerra-López, MD*

Keywords:
High blood pressure, clinical practice guidelines, implementation, barriers.

Palabras clave:
Hipertensión arterial, guías de práctica clínica (GPC), implementación, barreras.

ABSTRACT

The rapid evolution in medical knowledge, as well as the introduction of Evidence-Based Medicine, have highlighted a need for documents which facilitate acquiring the best information for the benefit of the patient. This has led to the development of medical guidelines in practically all specialties. In the case of high blood pressure (HBP) there are several guidelines developed by diverse Cardiology Societies throughout the world, each of them with different definitions for «normal» values for blood pressure, as well as differences in both management and treatment strategies. Furthermore, guidelines are updated periodically, which increases complexity for the physician to keep up to date. Amongst the barriers which limit physician adherence to the guidelines, are the lack of interest, inadequate medical preparation, excess of information, reliability, or preferences. Physician preference may favor guidelines developed within their country of practice or internationally; however, whichever the preference may be, evidence indicates that adherence to guidelines is generally low. In this review, we recapitulate the evidence on guideline adherence and its potential causes.

RESUMEN

La rápida evolución de los conocimientos médicos, así como la introducción de la Medicina Basada en la Evidencia, han puesto de manifiesto la necesidad de disponer de documentos que faciliten la adquisición de la mejor información en beneficio del paciente. Esto ha llevado al desarrollo de guías médicas en prácticamente todas las especialidades. En el caso de la hipertensión arterial (HTA), existen varias guías desarrolladas por diversas Sociedades de Cardiología de todo el mundo, cada una de ellas con diferentes definiciones de los valores «normales» de la presión arterial, así como diferencias tanto en el manejo como en las estrategias de tratamiento. Además, las directrices se actualizan periódicamente, lo que aumenta la complejidad para que el médico se mantenga al día. Entre las barreras que limitan la adhesión del médico a las directrices, se encuentran la falta de interés, la preparación médica inadecuada, el exceso de información, la fiabilidad o las preferencias. La preferencia de los médicos puede favorecer las directrices desarrolladas dentro de su país de práctica o a nivel internacional; sin embargo, sea cual sea la preferencia, la evidencia indica que la adherencia a las directrices es generalmente baja. En esta revisión, recapitulamos la evidencia sobre la adherencia a las guías y sus posibles causas.

INTRODUCTION

Clinical Practice Guidelines (CPGs) are instruments which aim to facilitate physician practices by presenting evidence of the best scientific quality, obtained in extensive literature reviews carried out by experts in the field. Despite presenting evidence which supports the physician in making clinical decisions, guidelines are also helpful in generating health care policies, standardizing diagnosis, and treatment, particularly at the institutional level. In addition, guidelines present pooled points of view by shared by a group of experts in the field; this may help physicians to make decisions beyond their own clinical experience with more updated and comprehensive overviews. This approach may lead to decisions which are attached to the best clinical practice standards.

CPGs contribute to the distribution of the most updated medical knowledge.

* Excel Hospital. Tijuana, Baja California, México, Miembro GREHTA.

How to cite: Guerra-López A. Implementation and barriers of high blood pressure guidelines and standards. Cardiovasc Metab Sci. 2022; 33 (s3): s179-s182. https://dx.doi.org/10.35366/105182

This is relevant since information obtained primarily from textbooks, noticeably in terms of treatment or new diagnostic techniques, are not necessarily updated. CPGs play a significant role in clinical practice by presenting the most updated evidence available. Even though not all recommendations provided by CPGs are based on evidence from randomized double-blind placebo-controlled studies, CPGs also summarize information which shows aspects that may be debatable, depending on the level and quality of evidence, and very useful recommendations that discourage implementing a treatment or procedure. Another aspect of CPGs, which is not prominently mentioned in the literature, is that the correct application of a therapeutic measure taken from CPGs is the better protection against medical-legal claims. On the other hand, the origin of CPG must be carefully evaluated, the sources and references need to be analyzed, and that they present findings from all included articles with scientific accuracy.[1]

Although here is an agreement on the adequate use of CPGs, the physician usually has problems in selecting which is the most useful, given the large number of available CPGs. In Mexico, for example, there are the CENETEC Institutional Guides[2] enforced for all public sector institutions, the Official Mexican Norm project,[3] the Mexican Institute of Social Security (IMSS) algorithms,[4] just to name a few. On the other hand, there are physicians who prefer to use foreign CPGs, usually European, Latin American, American or World Health Organization (WHO) CPGs[5-8] with important differences in terms of the values to classify high blood pressure (HBP), as well as hypertension stages. These differences usually complicate the adequate selection of guidelines by physicians for clinical decision making. The large number of CPGs regarding HBP, makes it difficult for the physician to select the most useful. However, the point is not only to select the most appropriate CPG, but also to identify the precise application and monitoring of the recommendations for decision making.

The mere fulfillment of CPG recommendations is not enough. Adequate use of CPGs must cover four fundamental aspects: **development, distribution, implementation and evaluation**. There are multiple barriers to these aspects, so that a CPG is not only read but correctly applied. In an analysis performed by Dr. Uchmanowicz,[9] the author identifies possible barriers which can be conditioned not only by the physician, but also by the institutions and the patients themselves. Physicians may do their job correctly, following the best evidence; however, if the patient does not comply with what is recommended, evidence-based interventions will not work correctly. Barriers attributable to healthcare personnel include misinterpretation of CPGs and poor skills, lack of knowledge about CPGs, bad attitudes, lack of motivation, as well as not believing or not being convinced of the usefulness of a given guide.[9] Regarding the CPG itself barriers poor quality of evidence, little relevance or applicability for different health professionals, complex recommendations which are too confusing or that contain too much information. Regarding aspects of the organization, barriers are excessive workload as well as the lack of appropriate leadership who motivates to follow the CPG. Finally for the patient barriers include poor understanding of the indications, lack of interest and non-adherence to treatment. External barriers such as poor health policies, or lack of supervision can also be relevant.

However, barriers for implementation of CPGs could be overcome by developing short, user-friendly CPGs, with reduced complexity, and which use tools that facilitate clinical decision making. Additional measures include training healthcare personnel in the interpretation of CPGs, relying on the opinion of leaders and experts, and promote the dissemination of CPGs. In Mexico, Gutiérrez-Alba et al studied the behavior regarding adherence to and rejection of CPGs by Physicians in the Healthcare Sector, the analysis showed that the main barriers to following CPGs by physicians were their attitude, lack of commitment, inertia and not overcoming obstacles.[10] The main institutional barriers included the lack of incentives, insufficient time to consult and apply the CPGs, little access to CPG consultation, and lack of effective leadership. We can also

complement all this with the lack of continuing medical education programs. Differences in attitude to CPGs were observed according to age, where older physicians are the most resistant to change, while residents and younger physicians are the most eager for new information. Interestingly, evidence from other countries practically identify similar which include attitude, misinterpretation of the guidelines, lack of awareness and inertia to continue doing the things the same way by physicians.[11,12] In the Mexican context, other investigations showed that about 50% of physicians are not interested in CPGs and the most often used is the Official Mexican Norm.[13,14]

In conclusion, evidence-based medicine is essential for good clinical practice and should always be carried out with the good judgment by the physician with correct interpretation of the available information. CPGs are the link between physicians and the best scientific evidence, made by experts in the field. The fast advances of knowledge in medicine, the development of new drugs, procedures and technologies, forces CPGs to be continuously updated, which makes it more difficult for the physician to follow and stay up to date. It is precisely at this point, where medical societies, associations, and government leaderships, must do their best to promote continuing medical education, and ensure the best care for our patients for our goal: to give patients years of life with quality.

REFERENCES

1. Gómez Doblas JJ, Rodríguez-Padial L. Implementación de las guías de práctica clínica: deseo o realidad. Algoritmo de decisión. Clin Investig Arterioscler. 2021; 33 Suppl 1: 33-39. Disponible en: https://doi.org/10.1016/j.arteri.2021.03.001
2. Promoción, prevención, diagnóstico y tratamiento de la hipertensión arterial en el primer nivel de atención – CATÁLOGO MAESTRO n.d. [accessed March 29, 2022] Disponible en: https://cenetec-difusion.com/gpc-sns/?p=985
3. DOF - Diario Oficial de la Federación n.d. [accessed March 29, 2022] Disponible en: https://www.dof.gob.mx/nota_detalle.php?codigo=5480159&fecha=19/04/2017
4. Hipertensión arterial n.d. [accessed March 29, 2022] Disponible en: http://www.imss.gob.mx/salud-en-linea/hipertension-arterial
5. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39 (33): 3021-3104. doi: 10.1093/eurheartj/ehy339.
6. Task Force of the Latin American Society of Hypertension. Guidelines on the management of arterial hypertension and related comorbidities in Latin America. J Hypertens. 2017; 35 (8): 1529-1545. doi: 10.1097/HJH.0000000000001418.
7. Guideline for the pharmacological treatment of hypertension in adults [Internet]. Geneva: World Health Organization; 2021. [Accessed March 29, 2022] Available in: https://www.who.int/publications-detail-redirect/9789240033986
8. New Guidance on Blood Pressure Management in Low-Risk Adults with Stage 1 Hypertension. American College of Cardiology n.d. [Accessed March 29, 2022] Avaialable in: https://www.acc.org/latest-in-cardiology/articles/2021/06/21/13/05/http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2farticles%2f2021%2f06%2f21%2f13%2f05%2fnew-guidance-on-bp-management-in-low-risk-adults-with-stage-1-htn
9. Uchmanowicz I, Hoes A, Perk J, McKee G, Svavarsdóttir MH, Czerwinska-Jelonkiewicz K et al. Optimising implementation of European guidelines on cardiovascular disease prevention in clinical practice: what is needed? Eur J Prev Cardiol. 2020: 2047487320926776. doi: 10.1177/2047487320926776.
10. Gutiérrez-Alba G, González-Block MA, Reyes-Morales H. Desafíos en la implantación de guías de práctica clínica en instituciones públicas de México: estudio de casos múltiple. Salud pública Mex. 2015; 57 (6): 547-554.
11. Lugtenberg M, Zegers-van Schaick JM, Westert GP, Burgers JS. Why don't physicians adhere to guideline recommendations in practice? An analysis of barriers among Dutch general practitioners. Implement Sci. 2009; 4: 54. doi: 10.1186/1748-5908-4-54.
12. Francke AL, Smit MC, de Veer AJ, Mistiaen P. Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. BMC Med Inform Decis Mak. 2008; 8: 38. doi: 10.1186/1472-6947-8-38.
13. Salud S de. Comité Nacional de Guías de Práctica Clínica (CNGPC). gob.mx n.d. [Accessed March 29, 2022] Disponible en: http://www.gob.mx/salud/acciones-y-programas/comite-nacional-de-guias-de-practica-clinica-cngpc
14. Poblano-Verástegui O, Vieyra-Romero WI, Galván-García AF, Fernández-Elorriaga M, Rodríguez-Martínez AI, Saturno-Hernández PJ. Quality and compliance with Clinical Practice Guidelines of Chronic Noncommunicable Diseases in primary care. Salud Publica Mex. 2017; 59: 165-175. Disponible en: https://doi.org/10.21149/8285

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability

for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: The authors declare that they have no conflict of interests.

Correspondence:
Arturo Guerra-López, MD
E-mail: guerradr@prodigy.net.mx

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105183

Measurement of systemic arterial blood pressure

Medición de la presión arterial sistémica

Luis Alcocer Díaz-Barreiro, MD,* José Manuel Enciso-Muñoz, MD‡

Keywords:
High blood pressure, measurement, blood pressure goals.

Palabras clave:
Hipertensión arterial, medición, objetivos de presión arterial.

ABSTRACT

Blood pressure levels are the looking glass into the complex world of high blood pressure (HBP). HBP is diagnosed with blood pressure measurements, which is also helpful for classification, risk management, need for treatment initiation and adjustment and establishing management goals. In this paper, we discuss the validity and usefulness of methods to evaluate blood pressure, with particular focus on casual measurement using mercury sphygmomanometer in-office automated measurement, Ambulatory Blood Pressure Measurement, Home Measurement of Blood Pressure, and measurement of central blood pressure. We will also discuss the influence of this measurement on interpretation and the role of white coat HBP and masked HBP in influencing blood pressure measurements.

RESUMEN

Los niveles de presión arterial son el espejo del complejo mundo de la hipertensión arterial (HTA). La HTA se diagnostica con mediciones de la presión arterial, que también son útiles para la clasificación, gestión del riesgo, necesidad de iniciar y ajustar el tratamiento y el establecimiento de objetivos de gestión. En este artículo se analiza la validez y la utilidad de los métodos para evaluar la presión arterial, con especial atención a la medición casual con esfigmomanómetro de mercurio en el consultorio, la medición ambulatoria de la presión arterial, medición domiciliaria de la presión arterial y la medición de la presión arterial central. También discutiremos la influencia de esta medición en la interpretación y el papel de la HTA de bata blanca y la HTA enmascarada en la influencia de las mediciones de la presión arterial.

INTRODUCTION

Blood pressure levels are the looking glass into the complex world of high blood pressure (HBP). HBP is the most prevalent and relevant manageable risk factor for premature death in adults world-wide. Overall, HBP represents a very relevant disease burden for the development of coronary heart disease, cerebrovascular disease, peripheral arterial disease, heart failure, kidney damage, cognitive impairment, and atrial fibrillation.[1,2]

HBP is diagnosed with blood pressure measurements, which is also helpful for classification, risk management, need for treatment initiation and adjustment and establishing management goals.[3,4] Methods available for the measurement of blood pressure include:

1. Casual measurement using mercury sphygmomanometer (currently prohibited in Mexico and many countries), aneroid devices or digital electronic devices.
2. In-office automated measurement (AOBPM) with equipment in which blood pressure is measured without the presence of an operator.
3. Ambulatory blood pressure measurement (ABPM).
4. Home measurement of blood pressure (HMBP).
5. Measurement of central blood pressure, which is carried out with varied and not entirely standardized methodologies.

CASUAL OFFICE MEASUREMENT OF BLOOD PRESSURE

Conventional measurement or casual measurement of blood pressure continues to be the most used and simplest indicator, although not the most desirable or optimal one, which

* Director del Instituto Mexicano de Salud Cardiovascular, Miembro GREHTA.
‡ Presidente de la Asociación Nacional de Cardiólogos de México, Miembro GREHTA.

Ciudad de México, México.

How to cite: Díaz-Barreiro LA, Enciso-Muñoz JM. Measurement of systemic arterial blood pressure. Cardiovasc Metab Sci. 2022; 33 (s3): s183-s189. https://dx.doi.org/10.35366/105183

allows the diagnosis of HBP, treatment strategies and quality control.[5] Much of the information that exists on HBP has been obtained with this measurement method; however, more recently, the use of ambulatory blood pressure measurement has required in research studies, to improve reliability and reproducibility. Casual measurement has the advantages of being an easy technique, with various degrees of standardization, cheap and accessible; however, it is very susceptible to operator-dependent and equipment errors, introducing wide intra and inter-observer variability. Overall, casual BP measurement works like a snapshot taken to a continuous and highly variable phenomenon such as blood pressure. For this reason, it is increasingly considered that the clinical measurement of BP is a technique with little reproducibility and high variability; therefore, to perform an adequate diagnosis and control of elevated BP, other means should be considered.

The most important problem with casual BP measurement is that current guidelines establish precise cut-off points for pressure levels which are used in the diagnosis of HBP, for its classification, risk calculation, treatment initiation and goals achievement, even though the limited reproducibility of the office BP measurement is one of its main limitations. Sensitivity and specificity of casual BP measurement is < 75%, so 74 measurements would be needed to guarantee the validity of a difference of 5-7 mmHg. In contrast, the difference of 1mmHg would serve to declare someone with HBP or without it, e.g. with 139/89 would not be HBP and instead 140/90 would be, indicating precise cut-off points, with inexact measurements. That is why the most recent guidelines, although they accept that casual measurement is still the initial measurement technique, consider it valid and make precise recommendations for its measurement.

The ACC/AHA 2017, ESC/ESH 2018 guidelines and the «Scientific Statement of the AHA-2019» and the LASH 2020 Consensus agree that the confirmation of the diagnosis of HBP should be based on: 1) Repeated BP determinations at each visit at least 3 measurements separated by 1-2 min and at least in 2 visits and 2) BP measurement is obtained from the mean of the last 2 measurements, with the first being discarded, except for grade 3 HBP, in which it is enough their presence at a visit to ensure diagnosis.[3-5] The above is impractical and unrealistic. Casual blood pressure should always be measured carefully, following the rules established in all existing guidelines and consensus. The proper casual blood pressure measurement technique according to most recommendations includes:

1. Appropriate equipment validated and in good condition, which includes a cuff of appropriate size to the thickness and size of the patient's arm. The standard cuff is 12-13 cm wide and 35 cm long and can be useful for most patients, but for patients with arm circumference > 32 cm and for children special cuffs are required, which in most common electronic equipment are not available. Bracelets are not interchangeable in electronic equipment) and this is a major problem in the daily practice. Remember that a small bracelet, a frequent situation due to the high prevalence of obesity, can give a false high measurement between 10 and up to 40 mmHg.
2. The patient must be comfortably seated for 5 minutes before the recording, without having smoked, not having ingested caffeine and without having exercised in the previous thirty minutes. Without speaking, sitting with your back straight and feet flat on the floor. The patient should keep the arm with the cuff supported on a flat surface such as a table at heart level.
3. **At the first consultation:** measure BP in both arms. Use the arm with the highest BP value for future reference. Take 3 shots at an interval of 1-2 minutes between them, discard the first shot and average the last two. Some authors recommend two measurements and make a third when the differences between the previous two is > 10 mmHg.
4. Additional measurements may be necessary in patients with unstable BP values due to arrhythmias, such as patients with AF, in whom the manual auscultation method should be used since most automatic devices use the oscillometric method and are not validated

for measure BP in patients with AF. If an aneroid device is used, it should be calibrated frequently and Korotkoff sounds used in phase I (appearance of sounds) to determine systolic pressure and phase V (disappearance of sounds) to determine diastolic pressure.
5. Measure BP in both arms at first visit to detect possible differences. Reference the arm with the highest value.
6. At the first consultation, the BP of all patients is measured in the standing position, after 1 and 3 minutes of sitting, to exclude orthostatic hypotension.
7. Measurement of recumbent and standing BP is considered at subsequent consultations for the elderly, patients with diabetes, or those with other conditions in which orthostatic hypotension is common.
8. It is recommended to measure the heart rate by palpation of the pulse to rule out arrhythmia and to ensure the value of systolic blood pressure when the auscultatory method is used and in elderly patients to detect pseudo-HBP secondary to arterial hardening, which is determined by the Osler's maneuver if the radial pulse remains palpable, when the pressure cuff is inflated above the recorded systolic pressure.

We can summarize that the reliable measurement of casual blood pressure includes: its performance with adequate, validated, and calibrated equipment, with a technique carefully adhered to the recommendations and with multiple measurements in the same session and preferably in different visits.

MEASUREMENT OF BLOOD PRESSURE OUTSIDE THE OFFICE (ABPM AND MDDPA)

Importance and technique for obtaining the ABPM

Measurement of blood pressure outside the office, either through ABPM or a home measurement protocol, adds very valuable data on the characteristics of the hypertensive process. As BP is a parameter that varies greatly over time and can be influenced by the presence of an operator unfamiliar to the patient, the values obtained in the consultation, even under the best measurement conditions, may not be representative of the individual's BP throughout the day. Therefore, the measurement of pressure outside the office is used and recommended by guidelines and consensus more frequently.[6]

In the recommendations for the Latin American ABPM registry of 2021, the following are marked as advantages of ABPM:

1. Provides highly reproducible 24-hour, diurnal and nocturnal average values, capturing a circadian vision of the biological phenomenon.
2. Identifies white coat HBP and the phenomenon of masked HBP in treated and untreated individuals.
3. Detects nocturnal HBP and nocturnal descent patterns.
4. Evaluates the variability of blood pressure during a 24-hour period
5. Evaluates the efficacy of antihypertensive medication in 24 hours.
6. Detects the existence of periods of excessive drop in blood pressure.
7. Detects the existence of significant elevations in blood pressure upon awakening.

To this we must add that ABPM provides a greater number of readings than office blood pressure measurements and that it provides a profile of the behavior of blood pressure in the usual daily environment, which is a more accurate predictor of cardiovascular morbidity and mortality than casual measurement.[6]

The methodology for ABPM is reasonably standardized in multiple guidelines, consensuses, and recommendations, both for HBP and specific for this technique. The 2018 guidelines from the European Societies of Arterial Hypertension and Cardiology provide a very comprehensive description of out-of-office blood pressure measurement, and many of the concepts expressed here come from those guidelines:

For ABPM measurement, a validated commercial system cuff is placed on the patient's non-dominant arm, appropriate to the thickness of the arm, consisting of a cuff that inflates intermittently and automatically, at predetermined times for 24 hours, connected to a portable pressure recorder to measure blood

pressure day and night, during the patient's normal activities, so the patient should be instructed not to change their habits due to the presence of the device. It is recommended that when the patient feels that the cuff is inflated, they suspend their activities and, if possible, place their arm at heart level. It is convenient for the patient to write down in a diary if any type of symptomatology appears, the time of meals and taking medications, as well as the time of going to bed and getting out of bed.

The device is adjusted to take measurements every 15 minutes during the patient's activity time and every 30 minutes during sleep, in another way used in some centers the equipment is programmed to measure the pressure every 20 minutes uniformly throughout the day.[3]

The requirements to accept a MAP as valid are:

1. Validated device
2. ≥ 70% of the expected measurements must be valid.
3. 20 valid measurements in the awake phase (09:00-21:00 hours).
4. 7 valid in the sleeping phase (01:00-06:00 hours).
5. Circadian variability of blood pressure.

The most accepted indications for obtaining the ABPM are:

1. Suspicion of white coat phenomenon in untreated patients and unnecessary dose readjustments due to white coat in treated patients.
2. Suspected masked HBP in untreated patients and masked lack of control in treated patients.
3. Resistant HBP in treated subjects.
4. Obstructive sleep apnea.
5. Study of blood pressure variability.
6. Treatment evaluation.
7. Evaluation of HBP in the elderly.
8. Evaluation of HBP in children and adolescents.
9. Evaluation of HBP in pregnancy.
10. Evaluation of HBP in high-risk patients.
11. Identification of ambulatory hypotension.
12. Identification of blood pressure patterns in Parkinson's disease.

Home measurement of blood pressure or self-measurement of blood pressure

The widespread availability and relatively low price for the general population of semi-automatic digitized electronic devices for BP measurement offers an important alternative to self-monitoring of blood pressure (SBP); however, it is not recommended for home measurements at the time and in the form that the patient or their relatives decide, especially for immediate decision-making on the state of health and the modification of the treatment by the patient himself.[1,3,4]

Proper use of SBP requires an established protocol, which may represent a cheaper, albeit incomplete, alternative to ABPM, which we could call home blood pressure measurement (BPM). For this technique, as it has been described by the 2019 ESH/ESC guidelines, a minimum user training in the technique is required to the patient himself or a family member by the doctor, nurse, or health educators. This allows obtaining reliable measurements and the use of previously validated monitors must be ensured, so before purchasing the device, check if it is on a validated list. For example, the British Hypertension Society: (http//www.bhsoc.org/blood_pressure_list.stm) or the Italian Society: (www.pressionearteriosa.net) or the DABL (dableducational.org).

Although the devices that can be used for BPM are the same as for clinical measurement, in practice only oscillometric-type automatic electronic sphygmomanometers where cuff inflation is performed by a compressor that measure BP in the arm are recommended. Wrist braces are discouraged because they can lead to significant errors resulting from incorrect arm position and wrist flexion or hyperextension status, although the use of wrist gauges could be justified in obese patients with arm circumference extremely large. For diagnostic evaluation, BP should be measured daily for at least 3-4 days and preferably 7 consecutive days in the morning and in the afternoon. BP should be measured in a quiet room. The patient should sit down, with his back and arm supported, after 5 minutes of rest, and take two measurements each time 1-2 minutes apart.[7]

The results must be written down immediately after each measurement in a notebook specially designed for this purpose. The final value is the average of all readings except those from the first day of monitoring. The definition of normal values for home BP has been carried out based on cross-sectional population and cohort studies. It is accepted that the BP obtained by SBP is about 5 mmHg lower than that obtained in the consultation, for which the Scientific Societies arbitrarily establish the limit of normality at values lower than 135/85 mmHg, and the optimal value is recognized as lower than 130/80mmHg.

Interpretation of office and out-of-office BP measurements

The accepted cut-off points for the diagnosis of HBP are:

1. Casual measurement: >140/90 ESC/ESH, LASH, NOM. >130/80 ACC/AHA (Obtained by AOBPM).
2. MAP: average of 24 hours. > 130/80, daytime average >135/85, nighttime average >120/70.
3. BPM: > 135/85.

With combined office and SBP blood pressure measurement, four different patterns of blood pressure status in any given person can be found:

1. Normal BP (Patients with normal blood pressure in the office and in the ABPM or BPM)
2. White coat HBP – patients with HBP in the office but normal by ABPM or BPM.
3. Masked HBP – patients with normal BP in the office, but with HBP outside the office.
4. Sustained HBP – patients with HBP in the office and in any of the medications outside the office *(Figure 1)*.

White coat high blood pressure

White coat HBP is a phenomenon that occurs in patients who are not receiving antihypertensive medications, who have persistently high office BP (≥ 140/90 mmHg) and who are found to have daytime pressure on ABPM or BPM a pressure < 135/85 mmHg. The prevalence of white coat HBP is between 15 and 25%, with the highest frequencies found in the elderly, females, and smokers. Out-of-office pressure monitoring to rule out white coat HBP is recommended in patients with office HBP without evidence of target organ damage, especially those with systolic pressures between 140 and 160 mmHg and diastolic between 90 and 100 mmHg. The prognosis of white coat HBP has traditionally and mistakenly been considered as benign; however, a high proportion of patients with this phenomenon progress to sustained HBP after one year and it is riskier for cardiovascular outcomes than pressure 121-139/81-89 mmHg, which indicates grade I HBP by ACC/AHA and high-normal by other guidelines.[3,4,8]

Masked high blood pressure

Individuals who have normal BP in consultations, but hypertensive in ambulatory blood pressure monitoring (ABPM) or in the protocolized home measurement, are considered to have masked HBP. Numerous terms have been used in the literature to refer to this type of HBP: masked, isolated ambulatory HBP, reverse white coat effect, or white coat normal BP, although the former is the most widely accepted. The prevalence of masked HBP varies according to the diagnostic criteria used and the characteristics of the population studied, but it is generally accepted that it ranges between 10-17%. Several factors have been described which can raise BP outside the office, such as young age, male

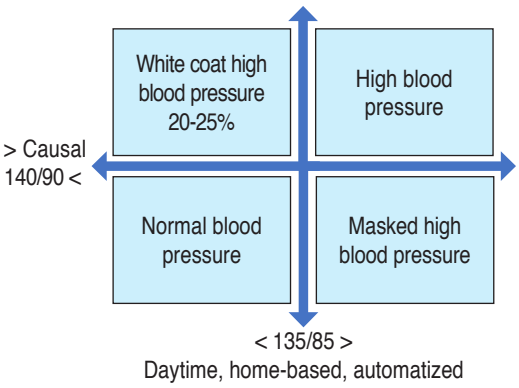


Figure 1: Circumstantial hypertension.

gender, smoking, alcohol consumption, physical activity, exercise-induced HBP, anxiety, work stress, obesity, and family history of HBP and it is especially prevalent in patients with diabetes or with kidney damage.

Masked HBP is frequently associated with other risk factors, such as asymptomatic organ damage and an increased risk of diabetes and sustained HBP and is more frequent in individuals with normal-high office BP figures. Individuals with masked HBP have greater organic involvement and worse cardiovascular prognosis than true normotensives. Some meta-analyses of prospective studies indicate that the incidence of cardiovascular outcomes is approximately two times higher than in true normotension and similar to the incidence in sustained HBP, although the fact that it is not detected in many cases, and therefore not treated, can contribute to these results.

Given that it is not feasible to study the population to detect masked HBP, efforts should be directed at detecting masked HBP in individuals with the highest index of suspicion and who will probably be the ones who can benefit most from treatment. Masked HBP should be suspected in normotensive individuals or with high-normal BP in the consultation, with other cardiovascular risk factors, signs of organic involvement inappropriate for BP values, and a family history of HBP in children or adolescents. It should also be suspected in hypertensive patients apparently well controlled by BP in consultation, in whom the expected regression of left ventricular hypertrophy or microalbuminuria progression or is not observed, and in those who present new cardiovascular events, such as stroke or heart failure decompensation congestive unexplained by other causes. In particular, the presence of masked HBP should be investigated in patients with diabetes mellitus with organ damage and borderline office blood pressures. In these patients, we should use 24-hours ABPM as the preferred method or BPM, which represents a good second option, especially for monitoring during treatment.[6,7]

CONCLUSIONS

Casual measurement of blood pressure is still the first recommended step to detect HBP in the population. The pressure measurement technique must be following very complete guidelines and according to the position document of the Alliance for a Healthy Heart. We recommend that blood pressure should be measured not necessarily by the doctor, but by trained health personnel equipped with adequate equipment, for which it would be very convenient to establish a blood pressure measurement module in each of the country's health centers. Here, the patient would receive an adequate measurement of his pressure figures before arriving at the consultation with the doctor. BPM is recommended, following an appropriate protocol, as a very useful alternative to ensure the correct diagnosis of HBP and rule out or confirm the presence of White Coat HBP and Resistant HBP. ABPM is an essential technique for data acquisition in research studies and its availability should be promoted in the first level of health care, to improve the control of HBP.

REFERENCES

1. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertens Dallas Tex 1979. 2018; 71: 1269-1324. Available in: https://doi.org/10.1161/HYP.0000000000000066
2. Alcocer L, Coca A, Ferrario CM. Revisión de las guías internacionales de hipertensión arterial. 978-84-17221-72-0 n.d. [Accesado Marzo 29, 2022] Disponible en: https://www.todostuslibros.com/libros/revision-de-las-guias-internacionales-de-hipertension-arterial_978-84-17221-72-0
3. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018; 39: 3021-3104. Available in: https://doi.org/10.1093/eurheartj/ehy339
4. Muntner P, Shimbo D, Carey RM, Charleston JB, Gaillard T, Misra S et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. Hypertension. 2019; 73: e35-66. Available in: https://doi.org/10.1161/HYP.0000000000000087.
5. Alcocer L, Álvarez-López H, Borrayo-Sánchez G, Cardona-Muñoz EG, Chávez-Mendoza A, Díaz ED

et al. Hypertension as a persistent public health problem. A position paper from Alliance for a Healthy Heart, Mexico. Ann Clin Hypertens. 2019; 3: 009-30. Available in: https://doi.org/10.29328/journal.ach.1001015

6. Sánchez RA, Boggia J, Peñaherrera E, Barroso WS, Barbosa E, Villar R et al. Ambulatory blood pressure monitoring over 24 h: A Latin American Society of Hypertension position paper-accessibility, clinical use and cost effectiveness of ABPM in Latin America in year 2020. J Clin Hypertens Greenwich Conn. 2020; 22: 527-543. Available in: https://doi.org/10.1111/jch.13816.
7. Fabia MJ, Abdilla N, Oltra R, Fernandez C, Redon J. Antihypertensive activity of angiotensin II AT1 receptor antagonists: a systematic review of studies with 24 h ambulatory blood pressure monitoring. J Hypertens. 2007; 25: 1327-1336. Available in: https://doi.org/10.1097/HJH.0b013e3280825625
8. MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. Br Med J Clin Res Ed. 1985; 291: 97-104. Available in: https://doi.org/10.1136/bmj.291.6488.97

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: Nothing to disclose.

Correspondence:
Luis Alcocer Díaz-Barreiro, MD
E-mail: alcocerdb@hotmail.com

CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105184

The detection and study of patient with high blood pressure

Detección y estudio del paciente con hipertensión arterial

José Manuel Enciso-Muñoz, MD* Rafael Olvera-Ruiz, MD‡ Alfredo Manuel Patiño-Llamas, MD§

Keywords:
High blood pressure, paraclinical studies in high blood pressure, cardiovascular risk.

Palabras clave:
Hipertensión arterial, estudios paraclínicos en hipertensión arterial, riesgo cardiovascular.

ABSTRACT

High blood pressure (HBP) is the most important cardiovascular risk factor for cardiovascular disease. Patients with uncomplicated HBP without target organ damage are usually asymptomatic. This leads to significant underdiagnosis of HBP, which contributes to a great extent to the poor control of the hypertensive population, which increases likelihood for complications. In this review, we summarize the clinical presentation of HBP, as well as the role of physical examination, laboratory, and complementary studies as well as the impact of these in the diagnosis of HBP. We also assess the role of HBP in mediating cardiovascular risk, cardiovascular outcomes and pathophysiological changes which lead to impaired vascular and cardiovascular function in patients living with HBP.

RESUMEN

La hipertensión arterial (HTA) es el factor de riesgo cardiovascular más importante para las enfermedades cardiovasculares. Los pacientes con HTA no complicada y sin daños en los órganos diana suelen ser asintomáticos. Esto conduce a un importante infradiagnóstico de la HTA, que contribuye en gran medida al mal control de la población hipertensa, lo que aumenta la probabilidad de complicaciones. En esta revisión, resumimos la presentación clínica de la HTA, así como el papel de la exploración física, el laboratorio y los estudios complementarios, y el impacto de éstos en el diagnóstico de la HTA. También evaluamos el papel de la HTA en la mediación del riesgo cardiovascular, los resultados cardiovasculares y los cambios fisiopatológicos que conducen al deterioro de la función vascular y cardiovascular en los pacientes que viven con HTA.

INTRODUCTION

High blood pressure (HBP) is a cardiovascular disease (CVD), which in turn becomes one of the so-called main cardiovascular risk factors (CVRF), in such a way that it is studied and treated with this double role. Diagnosis of HBP is made with numerical variables, which has given rise to definitions and classifications that vary depending on the criteria of the organizations that are dedicated to their study or their geographical location and have even evolved by modifying the cut-off points to establish the diagnosis according to current epidemiological data and the supervening investigations of its deleterious effects. It is important to establish that its etiopathogenesis is multifactorial.

HBP took a relevant interest during the current COVID-19 pandemic, with proliferating articles about its interaction with COVID-19 disease in 2 main lines:

1. The association between COVID-19 and RAS inhibitors. This raised because there was concern that ACE2, which is upregulated by RAS inhibitors, could promote the proliferation of SARS-CoV-2 and enhance its capability for infection. Fortunately, Matsuzawa et al. clearly demonstrated that RAS inhibitors could be beneficial for the prevention severe forms of COVID-19 patients with HBP.[1]
2. Another hot topic considers that patients with HBP has been identified as the

* Hospital San Agustín. Zacatecas, México, Miembro GREHTA.
‡ Hospital Regional «Dr. Valentín Gómez Farías», ISSSTE. Guadalajara, Jalisco, México, Miembro GREHTA.
§ Hospital General ISSSTE. Zacatecas, México, Miembro GREHTA.

How to cite: Enciso-Muñoz JM, Olvera-Ruiz R, Patiño-Llamas AM. The detection and study of patient with high blood pressure. Cardiovasc Metab Sci. 2022; 33 (s3): s190-s196. https://dx.doi.org/10.35366/105184

most common comorbidity in COVID-19 patients and has shown an association with worse outcomes.[2]

A dramatic consequence of the times of this pandemic has been the regression in the detection and care of CVD, especially the study of population with HBP.[3] In this chapter we address the study of the hypertensive patient as well as the significance of HBP in cardiovascular risk (CVR).

High blood pressure patient clinic

HBP is the most important cardiovascular risk factor for acute coronary syndrome and chronic coronary syndrome, as well as heart failure, renal failure, and peripheral arterial insufficiency. HBP is very common worldwide and has been attributed as leading cause of death, underlining the estimate that said figure will increase by 50% in the next 20 years. It is therefore important to know the clinical presentation of the hypertensive patient.

Clinical manifestations of high blood pressure. Patients with uncomplicated HBP without target organ damage are usually asymptomatic. This leads to significant underdiagnosis of HBP, which contributes to a great extent to the poor control of the hypertensive population, which increases likelihood for complications. Because of this, HBP has been defined as a *silent killer*.[4] Within a minority of patients with HBP who manifest symptoms, headache is the most common manifestation, but it is more in those who know the diagnosis than in those who have the same level of blood pressure but are not aware that they are hypertensive. Stewart et al. reported a 17% prevalence of headaches in unaware hypertensives versus 71% in known hypertensives. In this context, headache appears to be more related to anxiety than to high blood pressure. Cooper et al. observed that the prevalence of headache was similar among patients with diastolic blood pressure of 95 mmHg and among those with 125 mmHg. Weiss et al pointed out that headaches were equally prevalent among hypertensive individuals unaware of their condition and in normotensive individuals. Furthermore, headaches reported during ambulatory blood pressure monitoring were not associated with concomitant increases in blood pressure.[5]

Comparing the symptoms between untreated hypertensive and normotensive patients of similar age, Bulpitt et al. observed a higher prevalence of morning headache, blurred vision, instability, depression and nocturia in the former. In a meta-analysis of 97 prospective randomized placebo-controlled trials, including 24,000 patients, reported that the prevalence of headache was reduced by lowering blood pressure without being related to the type of antihypertensive drug used, which implies that HBP is a reversible cause of headache and that different antihypertensive medications prevent a significant proportion of headaches. The headache is usually fronto-occipital and sometimes wakes the patient up in the early hours of the morning. In severe HBP, occipital headache is more constant and is one of the first symptoms which alerts the patient.

Other manifestations of HBP include epistaxis, tinnitus, dizziness, palpitations, and fatigue. It is useful to know if there has been sexual dysfunction prior to antihypertensive treatment, a topic that is often excluded from medical interviews and which later appears during treatment. Erectile dysfunction may be present in about one third of untreated hypertensive patients and is probably also related to their underlying vascular disease and can be considered one of the first manifestations of endothelial dysfunction. The presence of nocturia should also be interrogated, which can be due to various causes such as benign prostatic hypertrophy, sleep apnea, but it can also mean loss of the ability to concentrate urine, an early sign of kidney disease.[6]

Physical examination of patients with high blood pressure

In most patients with uncomplicated primary HBP, general inspection will not reveal any characteristic signs that differentiate it from a healthy person with normal blood pressure. Anthropometric measurements including weight, height, hip and waist circumference should be performed on all patients, which are essential and useful for detecting abdominal

obesity, which is considered a cardiovascular risk factor independent of body weight.

Blood pressure measurement. It is useful to measure blood pressure in both arms with the standard technique on the first visit. They should be similar, although if there is a time lag between the two measurements there may be differences between 5 and 10 mmHg. If the difference between the arms is greater than 15 to 20 mmHg in the systolic, there may be an atherosclerotic plaque in the circulation of the arm that registers a lower pressure number. The arm with the highest value should always be used for clinical controls.

Ocular fundus. Not very useful in most patients with mild HBP, but the presence of arterial crossings suggests chronicity. Hemorrhages, exudates, and papilledema associated with elevated blood pressure suggest severe end-organ damage and a poor prognosis unless therapy is instituted promptly.

Cardiac exam. Ectopic beats are not uncommon in hypertensive patients, especially if they have left ventricular hypertrophy. Atrial fibrillation may also be found which is of the utmost importance, and heart rhythm disorders must be immediately documented. There may be physical findings of cardiomegaly with strong apical impulse, the second aortic sound is accentuated. A fourth sound is found when there is little compliance of the left ventricular wall, in this context, it is most frequently due to left ventricular hypertrophy. If there is a third sound, it suggests left ventricular dysfunction.

Peripheral pulses. Helpful to evaluate peripheral arterial disease and rule out coarctation of the aorta. Palpation and auscultation of the carotids should also be evaluated to rule out arrhythmias and murmurs that indicate atherosclerotic plaques at that level or irradiation of heart murmurs, as is the case of aortic stenosis.

Abdomen. It is important to auscultate it to rule out murmurs that suggest renal artery stenosis and to palpate it to rule out masses as in polycystic kidney disease. Vigorous pulsations of the aorta may be normal in the young but suggest an abdominal aortic aneurysm in the elderly.[7]

Complementary studies

Also called «paraclinical» studies, they try to complement the most precise information possible in the study of the hypertensive patient. Inappropriately they are often called routine studies, understanding the term routine as the custom, or acquired habit of

Table 1: Comprehensive diagnostic approach

Indispensable		**Optional** (Subsequent or individualized)
Complete blood count		Transthoracic echocardiogram
Serum glucose and HbA1c		Microalbuminuria
Creatinine		Thyroid profile
	←	**Out-of-office blood pressure monitoring**
General urine test		Thorax X-ray
Complete lipid profile		Carotid ultrasound
Serum potassium and sodium		
Electrocardiogram		
Liver function tests	→	

Modified from Am Coll cardiol 2017;23976;DOI:10.1016/j.jacc.2017.07.745, where we propose transferring out-of-office blood pressure monitoring to those that are essential, be it 24-hour ambulatory (arrows) or home self-monitoring according to protocols previously established in the previous chapter of this document. In the same way, liver function tests could be considered as optional and individualized, whose utility in a generalized way could not be so essential, would increase the cost to the patient and are not widely available in our environment.

Table 2: Etiology and way of study.

Condition	Screening test
Chronic kidney disease	Glomerular filtration rate
Aortic Coarctation	Angiotomography
Cushing's syndrome	Dexamethasone suppression test
Pheochromocytoma	Metanephrines in 24-hour urine.
Renal vascular renovascular disease	Renal US with Doppler renal arteries
Primary hyperaldosteronism or Conn syndrome	Aldosterone in 24-hour urine and levels renin/aldosterone
Thyroid/parathyroid disease	Serum TSH and parathyroid

TSH = thyroid-stimulating hormone.

doing something in a certain way, which does not require having to reflect or decide. This implies a practice that over time develops almost automatically, without the need to use reasoning, and implies a practice, without the need intellectual exercise. By putting the word routine before it describes an irrational, biased and tendentious action, not free from certain pecuniary and dichotomous interests, which deviates from the primary academic-scientific interest of studying and establishing the individual pathophysiological mechanisms that will guide the making of the best therapeutic decisions and continue subsequently with the study and follow-up of each patient individually. It is probably better to define them as «basic tests».

Not indicating and not studying basic tests, also represents a highly objectionable failure by the treating physician, lacking interest in the precision of the individual pathophysiological mechanisms of his patient, it is a liable omission. Initiating and continuing treatments in this way, in addition to being improper, irresponsible, will result in poor decisions and poor control of the disease and its complications. The fundamental idea to obtain from paraclinical studies is to have a sufficient idea of the cardiometabolic context in which the patient with HBP finds himself. The American College of Cardiology in 2017 suggests the studies summarized in *Table 1*.

Each of the above studies, both those considered essential and optional, has its relevance and widely documented justification, since any anomaly in each of them modifies important variables that influence blood pressure and should be at the values closest to those desirable for good control of high blood pressure.

Another important purpose with paraclinical studies is the assessment of the possible damage to the target organ because of the multi-organ affectations of HBP, for which it is always recommended to search intentionally for those affectations that constitute the complications themselves, both those that show clinical and subclinical evidence. Thus, when the clinical review and the basic studies establish suspicion of involvement of one or several organs due to HBP or the suspicion of secondary HBP, the following studies have been recommended, which are summarized in *Table 2*.

A recurring theme is the case of the so-called resistant HBP, which is very useful to rule it out. Blood pressure monitoring outside the office in its two aspects, the 24-hour outpatient and home self-monitoring, should always be considered in these patients the possibility of secondary HBP. Frequent causes of resistant HBP include obstructive sleep apnea syndrome (OSAS) should be investigated, chronic kidney disease, renal artery stenosis, whether congenital or atherosclerotic, and infrequent in addition to what is mentioned in the previous table and especially in minors 30 years old coarctation of the aorta or brain tumor.

OSAS and sleep-disorders of breathing deserve special attention due to their frequency, not only do they raise BP, but they also

significantly increase the risk of cardiovascular events. During the awakenings or microarousal episodes, episodes of angina, acute myocardial infarction have been described. Also, OSAS can stimulate heart failure, arrhythmias, and conduction disorders. On the other hand, an association of this syndrome has been described, as well as its severity, with left ventricular hypertrophy, even after adjusting for the BP value. Obesity is a condition associated with patients with OSAS, HBP in general, and resistant HBP since these subjects require more antihypertensive drugs and the probability of achieving adequate control decreases. Compulsory studies include polysomnography, which consists of recording brain activity, breathing, heart rate, muscle activity and blood oxygen levels while sleeping. It is a test indicated for the study of different sleep disorders that is performed at night. Finally, in reference to paraclinical studies, we must mention advances in the study of **vascular function**, which we must have in mind because they indicate the future in the study of the patient with HBP *(Figure 1)*.

Resistant arterial hypertension, cardiovascular risk, and outcomes

Get your facts first, and then you can distort them as much as you please.
Mark Twain

HBP is defined as office blood pressure (BP) record ≥ 140/90, home BP monitoring ≥ 135/85, or ambulatory BP monitoring ≥ 130/80. Cigarette smoking, diabetes, and dyslipidemia are major modifiable risks factors for cardiovascular disease (CVD), there are several mechanisms that induce and increase the cardiovascular risk. In Mexico, HBP is the twelfth cause of death, even though it is also associated with the increased risk for comorbidities such as COVID-19, coronary heart disease (CHD), diabetes mellitus, stroke, and kidney disease. There are short and long-term consequences of HBP. Short-term consequences include stroke, CHD, heart failure (HF), and cardiovascular death; furthermore, long-term consequences include hypertensive cardiomyopathy, HF with preserved ejection fraction, atrial fibrillation, valvular heart disease, aortic syndromes, peripheral arterial disease, chronic kidney disease, dementia, diabetes, and erectile dysfunction.[8] We briefly mention those that in our opinion should be underlined:

1. **Oxidative Stress.** Is an imbalance between free radicals and antioxidants. The immune system produces oxidizing species and by phagocyte activation process reactive oxygen and nitrogen species as a lethal weapon to kill pathogens but also causes cellular damage. Hyperlipidemia, HBP, diabetes, and smoking generate oxidative stress which causes endothelial dysfunction and smooth muscle activation with nitric oxide impairment, increasing tissue angiotensin-converting enzyme, and angiotensin II.[9]
2. **Inflammation.** Chronic inflammation is a long-term stimulus which may last weeks, months, years, or even lifetime, and is characterized by the recruitment of monocytes and lymphocytes accompanied by tissue injury. It and a role in the development and progression of autoimmune disease, infectious disease like COVID-19, metabolic disorders such as atherosclerosis, obesity, and diabetes or hemodynamic disease as HBP, vascular and cardiac disease.[10]
3. **Renin-angiotensin-aldosterone system (RAAS).** RAAS is the cornerstone of blood pressure balance and is found in kidneys, adrenal glands, heart, vasculature, and nervous system. RAAS malfunction produces target organ or vasculature damage and is «the missing link» in long-term catastrophic consequences of HBP. The ying-yang effect of RAAS. Angiotensinogen (1-452 aa) is converted to angiotensin I (1-10 aa) by renin cleavage and is converted to angiotensin II (1-8 aa) by the angiotensin-converting-enzyme (ACE), which has two membrane receptor sites. angiotensin II binds angiotensin I receptor (AT1r) causes vasoconstriction, HBP, inflammation, fibrosis, and proliferation. On the other hand, the angiotensin II receptor (AT2r) is abundantly expressed in both immune and nonimmune cells in fetal tissue. Its

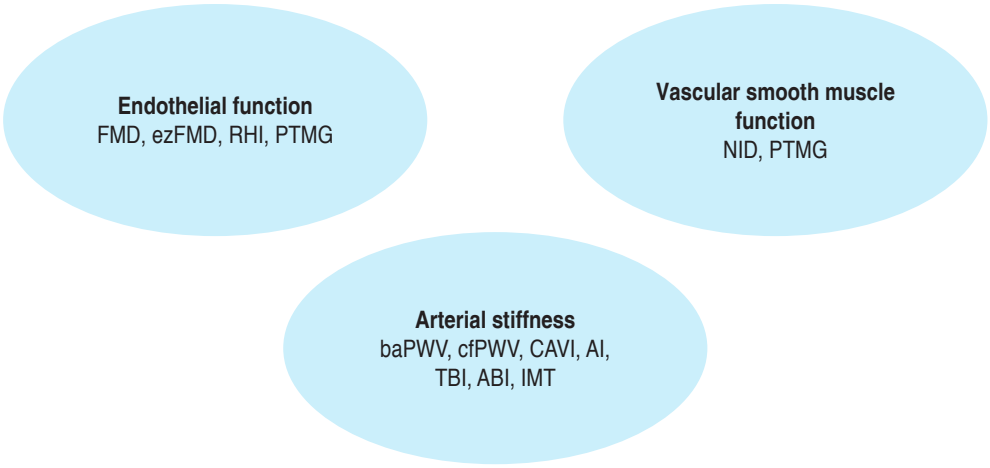


Figure 1: Methods for assessment of vascular function. FMD indicates flow-mediated vasodilation, ezFMD enclosed-zone FMD, RHI reactive hyperemia index, NID nitroglycerine-induced vasodilation, baPWV brachial- ankle pulse wave velocity, cfPWV carotid-femoral PWV, CAVI cardio-ankle vascular index, AI augmentation index, TBI toe brachial pressure index, ABI ankle-brachial pressure index, IMT intima media thickness. Modified from: Mogi M et al.[3]

expression is increased under pathological conditions in adult tissues and counteracting AT1r functions.[11] Angiotensin II is converted to Angiotensin 1-7 by angiotensin-converting enzyme 2 (ACE2) which has only one membrane receptor site located in the lungs, cardiovascular tissues, kidneys, gastrointestinal tract, and adipocyte tissue and is the doorkeeper of COVID-19. The pathways of Angiotensin 1-7 are degradation or stimulation of MAS membrane receptor which produce vasodilatation, vasoprotection, and maybe hypotension by nitric oxide synthase stimulation.

4. **High blood pressure-mediated organ damage.** High blood pressure-mediated organ damage (HMOD) describes functional changes in major organ systems (the heart, the brain, the retina, the kidneys, and the vasculature) and could be evaluated through an electrocardiogram, echocardiogram, computed tomography scan (CTs), or magnetic resonance (MR) for left ventricular hypertrophy (LVH), CTs or MR for brain disease, fundoscopy for retinopathy, estimated glomerular filtration (eGFR) or microalbuminuria (MAU) for kidney disease, carotid-femoral pulse wave velocity (PWV) for arterial stiffness (AS), and ankle-brachial index or carotid intimal-medial thickness for vasculature atherosclerosis (VA). Systolic pressure correlates positively in odds ratio HMOD except in eGFR, diastolic pressure correlates negatively in odds ratio HMOD except in eGFR, and pulse pressure correlates positively in odds ratio HMOD except in eGFR.

Unger et al published the 2020 International Society of Hypertension Global Hypertension Practice Guidelines which recommend a simplified classification of HMOD based on a 60-year-old male patient, but categories of risk will vary according to age and sex *(Figure 1)*. In summary, HBP is a major cardiovascular risk factor linked with chronic degenerative diseases, associated with bad outcomes which leads to the top mortality ranking in the world and each patient must be sufficiently studied to offer the best available therapeutic alternatives.

REFERENCES

1. Matsuzawa Y, Ogawa H, Kimura K, Konishi M, Kirigaya J, Fukui K et al. Renin-angiotensin system inhibitors and the severity of coronavirus disease 2019 in Kanagawa, Japan: a retrospective cohort study. Hypertens Res. 2020; 43 (11): 1257-1266. doi: 10.1038/s41440-020-00535-8.
2. Sheppard JP, Nicholson BD, Lee J, McGagh D, Sherlock J, Koshiaris C et al. Association Between Blood Pressure Control and Coronavirus Disease

2019 outcomes in 45 418 symptomatic patients with hypertension: an observational cohort study. Hypertension. 2021; 77 (3): 846-855. doi: 10.1161/HYPERTENSIONAHA.120.16472.
3. Mogi M, Higashi Y, Bokuda K, Ichihara A, Nagata D, Tanaka A et al. Annual reports on hypertension research 2020. Hypertens Res. 2022; 45 (1): 15-31. doi: 10.1038/s41440-021-00766-3.
4. Sierra C, Aguilera MT. Evaluación clínica del paciente hipertenso. Med Integral. 2001; 37: 210-214.
5. Ocampo DA. Fisiopatología de la hipertensión arterial esencial. n.d. pp. 351-357.
6. Ohishi M, Kubozono T, Higuchi K, Akasaki Y. Hypertension, cardiovascular disease, and nocturia: a systematic review of the pathophysiological mechanisms. Hypertens Res. 2021; 44 (7): 733-739. doi: 10.1038/s41440-021-00634-0.
7. Rosas M, Pastelín G, Vargas-Alarcón G, Martínez-Reding J, Lomelí C, Mendoza-González C et al. Guías clínicas para la detección, prevención, diagnóstico y tratamiento de hipertensión arterial sistémica en México. Arch Cardiol Mex. 2008; 78 (Suppl 2): 5-57.
8. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. Hypertension. 2020; 75 (2): 285-292. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.119.14240.
9. Lim HS, MacFadyen RJ, Lip GYH. Diabetes mellitus, the renin-angiotensin-aldosterone system, and the heart. Arch Intern Med 2004; 164: 1737-1748. doi: 10.1001/archinte.164.16.1737.
10. Harrison DG, Coffman TM, Wilcox CS. Pathophysiology of hypertension: the mosaic theory and beyond. Circ Res 2021; 128: 847-863. doi: 10.1161/CIRCRESAHA.121.318082.
11. Fatima N, Patel SN, Hussain T. Angiotensin II type 2 receptor: a target for protection against hypertension, metabolic dysfunction, and organ remodeling. Hypertension. 2021; 77 (6): 1845-1856. doi: 10.1161/HYPERTENSIONAHA.120.11941.

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: The authors declare that they have no conflict of interests.

Correspondence:
José Manuel Enciso-Muñoz, MD
E-mail: jmenciso2@hotmail.com
Rafael Olvera-Ruiz, MD
E-mail: rafaelolveraruiz@gmail.com
Alfredo Manuel Patiño-Llamas, MD
E-mail: drpatinoll@hotmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105185

Diagnostic and therapeutic phenotypes in patients with high blood pressure

Fenotipos diagnósticos y terapéuticos en pacientes con hipertensión arterial

Héctor Galván-Oseguera, MD,* Agustina Moreno-González, MD‡

Keywords:
High blood pressure, clinical phenotypes, cardiovascular outcomes.

Palabras clave:
Hipertensión arterial, fenotipos clínicos, resultados cardiovasculares.

ABSTRACT

In patients with high blood pressure (HBP), we can find different characteristics which can help us establish the diagnosis, prognosis, and treatment. With the advancement of technology and knowledge of the pathophysiology of HBP, we now have other diagnostic methods outside the office which allow us to measure BP in different circumstances. Within HBP individual patients may have disease attributes that, alone or in combination, describe different phenotypes between individuals in relation to parameters which have clinical significance. Some of the main characteristics that we identify are those related to BP measurement, to the origin of BP elevation, to the circumstance in which BP was taken, to patients with high BP variability, patients who do not respond to treatment, patients where elevation of their BP is an emergency and one of the most important according to cardiovascular risk. From these characteristics we were able to identify 29 different HBP phenotypes in the literature, which can help us better define diagnosis, prognosis, and treatment. Many authors and clinicians call it a "tailor-made suit"; however, we will call it the hypertensive phenotype.

RESUMEN

En los pacientes con hipertensión arterial (HTA) podemos encontrar diferentes características que nos pueden ayudar a establecer el diagnóstico, el pronóstico y el tratamiento. Con el avance de la tecnología y el conocimiento de la fisiopatología de la HTA, ahora disponemos de otros métodos de diagnóstico fuera de la consulta que nos permiten medir la PA en diferentes circunstancias. Dentro de la HTA, los pacientes individuales pueden tener atributos de la enfermedad que, solos o combinados, describen fenotipos diferentes entre los individuos en relación con parámetros que tienen importancia clínica. Algunas de las principales características que identificamos son las relacionadas con la medición de la PA, con el origen de la elevación de la PA, con la circunstancia en la que se tomó la PA, con los pacientes con alta variabilidad de la PA, con los pacientes que no responden al tratamiento, con los pacientes en los que la elevación de su PA es una urgencia y con uno de los más importantes según el riesgo cardiovascular. A partir de estas características pudimos identificar 29 fenotipos diferentes de HTA en la literatura, que pueden ayudarnos a definir mejor el diagnóstico, el pronóstico y el tratamiento. Muchos autores y clínicos lo llaman «traje a medida»; sin embargo, nosotros lo llamaremos fenotipo hipertensivo.

* Head of the Adult Degenerative and Congenital Valvular Cardiopathy, Member of GREHTA.
‡ Clinical cardiologist at the Adult Degenerative and Congenital Valvular Cardiopathy, Member of GREHTA.

Department at the Cardiology Hospital of Centro Médico Nacional Siglo XXI del Instituto Mexicano del Seguro Social.

INTRODUCTION

High blood pressure (HBP) is the main risk factor for mortality world-wide. In Mexico its prevalence reaches over 34% in adults over 20 years of age.[1,2] Being such an important and prevalent disease, it requires consistent methods for its diagnosis. This diagnosis is mainly based on taking blood pressure (BP) using a cuff to compress the upper arm, a technique that is still valid to this day and has not changed in more than 100 years. With the advancement of technology and knowledge of the pathophysiology of HBP, we now have other diagnostic methods outside the office which allow us to measure BP in different circumstances.[3]

Arterial BP is related to intrinsic biological rhythms of a periodic nature, generally 24 hours, called the circadian cycle. This circadian cycle shows that BP is a biological parameter

How to cite: Galván-Oseguera H, Moreno-González A. Diagnostic and therapeutic phenotypes in patients with high blood pressure. Cardiovasc Metab Sci. 2022; 33 (s3): s197-s210. https://dx.doi.org/10.35366/105185

with great variability, which can be observed beat by beat or minute by minute (short-term), day by day and visit by visit (medium-term) and year by year (long-term variability). There are many factors that influence this variability, such as the daily duration of sunlight, which in turn depends on the seasons of the year, day of the week, influenced by the work rhythm and the duration of rest or effort, sleeping, or eating schedule, exercise, including the place, time, and position in which the BP is taken, among other variables. In addition to these external factors, there are also factors specific to the individual, such as their genotype, age, gender, or body complexion, which make each BP intake different for each person.[4]

High blood pressure is a massive phenomenon; however, each patient may have attributes of the disease that, alone or in combination, describe differences between individuals in relation to parameters that have clinical significance. Many authors and clinicians call it a «tailor-made suit»; however, we will call it a hypertensive phenotype *(Figure 1)*.

Classification of patients with high blood pressure and its phenotypes

According to the Official Mexican Standard NOM-030-SSA2-2009, HBP in adults is classified according to the degree of BP elevation measured in mmHg taken in the office.[5] This classification is consistent with most of the Clinical Practice Guidelines in the world mainly from the WHO, Latin America, and Europe.[6-8] In recent years, with the advent of diagnostic methods outside the office, such as Ambulatory Blood Pressure Monitoring (ABPM) and Home Blood Pressure Monitoring (HBPM), other parameters measured in averages were added to the definition, these definitions are already the NOM-030-SSA2-2017 project and have been adopted in Mexico[9] *(Table 1)*.

Although these definitions prevail to make the diagnosis and make the corresponding therapeutic decisions, there is a set of different characteristics that each hypertensive patient presents because of the interaction between their genotype and the environment in which they live, which is known as phenotype. In the case of patients with AHT, we will see below the different phenotypes with their corresponding characteristics.

1. Phenotypes according to BP measurement

These phenotypes are generally found when making the diagnosis in the office:

1. Patients with isolated diastolic HBP
2. Patients with isolated systolic HBP
3. Patients with systolic-diastolic HBP

Although there are some differences in the cut-off points for the definition of HBP, mainly with the most recent guide published by the American Heart Association/American College of Cardiology (AHA/ACC) and the guidelines recently published by the International Society Hypertension (ISH),[10] in Mexico we use the one that resembles the European guide in accordance with NOM 00308.[5] Its identification can help us define both the pathophysiology and treatment, since some patients with isolated diastolic HBP respond better to the use of BB, while those with isolated systolic and systolo-diastolic HBP respond better to the use of combinations based on angiotensin inhibitors. angiotensin converting enzyme (ACE)/angiotensin 2 receptor antagonists (ARA 2), Calcium antagonists or thiazide-type diuretics.

2. Phenotypes according to origin

There are also phenotypes according to the origin or cause of HBP, in which «primary or essential» is the most prevalent, followed by secondary (where there are many phenotypes) and pregnancy related. These phenotypes are the most used in the clinic; we know that the origin of more than 95% of patients with HBP is unknown, what we call primary or «essential» HBP, although it is known that its etiology is multifactorial. Another important phenotype is related to secondary causes that we mainly find in children, young patients, or patients whose BP control is very difficult.

Finally, HBP during pregnancy, which is the main cause of maternal death in Mexico, so its identification is very important. Here we can find 3 different phenotypes:

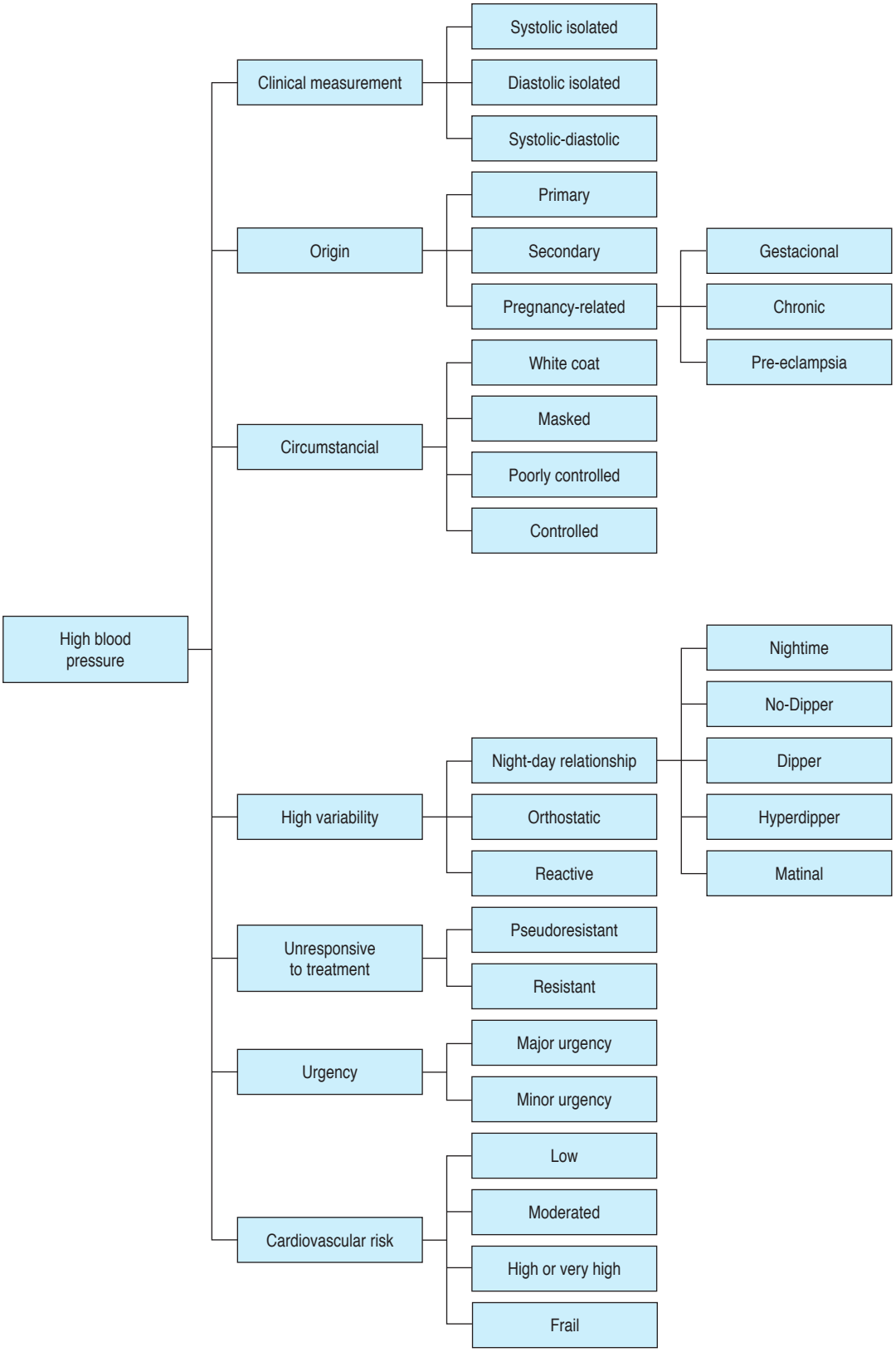


Figure 1:

High blood pressure phenotypes. Classification proposed by Dr. Héctor Galván Oseguera and Dra. Agustina Moreno González.

1. **Gestational HBP:** this is HBP that develops during pregnancy. It begins after 20 weeks of pregnancy.
2. **Chronic HBP in pregnancy:** this is high BP that begins before the 20th week of pregnancy or before becoming pregnant.
3. **Preeclampsia:** it is a sudden increase in blood pressure after the 20th week of pregnancy. In general, it occurs in the last trimester and can continue in the postpartum period.

Table 1: Definiton of high blood pressure based on BP measurement

Modality	Systolic BP mmHg	Diastolic BP mmHg
In office	≥ 140	≥ 90
Out-of-office		
Daytime (vigil)	≥ 135	≥ 85
Nightime (sleep)	≥ 120	≥ 70
24-hour average	≥ 130	≥ 80
Home-based	≥ 135	≥ 85

BP = blood pressure.
Source: 2018 ESC/ESH guidelines for the diagnosis and treatment of high blood pressure.[7]

The characteristics of these phenotypes can be seen in *Table 2*.

3. Circumstancial high blood pressure phenotypes

Other phenotypes are those given by diagnostic methods outside the office such as ambulatory blood pressure measurement (ABPM) and home blood pressure monitoring (HBPM) called «circumstantial» HBP, which includes 4 other phenotypes such as white coat HBP, masked HBP, sustained or uncontrolled HBP and controlled HBP or normotension *(Table 3)*. This differentiation depends on the place and time in which the blood pressure measurement is done, the so-called «white coat» HBP is characterized when the patient has high BP in office measurements and normal outside the office, while in "masked" HBP the opposite happens: BP inside the office is normal, while intake outside the office is high, when BP is high both in office and outside the office, we are dealing with a patient with sustained or uncontrolled HBP. This is also the case of patients with normal BP inside and outside the office, which allows us to rule out the diagnosis

Table 2: High blood pressure phenotypes according to clinical measurements.

Phenotype	Isolated diastolic high blood pressure	Isolated systolic high blood pressure	Systolic-diastolic high blood pressure
Definition	ESH: DBP > 90 mmHg, SBP < 140 mmHg AHA/ACC: DBP > 80 mmHg, SBP < 130 mmHg NOM 0030: DBP > 90 mmHg, SBP < 140 mmHg	ESH: DBP < 90 mmHg, SBP > 140 mmHg AHA/ACC: DBP < 80mmHg, SBP > 130 mmHg NOM 0030: DBP < 90 mmHg, SBP > 140 mmHg	ESH: DBP > 90 mmHg, SBP > 140 mmHg AHA/ACC: DBP > 80 mmHg, SBP > 130 mmHg NOM 0030: DBP > 90 mmHg, SBP > 140 mmHg
Etiology	Multifactorial, mainly in young adults	Multifactorial, mainly in older adults	Multifactorial, mainly in adults > 40 years
Pathophysiology	Mainly by increases in sympathetic and heart output activity	Mainly by increases in arterial stiffness	Mainly by increases in vascular resistance
Prognosis	Long-term morbidity and mortality	High mortality and morbidity	High mortality and morbidity
Treatment	ACEI/ARB and in some patients BB	Combinations of ACEI/ARB, calcium channel blockers and thiazide diuretics	Combinations of ACEI/ARB, calcium channel blockers and thiazide diuretics

ESH = European Society high blood pressure; ACEI = Angiotensin-converting enzyme inhibitors; ARB = Angiotensin receptor blockers; BB = Beta-blockers.

Table 3: High blood pressure phenotypes according to origin or cause .

Phenotype	Primary or essential	Secondary	Pregnancy-related
Definition	Permanent elevation of systolic and/or diastolic BP without defined cause	Permanent elevation of systolic and/or diastolic BP with a defined cause. It is suspected when it begins in childhood or young patients, or patients with refractory or resistant high blood pressure.	Gestational high blood pressure: Elevated blood pressure during pregnancy. It begins after 20 weeks of pregnancy. Chronic high blood pressure in pregnancy: High blood pressure that begins before the 20th week of pregnancy or before becoming pregnant. Preeclampsia: Sudden increase in blood pressure after the 20th week of pregnancy. In general, it occurs in the last trimester and can continue in the postpartum period.
Etiology	Multifactorial: genetic, cultural and environmental causes.	Frequent: Primary hyperaldosteronism, renal parenchymal diseases and renal artery stenosis. Rare: Aortic coarctation, Pheochromocytoma, Cushing's syndrome, Hyperparathyroidism, Brain tumors, Takayasu's disease and other vasculitides, etc.	Unknown
Pathophysiology	Mainly due to increased vascular resistance and cardiac output	Depends on the cause	Generalized inflammation, prothrombosis and proteinuria.
Prognosis	High mortality and morbidity.	Variable	Premature birth, fetal and maternal death.
Treatment	ACEI/ARB combinations, calcium antagonists and thiazide-type diuretics are preferred.	Depends on the cause	Acetyl-salicylic acid, Calcium antagonists, alpha-blockers and beta-blockers.

ESH = European Society high blood pressure; ACEI = Angiotensin-converting enzyme inhibitors; ARB = Angiotensin receptor blockers; BB = Beta-blockers.

or to know that the hypertensive patient is well controlled. We will delve deeper into these phenotypes due to their clinical importance.

White coat high blood pressure (or isolated clinical high blood pressure)

White coat HBP (WCHBP) is an important phenotype as it is a proposed risk factor for the development of sustained HBP, target organ damage, and possibly the occurrence of cardiovascular (CV) events. Recently, interest in this phenotype has increased since, some studies have identified that WCHBP increases the relative risk of sustained HBP, almost three times compared to patients with normal BP, as well as the risk of carotid atherosclerosis and impaired cardiac function. Current evidence suggests that WCHBP is an intermediate risk category located somewhere between those with normotension and sustained HBP.[11] This contrasts with other studies, which have found that patients with WCHBP have no additional CV risk; this apparent lack of clarity

deserves further investigation.[12,13] Evidence based on randomized controlled trials is scarce and the results of existing studies are controversial so far on WCHBP. The white coat effect is not necessarily the same as the alert reaction produced by the presence of health personnel when taking BP, since other factors can contribute to the white coat effect, such as patient anxiety.[14,15] This effect can be reduced with a correct and repeated measurement of BP in consultation, it is usually lower in nursing consultations and tends to disappear with non-face-to-face clinical measurement.[16]

Prevalence: the prevalence of WCHBP varies according to the studies because its definition has been based both on mean daytime blood pressure cut-off points and 24-hour blood pressure values. Based on cut-off points of 140/90 mmHg for normal office BP and 135/85 mmHg for normal daytime BP, the prevalence of white coat HBP ranges from 20 to 45%.[17] Regarding the factors that predispose to the development of the WCHBP phenotype, non-smokers, women over 55 years of age, obese and with higher clinical systolic blood pressures (mild HBP) are more likely to develop white coat HBP.[18]

Etiology and pathophysiology: there are several proposed triggers for the development of WCHBP. Patients have a slight elevation in BP on arrival at the consultation and during manual recordings of BP with a cuff and manometer, these elevations in BP exceed those recorded by ABPM during the episodes of anxiety or aggravation. Psychological characteristics, particularly anxiety, could be responsible for the presence of WCHBP. Anxiety is an emerging risk factor for CV disease, but its role in WCHBP is less clear. In patients treated with antihypertensives, high levels of anxiety have been shown to increase the risk of pseudo resistant HBP due to the white coat effect. These findings contrast with previous work showing that psychological characteristics do not differ between those with WCHBP and sustained HBP.

A hypothesis has been described which involves the sympathetic and endocrine systems as being involved in the genesis of WCHBP. This has been investigated by simultaneously measuring arterial BP, heart rate, and sympathetic nerve activity in the skin and postganglionic muscles during a visit to the doctor, where subjects showed elevation in both BP and heart rate during the visit. This was accompanied by an increase in skin sympathetic nerve stimulation and a corresponding reduction in muscle sympathetic nerve stimulation. Except for sympathetic nerve stimulation of the skin, these changes persisted for several minutes after the visit ended. A nurse visit elicited a significantly attenuated response compared to a physician visit. The endocrine system may play an important role in BP recovery in the hours rather than minutes after a clinic visit. Hospital-initiated ABPM shows that it takes 2 to 3 hours for BP to reach usual daytime values. This could be explained by a prolonged sympathetic response or by some endocrine contribution.[5]

Cardiovascular risk: WCHBP is well characterized in the medical literature, but there is still no consensus on its prognostic importance in cardiovascular disease (CVD). However, growing evidence has begun to establish a link between WCHBP and risk factors associated with CVD, namely the development of Sustained HBP (SH) and the presence of target organ damage. Both are important and independent predictors of CV risk. Some patients with WCHBP may have an increased cardiovascular risk due to concomitant risk factors (smoking, dyslipidemia, diabetes, metabolic syndrome) or the presence of target organ damage or associated cardiovascular disease. There are doubts about the long-term prognosis, but there is sufficient evidence to show that cases with WCHBP have lower cardiovascular morbidity and mortality than sustained hypertensives and masked hypertensives, although higher than normotensives. Therefore, their cardiovascular risk would be intermediate between normotension and sustained HBP. Regarding the prevalence of target organ damage, most studies conclude that WCHBP presents greater subclinical organ involvement than normotension.[19]

Treatment: the need for pharmacological treatment is the most controversial point in the management of these patients. If we consider that subjects with WCHBP would

have a better prognosis than hypertensive, but worse than normotensive individuals, it might not be essential to prescribe antihypertensive treatment, unless there is evidence of organ involvement. Antihypertensive drugs have been shown to reduce clinical blood pressure more than ambulatory blood pressure in these patients, and there is little evidence of the potential benefit of pharmacological treatment. However, the decision to start antihypertensive drugs must be individualized and will depend on concomitant risk factors, the presence of subclinical organ damage, as well as associated cardiovascular diseases.[20]

In the HALT (Hypertension and Lipid Trial) study, Pickering et al. reported that administration of doxazosin, a long-acting alpha-1-blocker, lowered BP in patients with sustained HBP but not in those with WCHBP; however, it was equally effective on clinical blood pressure maintenance in both groups. Other investigators have reported similar results using different calcium channel blockers. On the other hand, Herpin et al. found that calcium channel blockers were ineffective in lowering ambulatory blood pressure (ABP) in patients with WCHBP, whereas angiotensin-converting enzyme (ACE) inhibitors were effective. However, both classes of drugs were effective in lowering clinical blood pressure. Similar results were reported by Kristensen et al. using felodipine (a dihydropyridine-type calcium channel blocker) and benazepril (an ACE inhibitor). In patients with WCHBP, benazepril was more effective in lowering BP. These studies suggest that the efficacy of various antihypertensive drugs in lowering BP in patients with WCHBP may differ. However, resistance to drug effect is most likely due to ABP level because patients with low-normal ABP were more resistant to treatment. This was confirmed by the studies by Fagard et al.; these authors used lisinopril and isradipine to treat HBP and found a daytime resistance PAA of 128/88 mmHg. Given the studies showing resistance to pharmacological treatment in patients with WCHBP and the results of the recent Hypertension Optimal Treatment (HOT) study showing no cardiovascular benefit in reducing blood pressure below 138.5/86.5 mmHg, except in diabetic patients, drug treatment of WCHBP should be discontinued. Instead, a nonpharmacologic management approach should be instituted.

From the outset, early intervention should be carried out on the patient's other cardiovascular risk factors. In addition, all patients with WCHBP should be treated with an intensive and comprehensive lifestyle improvement intervention. The non-pharmacological approach should include the following: modification of the patient's lifestyle, moderate salt restriction, weight loss if the patient is obese, regular exercise, smoking cessation, moderation of alcohol consumption, correction of abnormalities of blood glucose and lipids and regular follow-up for control every 6 or 12 months. By doing so, those patients who will develop sustained HBP could be detected early.

The European Society of Hypertension (ESH) has developed guidelines for the treatment of WCHBP. They suggest that patients with WCHBP and no additional CV risk factors should be managed with lifestyle changes and closely followed due to their increased risk of developing cardiovascular complications. In individuals with WCHBP and evidence of HBP-mediated organ damage or elevated CV risk, it may be appropriate to offer recommendations for lifestyle changes in conjunction with pharmacological treatment *(Figure 2)*.

Masked high blood pressure

Definition: Masked HBP (MHBP) describes a situation that occurs when clinic BP in individuals without antihypertensive treatment is < 140/90 mmHg and ambulatory BP is above reference values (130/80 mmHg in 24 h, 135/85 mmHg during daytime, or 120/70 mmHg during nighttime). In 2002, Pickering coined the term MH; MH or masked uncontrolled HBP is defined as a person who has normal blood pressure in the office and hypertensive blood pressure outside the office. The term MHBP is reserved for treatment-naïve patients and uncontrolled HBP for patients with treated HBP. Although recent emphasis on out-of-office BP measurement has led to increased recognition of the masked phenomenon, there is a lack of awareness of this phenomenon among clinicians. Furthermore, many aspects of this phenomenon remain unclear.[21]

Classification: MH can also be classified according to ABPM into two types:

1. Masked daytime HBP: this pattern is seen in people with job stress, smoking, poor exercise tolerance, or excessive alcohol use.
2. Masked nocturnal HBP: this is seen in the context of obstructive sleep apnea (OSA), diabetes, chronic kidney disease (CKD), sleep deprivation, or metabolic disorders.[22]

Prevalence: Current data on the prevalence of MH are highly variable due to differences in the ethnic origin of the study groups, the heterogeneous definition of MH, and the measurement tools used (ABPM/Daytime/Nighttime ABPM/24-hour ABPM) for its measurement diagnosis. In general, the prevalence of MH in the general population ranges between 8.5 and 16.6%. The prevalence increased to 30.4% in populations with high normal clinical BP. In a systematic review by Thakkar et.al, the prevalence of MH was significantly higher in patients of African ethnicity with a prevalence of up to 52.5% in African Americans compared to lower values in Korean patients (5.7%). and Omanis (6.0%) offspring. The presence of comorbidities also influenced the prevalence of MH, with 30% in OSA, 13.3 to 66.4% in diabetes, 7 to 32.8% in CKD, 15% on hemodialysis and 16 to 39% in kidney transplant recipients.[21]

Etiology and pathophysiology: Mechanisms which lead to MH can be classified into two groups that may not be mutually exclusive:

1. **Low office BP relative to ambulatory BP.** The exact cause of low office BP relative to ambulatory BP is unknown. But extrapolating from our understanding that WCHBP may be in part a conditioned anxiety response that is relatively specific to the clinical setting, the reverse might be true in MH, where the anxiety or stress response is greater outside of the doctor's office. Office BP in some elderly hypertensives measured after meals may show a significant postprandial reduction leading to a diagnosis of MH.
2. **Selectively high ambulatory BP.** Lifestyle factors such as smoking, alcohol, physical inactivity, interpersonal relationships. mental anxiety and work stress could selectively increase ambulatory BP. Sedentary and obese individuals may have poor exercise tolerance through daily activity and show prehypertensive office BP values when measured at rest. Exaggerated BP response to exercise (EBPRE) is also associated with MH. Kayrak et al studied sixty-one

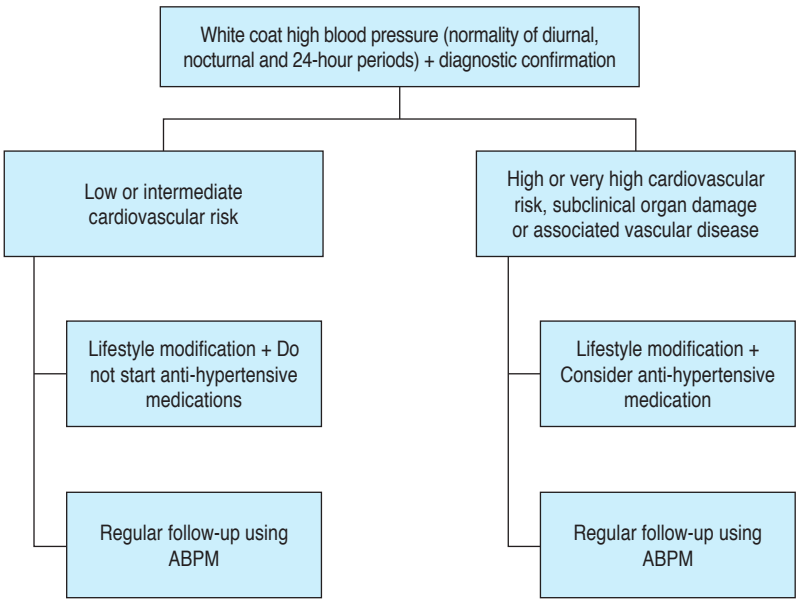


Figure 2:

Management of White coat high blood pressure. Source: Vinyoles et al, 2020.

normotensive patients with EBPRE by ABPM. The prevalence of MH in subjects with EBPRE was 41%. Diastolic BP measured at maximal exercise was an independent predictor of MH in EBPRE. Because of these factors, BP measurement should be based on anxiety-neutral approaches, such as automated office blood pressure (AOBP) and ABPM or LMWH outside the office.

Therefore, MH is higher in subjects with normal-high BP and being male, young age, being a smoker and drinker, a high level of physical activity, anxiety and work stress are predictive factors. Family history of HBP and associated CVD risk factors, such as diabetes, hypercholesterolemia, the presence of organ damage, and chronic kidney disease, are associated with a higher risk of masked HBP. Exercise-induced HBP also increases the probability of MH. Sleep apnea hypopnea syndrome also increases the presence of MH, especially elevated BP levels at night. Recent studies show that the risk of cardiovascular events in MH is higher than normotension and is equal to or even higher than in sustained HBP. In individuals under antihypertensive treatment, this situation is called masked uncontrolled HBP. The prevalence in the national ABPM registry is around 30% among individuals apparently controlled in the clinic. When the definition of HBP or control is established at 130/80 mmHg, the prevalence of masked HBP can double and reach 60%. The absence of identification of this situation would cause antihypertensive undertreatment.

Target organ damage: MH is associated with cardiovascular and renal events, as well as all-cause mortality. This has been shown in several studies in the general population.[23] MH has often been shown to progress to sustained HBP, even in older people, and confers cardiovascular risk almost like sustained HBP in both the general population and in patients with diabetes and CKD. Most of the previous studies, according to the results of the present analysis, have confirmed that MH had higher cardiovascular risk and similar to sustained HBP. Studies have also shown that the increased risk is independent of the method of out-of-office BP assessment.

In addition to patient-relevant outcomes, studies have also shown a significant association between this masked phenomenon and indirect cardiovascular outcomes, such as left ventricular hypertrophy, increased carotid intima-media thickness, albuminuria, aortic stiffness, high velocity pulse wave, silent and early cerebral infarcts, hypertensive retinal changes in patients with MH.[24]

Diagnosis: Accurate diagnosis of MH depends on reliable BP measurement in the office and out-of-office, through the different devices authorized for BP measurement. In individuals who have normal BP (< 140/90 mmHg) during clinical measurement, it can be stratified into 3 categories:

1. Optimal office BP (< 120/80 mmHg)
2. Normal BP (120-129/80-84 mmHg)
3. High normal BP (130-135/85-89 mmHg)

In people with high normal BP, the possibility of MH should be considered and an out-of-office BP measurement by ambulatory home monitoring or ABPM should be sought. In all categories, evaluation should include clinical history, physical examination, and diagnosis of HBP-mediated target organ damage. Basic screening tests include 12-lead electrocardiogram to look for left ventricular hypertrophy, urine albumin/creatinine ratio, blood creatinine, and estimated glomerular filtration rate to check for retinopathy.

Treatment. MH is a high-risk HBP phenotype and should not be left untreated. Unfortunately, many patients with MH have been excluded from HBP trials due to normal office BP values, leading to a paucity of data on how best to treat MH. No prospective clinical trials have been conducted to assess the effect of MH treatment and its impact on cardiovascular events and mortality. However, consistent evidence pointing to CV risk in patients with MH suggests treatment initiation of MH despite a lack of evidence.

It is reasonable to consider pharmacological management in identified MH patients after optimizing their metabolic profile by treating modifiable risk factors such as obesity, diabetes, OAS, alcohol avoidance, smoking, addressing work, if any, and psychosocial factors. Another

approach is to use antihypertensives to lower ambulatory BP despite the absence of elevated office BP and to monitor response to treatment by periodic ABPM. Several ongoing clinical trials are investigating the impact of antihypertensive treatment in MH. The results of an angiotensin-converting enzyme (ACE) inhibitor are awaited to assess the effect of antihypertensives on clinical and ambulatory BP, proteinuria, and target organ damage in patients with MH. Another large, prospective, multicenter, randomized, 4-year study aims to understand MH treatment based on office and out-of-office ABPM measurements and differences in outcome with a focus on cardiovascular endpoints and events (left ventricular hypertrophy) and renal (proteinuria) including all-cause mortality, CV morbidity and mortality, cerebral morbidity, and mortality. An interventional trial from China also aims to study the role of alisartan isoproxil in the treatment of MH for the protection of the target organs.[25]

4. Phenotypes based on blood pressure variability

We can also find phenotypes in relation to a high BP variability, such as patients with morning, night, or orthostatic HBP and the one that is related to significant elevations in BP with physical effort or emotional changes called by some authors as «reactive».[5,26] For the identification of these phenotypes, the use of ABPM is essential. The main characteristics of these phenotypes are summarized in *Table 4*.

5. Hypertensive phenotypes unresponsive to treatment

We also have patients who do not respond to conventional pharmacological treatment, known as patients with pseudo-resistant HBP and refractory or resistant HBP. These types of patients should generally be referred to specialists in HBP, very common causes

Table 4: High blood pressure phenotypes according to circumstancial high blood pressure.

Phenotype	White coat high blood pressure	Masked high blood pressure
Definition	Normal office blood pressure and normal out-of-office blood pressure.	Factors such as smoking, alcoholism, physical inactivity, exaggerated response to exercise (exercise high blood pressure), interpersonal relationships, mental anxiety and work stress.
Etiology	Psychological factors (stress, anxiety)	Significant association between masked phenomenon and indirect cardiovascular outcomes, such as left ventricular hypertrophy, increased carotid intima-media thickness, albuminuria, aortic stiffness, high pulse wave velocity, silent cerebral infarcts, and early cerebral infarcts, hypertensive retinal changes.
Pathophysiology	Poorly understood. Hypothesis of involvement of the sympathetic and endocrine system.	Variable
Prognosis	Increases the risk of sustained high blood pressure compared to normotensives. Causes target organ damage compared to normotensives. Some studies have found an increased cardiovascular risk compared to normotensive patients.	Increased cardiovascular risk
Treatment	Correction measures in risk factors. Pharmacology should be individualized according to the presence of risk factors and target organ damage.	Pharmacological, studies with ACEI and ARB.

ESH = European Society high blood pressure; ACEI = Angiotensin-converting enzyme inhibitors; ARB = Angiotensin receptor blockers; BB = Beta-blockers.

Table 5: High blood pressure phenotypes according high blood pressure variability.

Phenotype	Nocturnal and day-night variety high blood pressure	Orthostatic high blood pressure	Reactive high blood pressure
Definition	Nocturnal: Mean diastolic > 70 mmHg systolic < 120 mmHg during sleep. Dipper: decrease between 10 - 20%. Hyper-dipper: decrease > 20% Non-Dipper: decrease < 10% Reverse riser or dipper: Lack of descent (0%) or ascent.	Difference between lying and standing position: > 15 to 20 mmHg	Disproportionate increase in BP due to physical exertion or emotional changes. Disproportionate increase in the double product (heart rate x blood pressure) during physical exercise.
Etiology	Obesity, sleep disorders, inadequate antihypertensive therapy.	Unknown	Personality disorders.
Pathophysiology	Due to increased cardiac output and peripheral vascular resistance and in some cases due to sleep apnea.	Autonomic dysfunction.	Increased cardiac output and peripheral vascular resistance.
Prognosis	Increased risk for subclinical cardiovascular and renal damage and increased mortality.	Increased risk of syncope and cognitive impairment.	Increased cardiovascular and renal risk.
Treatment	Treatment of sleep disorder and use of fixed combinations. Chronotherapy?	Evaluate monotherapy.	Psychological and adjustment of pharmacological treatment.

Table 6: Hypertension phenotypes according to responsiveness to treatment.

Phenotype	Pseudo resistant	Resistant
Definition	When treatment control objectives are not achieved with a combination of three drugs at correct doses, including a thiazide-type diuretic, but adequate non-pharmacological measures have not been established or secondary causes have not been ruled out.	When the BP control goals are not achieved despite having established the appropriate non-pharmacological measures and treatment with a combination of three drugs at correct doses, one of which must be a thiazide diuretic.
Etiology	Poor adherence to treatment. Suboptimal doses and/or pharmacological combinations. Improper lifestyle Unidentified secondary cause White or masked coat effect Concomitant use of drugs that stimulate the increase in BP such as NSAIDs, vasoconstrictors, etc.	Multifactorial
Pathophysiology	Unknown	Unknown
Prognosis	Increased cardiovascular and renal risk.	Increased cardiovascular and renal risk.
Treatment	Education and eliminating the cause of pseudo resistance.	Evaluate therapies with the addition of a 4th drug such as spironolactone and rule out a secondary cause. Use alternatives such as renal denervation and carotid stimulation devices in specialized centers.

BP = Blood pressure, NSAID = Non-steroidal anti-inflamatory drugs

of pseudo-resistance should be thoroughly investigated before being designated as resistant *(Tables 5 and 6)*.

Resistant HBP is defined when BP control goals are not achieved despite having instituted appropriate non-pharmacological measures and treatment with a combination of three drugs at correct doses, one of which must be a thiazide diuretic. In these cases, it is often necessary to add a 4th drug such as low-dose spironolactone or refer to specialized centers for invasive therapeutic alternatives such as renal denervation or the implantation of carotid stimulation devices.

Table 7: High blood pressure phenotypes based on urgency or cardiovascular risk

Phenotype	Urgency	Cardiovascular risk
Definition	Major: Severe elevation of diastolic BP > 90 mmHg systolic > 180 mmHg that carries the risk of target organ damage and/or death. Minor: Severe elevation of diastolic BP > 90 mmHg systolic < 180 mmHg that does not carry a risk of target organ damage and/or death.	It depends on the severity of high blood pressure and the association with conventional cardiovascular risk factors and/or metabolic syndrome (MS).
Etiology	Multifactorial	Multifactorial
Pathophysiology	Unknown	Increased cardiac output and vascular resistance, in patients with MS an increase in insulin resistance is observed.
Prognosis	Increased risk of death and cardiovascular and cerebral morbidity.	It depends on severity which is divided into low when the risk of cardiovascular mortality is less than 2%, moderate between 2 and 10%, and high to very high when it is 10%. Patients with diabetes mellitus, target organ damage, frail or MS are considered to be at very high risk.
Treatment	Major: It is treated in an emergency department with specialized treatment mainly with intravenous antihypertensive drugs. Minor: Can be treated in the office with fast-acting drugs and combinations.	Low risk: Changes in lifestyle and monotherapy. Moderate, high and very high risk: Changes in lifestyle and combination therapy. Frail: Changes in lifestyle and monotherapy.

MS = Metabolic syndrome

Table 8: Calculation of total cardiovascular risk (TCR) according to NOM-037-SSA2-2012, for the prevention, treatment and control of dyslipidemias suggests the following levels of total cardiovascular risk.

Level of risk	10-year estimated total cardiovascular risk	Characteristics
Low	< 5%	0-1 risk factors excluding high-risk conditions
Intermediate	5-19%	≥ 2 risk factors excluding high-risk conditions
High	≥ 10%	High-risk conditions: Established cardiovascular disease, diabetes mellitus, severe risk factor, familial hypercholesterolemia, mixed dyslipidemia, familial combined hyperlipidemia, subclinical target organ damage, family history of early stroke, metabolic syndrome, estimated cardiovascular risk ≥ 20%

6. Phenotypes derived by cardiovascular risk or urgency

There are circumstances where HBP can significantly increases the risk of target-organ damage, especially at the brain (malignant), cardiovascular or renal level, called hypertensive urgency. When this damage can be reversible and the life of the patient is not at risk it is called a minor hypertensive emergency or «hypertensive crisis», whereas when this damage puts the patient's life at risk, it is called a major hypertensive emergency or hypertensive «emergency». Cardiovascular risk of patients with HBP depends on the degree of HBP and the association with conventional cardiovascular risk factors and/or metabolic syndrome (MS).

These phenotypes are classified depending on the severity of HBP. It is considered low when the risk of cardiovascular mortality is less than 5% at 10 years, moderate or intermediate between 5-19%, and high to very high when it is greater than 20%. Patients with diabetes mellitus, target organ damage, frail, with MS and other conditions are considered at very high risk *(Tables 7 and 8)*. Increased risk in patients with MS is fundamentally due to abdominal obesity, which leads to carbohydrate metabolism disorders, insulin, and lipid resistance, as well as a proinflammatory and prothrombotic state, along with various other atherogenic factors. Currently available evidence indicates that the diagnosis of MS is more useful in predicting cardiovascular mortality than overall mortality. Finally, estimating the frailty of hypertensive patients, especially older adults, is essential for the treatment to be followed.

Identification of these hypertensive phenotypes can help us decide on the therapeutic approaches to follow. For example, in low-risk patients, changes in lifestyle and monotherapy are started; in patients with moderate, high, and very high risk, changes in lifestyle and combined therapy, while in frail patients changes in lifestyle and monotherapy.

Although we know that there may be many other phenotypes, these are the most common that we face in our daily practice in patients with HBP. Undoubtedly, identifying these phenotypes will allow us to carry out a better daily clinical practice.

REFERENCES

1. Keasley J, Oyebode O, Shantikumar S, Proto W, McGranahan M, Sabouni A et al. A systematic review of the burden of hypertension, access to services and patient views of hypertension in humanitarian crisis settings. BMJ Glob Health. 2020; 5: e002440. Available in: https://doi.org/10.1136/bmjgh-2020-002440
2. Encuesta Nacional de Salud y Nutrición. ENCUESTAS n.d. https://ensanut.insp.mx/encuestas/ensanut2018/informes.php (accessed March 29, 2022).
3. Oseguera HG, Peralta MR, Muñoz JME, Hbpm A group for. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control in Mexico. Ann Clin Hypertens. 2018; 2: 017-023. Available in: https://doi.org/10.29328/journal.ach.1001007
4. Kario K. Blood pressure variability in hypertension: a possible cardiovascular risk factor. Am J Hypertens. 2004; 17: 1075-1076. Available in: https://doi.org/10.1016/j.amjhyper.2004.06.021.
5. Hernández HH y, Moctezuma CM, Solís GO, Farías AG de L, Garibay DLL, Pérez MLV et al. Resumen integrado Norma Oficial Mexicana NOM-030-SSA2-2009, para la prevención, detección, diagnóstico, tratamiento y control de la hipertensión arterial sistémica. Rev Mex Cardiol. 2012; 23: 4-38.
6. World Hypertension League | Journal of Human Hypertension n.d. (Accessed March 29, 2022) Available in: https://www.nature.com/jhh/partners/whl
7. Sanchez RA, Ayala M, Baglivo H, Velazquez C, Burlando G, Kohlmann O et al. Latin American guidelines on hypertension. Latin American Expert Group. J Hypertens. 2009; 27: 905-922. Available in: https://doi.org/10.1097/HJH.0b013e32832aa6d2
8. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018; 39: 3021-3104. Available in: https://doi.org/10.1093/eurheartj/ehy339
9. Alcocer L, Álvarez-López H, Borrayo-Sánchez G, Cardona-Muñoz EG, Chávez-Mendoza A, Díaz ED et al. Hypertension as a persistent public health problem. A position paper from Alliance for a Healthy Heart, Mexico. Ann Clin Hypertens. 2019; 3: 009-030. Available in: https://doi.org/10.29328/journal.ach.1001015
10. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D et al. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens. 2020; 38: 982-1004. Available in: https://doi.org/10.1097/HJH.0000000000002453
11. Sivén SSE, Niiranen TJ, Kantola IM, Jula AM. White-coat and masked hypertension as risk factors for progression to sustained hypertension: the Finn-Home study. J Hypertens. 2016; 34: 54-60. Available in: https://doi.org/10.1097/HJH.0000000000000750
12. Briasoulis A, Androulakis E, Palla M, Papageorgiou N, Tousoulis D. White-coat hypertension and cardiovascular events: a meta-analysis. J Hypertens.

2016; 34: 593-599. Available in: https://doi.org/10.1097/HJH.0000000000000832
13. Hanninen M-RA, Niiranen TJ, Puukka PJ, Johansson J, Jula AM. Prognostic significance of masked and white-coat hypertension in the general population: the Finn-Home Study. J Hypertens. 2012; 30: 705-712. Available in: https://doi.org/10.1097/HJH.0b013e328350a69b
14. Bargalló EV. Hipertensión de bata blanca. Criterios de abordaje y pronóstico. FMC - Form Médica Contin En Aten Primaria. 2020; 27: 515-519. Available in: https://doi.org/10.1016/j.fmc.2020.03.014
15. Nuredini G, Saunders A, Rajkumar C, Okorie M. Current status of white coat hypertension: where are we? Ther Adv Cardiovasc Dis. 2020; 14: 1753944720931637. Available in: https://doi.org/10.1177/1753944720931637
16. Gijón-Conde T, Gorostidi M, Banegas JR, de la Sierra A, Segura J, Vinyoles E et al. [Position statement on ambulatory blood pressure monitoring (ABPM) by the Spanish Society of Hypertension (2019)]. Hipertens Riesgo Vasc. 2019; 36: 199-212. Available in: https://doi.org/10.1016/j.hipert.2019.05.002
17. Chrysant SG. Treatment of white coat hypertension. Curr Hypertens Rep. 2000; 2: 412-417. Available in: https://doi.org/10.1007/s11906-000-0046-7
18. Hozawa A, Ohkubo T, Obara T, Metoki H, Kikuya M, Asayama K et al. Introversion associated with large differences between screening blood pressure and home blood pressure measurement: The Ohasama study. J Hypertens. 2006; 24: 2183-2189. Available in: https://doi.org/10.1097/01.hjh.0000249695.81241.35
19. Huang Y, Huang W, Mai W, Cai X, An D, Liu Z et al. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. J Hypertens. 2017; 35: 677-688. Available in: https://doi.org/10.1097/HJH.0000000000001226
20. Mancia G, Facchetti R, Parati G, Zanchetti A. Effect of long-term antihypertensive treatment on white-coat hypertension. Hypertens Dallas Tex 1979. 2014; 64: 1388-1398. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.114.04278
21. Thakkar HV, Pope A, Anpalahan M. Masked hypertension: a systematic review. Heart Lung Circ. 2020; 29: 102-111. Available in: https://doi.org/10.1016/j.hlc.2019.08.006
22. Yano Y, Bakris GL. Recognition and management of masked hypertension: a review and novel approach. J Am Soc Hypertens JASH. 2013; 7: 244-252. Available in: https://doi.org/10.1016/j.jash.2013.02.002
23. Babu M, Drawz P. Masked hypertension in CKD: increased prevalence and risk for cardiovascular and renal events. Curr Cardiol Rep. 2019; 21: 58. Available in: https://doi.org/10.1007/s11886-019-1154-4
24. Ibarra-González I, Cruz-Bautista I, Bello-Chavolla OY, Vela-Amieva M, Pallares-Méndez R, Ruiz de Santiago Y Nevarez D et al. Optimization of kidney dysfunction prediction in diabetic kidney disease using targeted metabolomics. Acta Diabetol. 2018; 55: 1151-1161. Available in: https://doi.org/10.1007/s00592-018-1213-0
25. Penmatsa KR, Biyani M, Gupta A. Masked hypertension: lessons for the future. Ulster Med J. 2020; 89: 77-82.
26. Kario K, Eguchi K, Hoshide S, Hoshide Y, Umeda Y, Mitsuhashi T et al. U-curve relationship between orthostatic blood pressure change and silent cerebrovascular disease in elderly hypertensives: orthostatic hypertension as a new cardiovascular risk factor. J Am Coll Cardiol. 2002; 40: 133-141. Available in: https://doi.org/10.1016/s0735-1097(02)01923-x

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: The authors declare that they have no conflict of interests.

Correspondence:
Héctor Galván-Oseguera, MD
E-mail: cardiomedicamx@hotmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105186

Understanding high blood pressure: pathophysiological advances

Entender la hipertensión arterial: avances fisiopatológicos

David Cardona-Müller, MD* Ernesto G Cardona-Muñoz, MD*

Keywords:
High blood pressure, pathophysiology, arterial function, cardiovascular disease.

Palabras clave:
Hipertensión arterial, fisiopatología, función arterial, enfermedad cardiovascular.

ABSTRACT

High blood pressure (HBP) has been identified as a major risk factor for cardiovascular events such as stroke and myocardial infarction. To understand the pathophysiology of high blood pressure and other diseases which affect the cardiovascular system, it is necessary to understand how they occur. Here, we discuss pathophysiological elements which lead to HBP including a discussion on arterial stiffness, as well as the biophysical and hemodynamic components which lead to the sustenance and increase in systemic blood pressure levels in adults. We also discuss humoral components which regulate blood pressure and which, when dysregulated, play a pivotal role in the pathophysiology of HBP.

RESUMEN

La hipertensión arterial (HTA) se ha identificado como uno de los principales factores de riesgo de eventos cardiovasculares como el ictus y el infarto de miocardio. Para entender la fisiopatología de la hipertensión arterial y otras enfermedades que afectan al sistema cardiovascular, es necesario comprender cómo se producen. En este artículo se analizan los elementos fisiopatológicos que conducen a la HTA, incluida una discusión sobre la rigidez arterial, así como los componentes biofísicos y hemodinámicos que conducen al mantenimiento y al aumento de los niveles de presión arterial sistémica en los adultos. También se analizan los componentes humorales que regulan la presión arterial y que, cuando están desregulados, desempeñan un papel fundamental en la fisiopatología de la HTA.

INTRODUCTION

For the last 70 years, high blood pressure (HBP) has been extensively studied and identified as major risk factor for cardiovascular events such as stroke and myocardial infarction. However, oftentimes we make the mistake of setting our goals only on lowering blood pressure levels and because of this, our knowledge regarding this pathology and its consequences is limited. To understand the pathophysiology of high blood pressure and other diseases which affect the cardiovascular system, it is necessary to understand how they occur. Thus, it is of vital importance to understand the neurohumoral systems involved in its regulation, as well as the physical and mechanical characteristics of its different components.

ARTERIAL STIFFNESS

Arterial stiffness is the discipline that arises to help understand the relationship between the mechanics of continuous media in the arterial wall and that of the fluids contained by them. For this it is necessary to know the composition of the arterial wall, which in turn has:

1. **Solid components:** extracellular matrix, collagen fibers and elastin.
2. **Liquids:** water, mucopolysaccharides and glycoproteins.
3. **Interaction** with external, internal and neurohumoral stimuli, mainly mediated by blood flow, which is a viscous fluid and conditions that vary cyclically according to the cardiac cycle. In addition to the

* Investigador Asociado, Universidad de Guadalajara, Jalisco, México. Asociación Nacional de Cardiólogos de México, Ciudad de México, México, Miembro GREHTA.

How to cite: Cardona-Müller D, Cardona-Muñoz EG. Understanding high blood pressure: pathophysiological advances. Cardiovasc Metab Sci. 2022; 33 (s3): s211-s215. https://dx.doi.org/10.35366/105186

cyclical variation that arteries face, they also present changes in their structure over time, both due to associated physiological and pathological conditions.

Arterial behavior also presents variations according to the caliber and arterial wall composition. In physiological conditions we can divide the arterial tree into arteries of large, medium, and small caliber, according to their caliber.

1. **Large-caliber arteries** have as a characteristic the ability to distend and comply to the challenges that arise due to cardiac activity.
2. **Small caliber arteries** act dissipating the energy and those of medium caliber with an intermediate function between both.[1,2]

Each of these types of arteries is responsible for carrying out a different function to guarantee blood flow to the organism.

1. **Conduction:** to channel blood from the heart to the capillaries. This function is carried out mainly by the large and medium caliber arteries.
2. **Pressure reservoir:** the ventricular systole and the pulsatile wave that it produces, generates a significant distension of the walls of the large-caliber arteries. During diastole, the elasticity that characterizes these arteries causes their diameter to return to normal, driving blood content in the distended artery in an antegrade direction. Thus, large-caliber arteries function as a reservoir for the volume and kinetic energy generated by the left ventricle during systole.
3. **Regulation of volume and blood flow:** this function corresponds to medium caliber arteries and arterioles. The high content of muscle fibers in these arteries allows the regulation of the arterial diameter according to the muscle tone that is present, either vasodilation or vasoconstriction. This function is tightly regulated by different neurohumoral factors.
4. **Dampening of pulsatility:** the cardiac cycle generates pulsatility with a significant variation between systolic and diastolic pressure. Arterioles are responsible for dampening this variation, functioning as sphincters which regulate blood flow to the capillary bed, thus favoring continuous capillary flow and pressure during systole and diastole.[2]

Aging produces functional and structural changes in the arterial system characterized primarily by the substitution of elastin for fibrin and collagen, causing originally elastic arteries to become rigid and non-compliant. This leads to changes in the interaction between the heart, blood and several organs which are more susceptible to these variations. This pulse wave represents the transmission of energy through a fluid (plasma) without necessarily implying a massive movement of this fluid. Energy is transmitted through an elastic tube (blood vessel), and the resulting pulse wave represents the interaction between the energy applied to the fluid, the characteristics of the blood, and of the blood vessel.[3]

Structural changes produced by aging also modify the pulse wave. Recently, the value of pulse wave velocity (PWV) has been associated to changes produced by aging, where an increase in PWV has a direct relationship with aging. Measurement of PWV is accepted as the simplest, non-invasive, robust, and reproducible method to determine arterial stiffness. Carotid-femoral PWV (cfPWV) is a direct measure and corresponds to the widely accepted propagative model of the arterial system and as the gold standard for PWV measurement. Of the different methods that assess arterial stiffness, cfPWV is considered the gold standard, due to its easy determination, reproducibility and high reliability, in addition to having evidence of its association with cardiovascular disease and mortality independent of traditional cardiovascular risk factors.[4-6]

Studies such as these have supported the inclusion of cfPWV as one of the markers considered to be equivalent to subclinical organ damage since the 2013 European guidelines for HBP. Elevated cfPWV (≥ 10 m/s) is a marker of arterial stiffness that due to its correlation with mortality and major cardiovascular events independent of traditional risk factors. cfPWV is

currently considered the gold standard to assess arterial stiffness and the equivalent of HBP-mediated organ damage, which is especially relevant in patients with low and intermediate cardiovascular risk.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) AND HIGH BLOOD PRESSURE

The RAAS is responsible for the regulation of BP, electrolyte balance and extracellular fluid. RAAS activation is a body defense system, which is preferentially activated in the presence of hypoperfusion, hyponatremia, sympathetic system activation and tissue damage. Dysregulation of the RAAS can lead to HBP, electrolyte disbalance, proliferation, fibrosis, apoptosis, thrombosis, fibrinolysis, and systemic inflammatory activity.[7,8] The traditional concept of RAAS changed radically in recent years, with the expression of tissue components becoming increasingly important in the genesis of tissue damage. Pro-renin, previously considered an inactive component of the system, seems to regulate the expression of the renin gene itself and of other components of the RAAS, highlighting the link between the RAAS and the natriuretic peptide system.[9] The harmful effect of the over-expression of RAAS components in the genesis and progression of organ damage in HBP and diabetes mellitus is incontrovertible.[10]

Another factor strongly linked to neurohumoral alterations is endothelial dysfunction. Vascular aging/damage reduces its vasodilator and antithrombotic capacity and increases oxidative stress and the presence of inflammatory cytokines which favor hypertrophy, atherogenesis and thrombosis. Clinical and experimental studies show that nitric oxide (NO) depletion is a key factor in endothelial dysfunction and the genesis of cardiovascular disease. Endothelial nitric oxide synthase (eNOS) is the enzyme responsible for producing NO from L-arginine in the presence of its co-factor tetrahydrobiopterin (BH4). The uncoupling between it and its co-factor BH4, decreases NO production and increases the production of pro-oxidant factors, which leads to chronic inflammation and increases NO degradation.[11]

SARS-CoV-2 AND HIGH BLOOD PRESSURE

The SARS-CoV-2 virus appears to employ receptor recognition mechanisms like those used by other coronaviruses. The spike protein of the coronavirus facilitates the entry of the virus into cells and increases expression for the angiotensin-converting enzyme 2 (ACE-2) as an entry receptor. The efficiency with which the virus binds to ACE2 is decisive for its transmissibility. Key mechanisms which may play a role in the pathophysiology of multiorgan injury secondary to SARS-CoV-2 infection include:

1. Direct viral toxicity.
2. Endothelial cell damage and thrombo/inflammation.
3. Dysregulation of the immune response.
4. Dysregulation of the renin-angiotensin-aldosterone system. (RAAS).

Direct viral toxicity. Histopathological studies show organotropism of SARS-CoV-2 beyond the respiratory tract, including the renal, myocardial, neurological, pharyngeal, and gastrointestinal systems. Furthermore, single-cell RNA sequencing studies have confirmed the expression of ACE-2 and TMPRSS2 in the pulmonary alveolar epithelium.[12]

Endothelial cell damage and thrombo/inflammation. Endothelial damage produced by the entry of SARS-CoV-2 into the cell mediated by ACE2 and the subsequent inflammation generate a prothrombotic environment, which is a significant pathophysiological mechanism in severe forms of COVID-19. ACE2 expression has been demonstrated in arteries and venous endothelium of various organs with increased thrombin production, inhibiting fibrinolysis and activating complement pathways, triggering a process of thrombosis and inflammation with microthrombi deposition and microvascular dysfunction.[13]

Dysregulation of the immune response.

Dysregulation of the RAAS. Recently, Carlos Ferrario, MD described the enzyme ACE2, a membrane-bound aminopeptidase, as a potent counter-regulator of the RAAS pathway. ACE2 converts angiotensin I to inactive angiotensin 1-9 and angiotensin II to angiotensin 1-7 (decreasing the adverse ACE/AngII/AT1 axis),

which has vasodilatory, antiproliferative, and antifibrotic properties. Although the mechanism of infection and damage of SARS-CoV-2 may not be limited exclusively to pathways related to ACE2, this enzyme plays a very significant role in both the mechanism of infection and damage, as well as many of the clinical manifestations of COVID-19. Chen et al found a decrease in the degradation of angiotensin II especially when the balance between the ACE and ACE2 was disrupted in COVID-19 patients. Increases in angiotensin II could lead to myocardial inflammation, oxidative stress, and myocyte apoptosis. This hypothesis explains why elevated blood pressure could occur in parallel with mild cardiac injury in COVID-19 patients.[14-16]

LIPID DISORDERS, OBESITY, AND HIGH BLOOD PRESSURE

Whilst obesity is commonly seen as an increase in weight, it can be better conceptualized as a state of excess adipose tissue. Although it is not a direct measure of adiposity, the most used method to define obesity is the body-mass index (BMI), which is equal to the individual's weight divided by height squared (kg/m^2). A BMI > 30 kg/m^2 is commonly used as the definition of obesity. Obesity is considered to play a part in the etiology of HBP, where multiple pathophysiological mechanisms participate in its development. Mechanisms which link both obesity and HBP include insulin resistance, inflammation, oxidative stress, modified adipokine secretion (such as adiponectin and leptin), increased activity of the sympathetic nervous system, and the renin-angiotensin aldosterone system. In obesity, when excess triglycerides exceed the storage capacity of peripheral adipocytes, these are stored in liver, skeletal muscle, and visceral adipocytes. This abnormal accumulation of triglycerides is associated with insulin resistance in the liver and muscles, leading to ectopic fat deposition.

The adipocyte was considered for a long time only as a fat depot, but recent evidence highlights it also as an endocrine cell, which secretes several hormones which together are known as adipokines. Notably, some of these adipokines are related to endothelial dysfunction and cardiovascular risk *(Table 1)*.

Table 1: Adipokines related to the pathophysiology of high blood pressure.

Increase with obesity	Decrease with obesity
Free fatty acids	Adiponectin
TNF-α	
Resistin	
Leptin	
PAI-I	
Angiotensinogen	

Excess free fatty acids which are present in obesity directly cause endothelial dysfunction, in addition to inhibiting glucose-stimulated insulin release, which can lead to progressive β-cell dysfunction in susceptible individuals and even sometimes to apoptosis. TNF-α is a cytokine produced by adipose tissue, most commonly by infiltrating macrophages, which directly suppresses insulin signaling by increasing serine phosphorylation on insulin receptor substrate 1 (IRS-1), thereby decreasing insulin receptor kinase activity leading to insulin resistance, in addition to being a proinflammatory factor related to atherosclerosis.[17]

Increased plasminogen activator inhibitor-1 (PAI-1) values are associated with antifibrinolysis while increased angiotensinogen concentration together with an increased activity of the RAAS is related to the appearance of HBP.[18] Obstructive sleep apnea, which is extremely common in obesity, also causes sympathetic stimulation, further contributing to elevated blood pressure in this patient population.[17] The combination of enhanced sympathetic nervous system activity and RAAS activity in obesity also causes impaired natiuresis, increased renal sodium reabsorption, and extracellular volume expansion, further propagating the development of HBP in obesity.

REFERENCES

1. Jordan J, Kurschat C, Reuter H. Arterial hypertension. Dtsch Arztebl Int. 2018; 115: 557-568. Available in: https://doi.org/10.3238/arztebl.2018.0557.

2. Koenigsberger M, Sauser R, Bény JL, Meister JJ. Effects of arterial wall stress on vasomotion. Biophys J 2006; 91: 1663-1674. Available in: https://doi.org/10.1529/biophysj.106.083311.
3. Attinger EO, Attinger FM. Frequency dynamics of peripheral vascular blood flow. Annu Rev Biophys Bioeng. 1973; 2: 7-36. Available in: https://doi.org/10.1146/annurev.bb.02.060173.000255.
4. Mitchell GF. Arterial stiffness and wave reflection in hypertension: pathophysiologic and therapeutic implications. Curr Hypertens Rep 2004; 6: 436-441. Available in: https://doi.org/10.1007/s11906-004-0037-1.
5. Maldonado J, Pereira T, Polónia J, Silva JA, Morais J, Marques M et al. Arterial stiffness predicts cardiovascular outcome in a low-to-moderate cardiovascular risk population: the EDIVA (Estudo de DIstensibilidade VAscular) project. J Hypertens. 2011; 29: 669-675. Available in: https://doi.org/10.1097/HJH.0b013e3283432063.
6. Sehestedt T, Jeppesen J, Hansen TW, Wachtell K, Ibsen H, Torp-Pedersen C et al. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. Eur Heart J. 2010; 31: 883-891. Available in: https://doi.org/10.1093/eurheartj/ehp546.
7. Azushima K, Morisawa N, Tamura K, Nishiyama A. Recent research advances in renin-angiotensin-aldosterone system receptors. Curr Hypertens Rep. 2020; 22: 22. Available in: https://doi.org/10.1007/s11906-020-1028-6.
8. Alcocer L, Álvarez-López H, Borrayo-Sánchez G, Cardona-Muñoz EG, Chávez-Mendoza A, Díaz ED et al. Hypertension as a persistent public health problem. A position paper from Alliance for a Healthy Heart, Mexico. Ann Clin Hypertens. 2019; 3: 9-30. Available in: https://doi.org/10.29328/journal.ach.1001015.
9. Patel S, Rauf A, Khan H, Abu-Izneid T. Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. Biomed Pharmacother Biomedecine Pharmacother. 2017; 94: 317-325. Available in: https://doi.org/10.1016/j.biopha.2017.07.091.
10. Santos RAS, Oudit GY, Verano-Braga T, Canta G, Steckelings UM, Bader M. The renin-angiotensin system: going beyond the classical paradigms. Am J Physiol Heart Circ Physiol. 2019; 316: H958-H970. Available in: https://doi.org/10.1152/ajpheart.00723.2018.
11. Dikalov SI, Nazarewicz RR. Angiotensin II-induced production of mitochondrial reactive oxygen species: potential mechanisms and relevance for cardiovascular disease. Antioxid Redox Signal. 2013; 19: 1085-1094. Available in: https://doi.org/10.1089/ars.2012.4604.
12. Cao W, Li T. COVID-19: towards understanding of pathogenesis. Cell Res. 2020; 30: 367-369. Available in: https://doi.org/10.1038/s41422-020-0327-4.
13. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020; 116: 1666-1687. Available in: https://doi.org/10.1093/cvr/cvaa106.
14. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020; 63: 364-374. Available in: https://doi.org/10.1007/s11427-020-1643-8.
15. Ravichandran B, Grimm D, Krüger M, Kopp S, Infanger M, Wehland M. SARS-CoV-2 and hypertension. Physiol Rep. 2021; 9: e14800. Available in: https://doi.org/10.14814/phy2.14800.
16. Chen G, Li X, Gong Z, Xia H, Wang Y, Wang X et al. Hypertension as a sequela in patients of SARS-CoV-2 infection. PloS One. 2021; 16: e0250815. Available in: https://doi.org/10.1371/journal.pone.0250815.
17. Cohen JB. Hypertension in obesity and the impact of weight loss. Curr Cardiol Rep. 2017; 19: 98. Available in: https://doi.org/10.1007/s11886-017-0912-4.
18. Miranda PJ, DeFronzo RA, Califf RM, Guyton JR. Metabolic syndrome: definition, pathophysiology, and mechanisms. Am Heart J. 2005; 149: 33-45. Available in: https://doi.org/10.1016/j.ahj.2004.07.013.

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: The authors declare that they have no conflict of interests.

Correspondence:
David Cardona-Müller, MD
E-mail: david.cardonamuller@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105187

Kidney and heart damage associated with high blood pressure: strategies for early detection in primary care settings

Daños renales y cardiacos asociados a la hipertensión arterial: estrategias para su detección precoz en el ámbito de la atención primaria

Silvia Palomo-Piñón, MD,* Vidal José González-Coronado, MD,‡
Neftali Eduardo Antonio-Villa, MD§

Keywords:
High blood pressure, kidney damage, heart damage.

Palabras clave:
Presión arterial alta, daño renal, daño cardiaco.

* Clinical Nephrology. Associated Researcher at Unidad de Investigación Médica en Enfermedades Nefrológicas Siglo XXI, UMAE Hospital de Especialidades «Dr. Bernardo Sepúlveda G», Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico. Programa de Posgrado en Ciencias Médicas, Odontológicas y de la Salud, Universidad Nacional Autónoma de México. Member of GREHTA.
‡ Interventional Cardiology. Head of Hemodynamics Department, Hospital General Regional «1 de Octubre», Instituto de Seguridad y Servicios Sociales para los Trabajadores del Estado, Mexico City, Mexico, Member of GREHTA.

ABSTRACT

High blood pressure (HBP) is a highly prevalent metabolic condition in the Mexican population that produces multisystem involvements with heterogeneous effects among individuals. In the long term, the complex relationship between cardiometabolic risk factors promotes the development of Atherosclerotic Cardiovascular Disease (ASCVD). A critical associated complication is the cardiorenal effect related to HBP, which leads to a high burden of chronic kidney disease (CKD) and heart damage. Hence, the importance of promptly identifying cardiorenal impairments at early stages of the disease within primary care (PC) personnel. This work aims to point out the early diagnosis strategies for kidney and heart damage in patients with HBP to systematize their search in a PC setting. A moderate decrease in the estimated glomerular filtration rate (eGFR) and the presence of any degree of albuminuria are excellent markers for screening kidney damage. Left ventricular hypertrophy (LVH) assessed with either an electrocardiogram (EKG) or echocardiography had well-defined criteria and validated indexes to identify cardiac damage. Finally, a severe complication is heart failure (HF), which needs to be fundamentally based on clinical and EKG findings. A correct interpretation of an EKG makes an accurate diagnosis in 75% of patients living with HF. The proper implementation of these strategies in a PC scenario is crucial to identify cardiorenal impairments and reduce the long-term incidence of ASCVD in the Mexican population.

RESUMEN

La hipertensión arterial (HTA) es una condición metabólica de alta prevalencia en la población mexicana que produce afectaciones multisistémicas con efectos heterogéneos entre los individuos. A largo plazo, la compleja relación entre los factores de riesgo cardiometabólico promueve el desarrollo de la enfermedad cardiovascular ateroesclerótica (ECAE). Una complicación crítica asociada es el efecto cardiorrenal relacionado con la HTA, que conduce a una alta carga de enfermedad renal crónica (ERC) y daño cardíaco. De ahí la importancia de identificar con prontitud las alteraciones cardiorrenales en las fases iniciales de la enfermedad en el personal de atención primaria (AP). Este trabajo pretende señalar las estrategias de diagnóstico precoz del daño renal y cardíaco en pacientes con HTA para sistematizar su búsqueda en el ámbito de la AP. La disminución moderada de la tasa de filtración glomerular estimada (TFGe) y la presencia de cualquier grado de albuminuria son excelentes marcadores para detectar el daño renal. La hipertrofia ventricular izquierda (HVI) evaluada con un electrocardiograma (EKG) o una ecocardiografía tenía criterios bien definidos e índices validados para identificar el daño cardíaco. Por último, una complicación grave es la insuficiencia cardíaca (IC), que debe basarse fundamentalmente en los hallazgos clínicos y del electrocardiograma. Una correcta interpretación del electrocardiograma permite realizar un diagnóstico preciso en 75% de los pacientes con IC. La implementación adecuada de estas estrategias en un escenario de AP es crucial para identificar las alteraciones cardiorrespiratorias y reducir la incidencia a largo plazo de la ECAE en la población mexicana.

How to cite: Palomo-Piñón S, González-Coronado VJ, Antonio-Villa NE. Kidney and heart damage associated with high blood pressure: strategies for early detection in primary care settings. Cardiovasc Metab Sci. 2022; 33 (s3): s216-s222. https://dx.doi.org/10.35366/105187

§ MD/PhD (PECEM), Faculty of Medicine, National Autonomous University of Mexico, Mexico City, Mexico, Member of GREHTA.

Abbreviations:
ASCVD = Atherosclerotic Cardiovascular Disease.
CKD = Chronic Kidney Disease.
PC = Primary Care.
CVD = Cardiovascular Disease.
HF = Heart failure.
ESRD = End-stage renal disease.
CV = Cardiovascular.
eGFR = Estimated glomerular filtration rate.
MACE = Mayor Cardiovascular Event.
ACR = Urinary albumin-creatinine ratio.
LVH = Left ventricular hypertrophy.
LV = Left ventricle.
HFpEF = Preserved ejection fraction.
HFrEF = Reduced ejection fraction.
HR = Hazard Ratio.
LR = Likelihood ratio.

INTRODUCTION

High blood pressure (HBP) has been recognized as significant risk factor for the development of cardiovascular diseases (CVD).[1] Its importance relies on its silent and hazardous manifestations in target organs such as the heart, cardiovascular system, and kidneys. At a public health level, strategies to diminish the burden of HBP, with an appropriate diagnosis and treatment to prevent complications in the long term have been developed. Nevertheless, Mexico is distinguished to have a high prevalence of undiagnosed and untreated HBP. The most recent evidence conducted from a sub-analysis of the May Measure Month 2019 at the Eastern zone in Mexico revealed an estimated prevalence of HBP of 32.4%. The same study reported that the proportion of patients without diagnosis and treatment was 28.3%.[2] At an individual level, HBP's systemic damage is translated into Atherosclerotic Cardiovascular Disease (ASCVD) with heterogeneous and diverse effects in magnitude among individuals, which is translated into cardiorenal associated diseases. Unstable angina, heart failure (HF), multivessel disease, CKD, and cerebrovascular disease are entities which have been posed to be severe cardiorenal complications related to HBP. Nevertheless, the detection, management, and treatment of cardiorenal diseases are often challenging in Primary Care (PC) settings due to limited resources, lack of advanced diagnostic elements, and awareness of healthcare workers for its systematically screening. Hence, there is a need to comprehend and understand current strategies to detect and screen cardiorenal associated complications early in a PC scenario. This work aims to detail a brief review of the current diagnosis strategies to screen kidney and heart damage in a PC scenario to help further its diagnosis, management, and prompt referral to specialized care setting.

Kidney damage

Pathophysiological pathways related to kidney injury attributable to HBP are complex. It has been recognized that increased blood pressure leads to microscopic impairments in glomerular capillaries in the nephron which overstimulate the renin-angiotensin-aldosterone system. This essentially creates hemodynamic impairments which favor non-hemodynamic changes. Both phenomena create a perfect environment to promote further cascades that consequently lead to a cardiorenal system injury. The interplay between hemodynamic and non-hemodynamic pathways has a bidirectional effect, which is translated into a higher incidence of CKD in patients living with HBP in patients with CKD.[3]

Glomerular filtration rate

It has been estimated that HBP is the second leading cause of end-stage renal disease (ESRD) in Mexico. Notably, ESRD is a strong predictor of cardiovascular (CV) morbidity and mortality. It has been proposed that the estimated glomerular filtration rate (eGFR) and albuminuria are the most appropriate and precise indicators to evaluate the extent and degree of kidney damage in patients living with HBP.[3] A moderate decrease in eGFR (GFR < 30 mL/min/1.73 m^2) and the presence of any degree of albuminuria are unequivocal signs of kidney damage. *Table 1* describe the values for each one.[4]

A study performed by Mafham et al. demonstrated that for every 20 mL/min/1.73 m^2 reduction of eGFR, the risk of presenting a fatal or non-fatal major cardiovascular event (MACE) increases by approximately 50%.[5] Laboratory measurements are needed to give an accurate approximation for the eGFR. The

Table 1: Categories of glomerular filtration rate and albuminuria.

GFR categories (mL/min/1.73 m^2)	Description	Range
G1	Normal or high	≥ 90
G2	Mildly decreased	60-89
G3a	Mildly to moderately decreased	45-59
G3b	Mildly to severely decreased	30-44
G4	Severely decreased	15-29
G5	Kidney failure	< 15
Persistent albuminuria categories		
A1	Normal to mildly increased	< 30 mg/g < 3 mg/mmol
A2	Moderately increased	30-300 mg/g 3-30 mg/mmol
A3	Severely increased	> 300 mg/g > 30 mg/mmol

Modified from: KDIGO 2012. Shlipak MG et al.[4]

most used and widely available are biomarkers are Serum Creatinine and Cystatin C, which then are applied to online-based equations for its interpretation. The most used equations are CKD-EPI and MDRD-4 (https://www.senefro.org/modules.php?name=calcfg), which consider essential aspects of the patients, such as the body surface, age, and ethnicity, to give an adjusted and expressed eGFR expressed on the surface of an average-sized person by 1.73 m^2. The Cockcroft-Gault formula is another important equation, which is weight-based and gives an estimated Creatinine Clearance; the Cockcroft-Gault formula has shown a better performance in subjects with mild or moderate renal function impairment, whereas CKD-EPI and MDRD can be used at any level of renal function. Although not achieving maximum precision, recent studies indicate that CKD-EPI could reduce bias and give a better estimation for the eGFR compared to MDRD-4.[6] Nevertheless, these equations should be interpreted with caution within certain circumstances, as it has been reported that body composition impairments could alter creatinine production, such as patients living with obesity, malnutrition, or cachexia, and in consequence, give inaccurate eGFR estimations. In these cases, the eGFR assessment should not be adapted to 1.73 m^2, with the objective to avoid its overestimation; consequently, its absolute value should be used. This same concern applies to the Cockcroft-Gault equation. Therefore, limitations and caution are awarned while using these formulas within these contexts.

Albuminuria

Another universally accepted marker to evaluate renal manifestation for generalized endothelial dysfunction is albuminuria, which is a strong predictor of progression to ESRD in subjects living with and without diabetes. The PREVEND study (Prevention of Renal and Vascular End-stage Disease Study), was one of the first studies that reported an estimated prevalence of albuminuria in healthy population of 6.6%, which increased to 7.2% in patients living with HBP or diabetes. Furthermore, the same study reported that even in healthy populations, its continuous excretion has a well-documented relationship with CV risk, as people with normal Albuminuria values (10-20 mg/L or 15-30 mg/24 h), had an increased CV risk compared with those without albuminuria.[7] Depending on the studied cohort, the worldwide prevalence of kidney damage in subjects living with HBP

varies from 5 to 60%.[3] However, in Mexico, the information for this topic is limited. Available data indicates that approximately 12% of the population living with HBP and diabetes have an eGFR ≤ 60 mL/min/1.73 m^2 and albuminuria > 30 mg/g.[8] According to the latest recommendations of KDIGO 2021, it is preferable to measure albuminuria instead of proteinuria since albuminuria helps to stratify the risk of progression to ESRD and makes an adequate stratification of renal function.[4] The estimation of albuminuria is highly reliable when measured using semi-quantitative methods, such as test strips or immunological methods in the laboratory. Nevertheless, the test strips are the most affordable and widely available method in PC settings. It has been reported that test strips have a sensitivity of 80-97% and a specificity of 33-80%, making them a good strategy for initial screening and follow-up. Finally, recent data indicate a more comprehensive approach involves using the Albumin/Creatinine Ratio (ACR), where a threshold of > 30 mg/g is considered abnormal. Regarding the scarce information from Mexico, there is no doubt that measurement of eGFR and detection of albuminuria should be crucial strategies in PC settings, as both indicators could lead to a prompt treatment to decrease CV risk in patients living with HBP.

Heart damage

The heart is a crucial organ that experiences impairments within its structure and functionality closely related with other organs, such as the kidney. Briefly, the increased tension and post-charge hemodynamic forces increases within higher HBP stages. These changes within the cardiovascular system, lead towards a progressive increase in myocardial tissue and enlargement in left ventricle, which ultimately ends in left ventricular hypertrophy (LVH).[9] The consequences have been described as progressive HF, as well as a thickening of the intima-media in carotids, which are also correlated with kidney damage. Both heart and kidney damage are conditioning the promote a higher incidence of CV events.[10]

Left ventricular hypertrophy

Variants which are described for LVH are concentric and eccentric hypertrophy and concentric remodeling. These variants predict an increased incidence of ASCVD and adverse renal outcomes. It has been described that concentric hypertrophy is the most consistent independent CV risk factor, as it increases ≥ 20% the risk for any MACE in 10 years.[11] Therefore, the presence of LVH is the most consistent marker of cardiac injury. The initial screening method to evaluate LVH is through an electrocardiogram (EKG). There are well-defined EKG criteria that have been correlated against more sophisticated methods such as echocardiography, magnetic resonance imaging, and histopathological samples. In *Table 2*, we present the most used EKG criteria (Sokolow-Lyon, Cornell, and Lewis's Indexes) which could help to identify the presence of LVH in a PC scenario.[12] The Sokolow-Lyon Index continues to have the highest sensitivity and specificity to identify LVH validated with

Table 2: Electrocardiographic criteria based on voltage.

Indexes	Formulas	EKG criteria
Sokolow-Lyon	S V1 + R V5 o R V6	≥ 3.5 mV = 35 mm
	R aVL	> 1.1 mV = 11 mm
Cornell	R aVL + S V3	H: ≥ 2.8 mV = 28 mm
		M: ≥ 2 mV = 20 mm
Lewis	(R D1 + S D3) – (R D3 + S D1)	> 1.7 mV = 17 mm

Modified from: Tsioufis C et al,[11] Rolon-Acosta et al.[12]

Table 3: Echocardiographic criteria by sex for left ventricular hypertrophy.

	Women			Men		
Markers of LVH	Mild	Moderate	Severe	Mild	Moderate	Severe
Thickness of the septum	10-12	13-15	≥ 16	11-13	14-16	≥ 17
Thickness of the posterior left ventricular wall	10-12	15-16	≥ 16	11-13	14-16	≥ 17

Data expressed in mm. Modified from: Tsioufis C et al,[11] Rolon-Acosta et al.[12]

echocardiogram imaging (Specificity: 83%; Positive Predictive Value: 85%, Likelihood Ratio: 2.28).[13] Other available indexes are the Novacode and the Romhilt-Estes.[9] Nevertheless, it has been reported that in obese subjects, the use of the Sokolow-Lyon Index, along with the Cornell index had reduced sensitivity and specificity; therefore, caution should be taken when using these markers to identify LVH.

Echocardiography

Echocardiography is a highly precise imaging technique which provides information on the structure and geometry of the left ventricle (LV), systolic and diastolic function, and other coexisting cardiac alterations. It is the most used method to assess follow-up pharmacological management of LVH. Nevertheless, its availability in PC scenarios in Mexico continues to be limited and insufficient.[9] *Table 3* describes the echocardiographic values to diagnose and stratify LVH by sex. Nevertheless, whether the reduction of LVH could provide long-term cardio-nephroprotection is an area of opportunity for further study.[11]

Heart failure

Heart failure (HF) is considered a long-term consequence of hypertensive heart disease. According to the Framingham Heart Study, approximately 39% of men and 59% of women living with HBP will develop HF.[13] In most patients, LV diastolic dysfunction is the first clinical manifestation, presenting with a preserved (HFpEF) or reduced (HFrEF) ejection fraction. Its terminal phase is characterized as a dilated cardiomyopathy with diastolic dysfunction and reduced ejection fraction. The diagnosis is usually made in the advanced stages: the patient who is diagnosed by dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, rales, ankle edema, third heart sound/gallop, jugular venous distension with or without hepatomegaly and sinus tachycardia at rest, has little chance of regaining his quality of life. Therefore, it is necessary to diagnose HF in early stages in PC settings, when it is asymptomatic, to reduce its associated morbidity and mortality. When HF progresses, a phenomenon is known as «decapitated hypertension» occurs, where blood pressure decreases to even low levels and represents a therapeutic challenge.[14]

The appropriate diagnosis of HF is based on clinical and EKG findings. A correct interpretation of an EKG makes and accurate diagnosis in 75% of patients living with HF (sensitivity of 81%, specificity of 51%, positive predictive value of 59% and negative predictive value of 75%.[15] Another widely used study is chest radiography (X-rays), which remains as an important complementary diagnosis tool to exclude other relevant causes of dyspnea, such as pulmonary diseases that could give similar symptomatology of decompensating HF. It has been proposed that the echocardiogram is the best diagnostic tool since it allows the identification of cardiac dysfunction in an accurately and non-invasive way. Its main utility in a PC scenario is to confirm the diagnosis. The use of echocardiography in a PC scenario, should be part of the diagnostic tools available to all PC settings in patients with high suspicious

of HF. Finally, Natriuretic Peptides are useful in the diagnosis of established HFrEF, but their accessibility and distribution continue to be limited in PC scenarios in Mexico. As its circulating levels are closely related to eGFR, its interpretation requires consideration of this parameter.[16]

Other cardio-renal impairments related to HBP

Pathological mechanisms linked to the modulation of traditional risk factors and their future interrelation with cardiorenal impairments are heterogenous. It has been described that an increase in the hemodynamic load and pressure elevates the intra-abdominal venous resistance, which lead to a stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. This essential physiopathological mechanism are often combined with low-grade chronic inflammation, endothelial dysfunction, and a high production of reactive oxygen species, which induces fibrosis in the heart, kidney, and blood vessels. Thus, it is not surprising to see that several organs and systems are simultaneously affected. Overall, there are other several conditions related to HBP that go beyond the scope of this work. These patients are likely to have a high prevalence of diabetes, glucose intolerance, obesity, and dyslipidemia which also contribute to an unfavorable interaction for vascular damage and the development of ASCVD manifestations, such as atrial fibrillation, ischemic heart disease, peripheral artery disease, among others.

Take-home messages

HBP is one of the main risk factors for the development of ASCVD whose subclinical onset is documented in various studies. Kidney and heart damage are just two examples of the complex interplay of pathophysiological mechanisms that explain multi-organ damage in HBP. The search for a decrease in eGFR, albuminuria, LVH, and HF in patients living with HBP is mandatory in a PC setting, as the prompt and early identification of these conditions are the only way to reduce the long-term incidence of ASCVD in Mexican population.

REFERENCES

1. Rosenblit PD. Extreme atherosclerotic cardiovascular disease (ASCVD) risk recognition. Curr Diab Rep. 2019; 19: 61. Available in: https://doi.org/10.1007/s11892-019-1178-6
2. Palomo-Piñón S, Antonio-Villa NE, García-Cortés LR, Álvarez-Aguilar C, González-Palomo E, Bertadillo-Mendoza OM et al. Prevalence and characterization of undiagnosed arterial hypertension in the eastern zone of Mexico. J Clin Hypertens Greenwich Conn. 2022; 24: 131-139. Available in: https://doi.org/10.1111/jch.14414
3. Mulè G, Castiglia A, Cusumano C, Scaduto E, Geraci G, Altieri D et al. Subclinical kidney damage in hypertensive patients: a renal window opened on the cardiovascular system. Focus on microalbuminuria. Adv Exp Med Biol. 2017; 956: 279-306. Available in: https://doi.org/10.1007/5584_2016_85
4. Shlipak MG, Tummalapalli SL, Boulware LE, Grams ME, Ix JH, Jha V et al. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. Kidney Int. 2021; 99: 34-47. Available in: https://doi.org/10.1016/j.kint.2020.10.012
5. Mafham M, Emberson J, Landray MJ, Wen C-P, Baigent C. Estimated glomerular filtration rate and the risk of major vascular events and all-cause mortality: a meta-analysis. PloS One. 2011; 6: e25920. Available in: https://doi.org/10.1371/journal.pone.0025920.
6. Tasa de filtración glomerular medida y estimada (Parte II). Ajuste a superficie corporal | Revista de Nefrología, Diálisis y Trasplante n.d. [Accessed March 29, 2022] Disponible en: https://www.revistarenal.org.ar/index.php/rndt/article/view/54
7. Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ et al. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. J Intern Med. 2001; 249: 519-526. Available in: https://doi.org/10.1046/j.1365-2796.2001.00833.x
8. Obrador GT, Villa AR, Olvera N, Gutiérrez V, Contreras D, Reyes R. Longitudinal analysis of participants in the KEEP Mexico's chronic kidney disease screening program. Arch Med Res. 2013; 44: 650-654. Available in: https://doi.org/10.1016/j.arcmed.2013.10.006
9. Orihuela-Rodríguez O, Carmona-Ruíz HA, Laredo-Sánchez F, Paniagua-Sierra JR. Left ventricular hypertrophy, fibrosis heart, and diastolic dysfunction in chronic kidney disease. Rev Medica Inst Mex Seguro Soc. 2017; 55: S195-200.
10. Cuspidi C. Cardio-renal organ damage and cardiovascular outcomes in hypertension. J Hypertens. 2009; 27: 702-706. Available in: https://doi.org/10.1097/HJH.0b013e3283295dbf
11. Tsioufis C, Tsiachris D, Kasiakogias A, Dimitriadis K, Petras D, Goumenos D et al. Preclinical cardiorenal interrelationships in essential hypertension. Cardiorenal Med. 2013; 3: 38-47. Available in: https://doi.org/10.1159/000346817
12. Rolon-Acosta PD, Saccomani HM, Galeano IO. Valor diagnóstico de los criterios electrocardiográficos de

hipertrofia del ventrículo izquierdo en la hipertensión arterial. Rev Virtual Soc Paraguaya Med Interna. 2019; 6: 39-46.

13. Alfonso DI, Puente MJ, Denis-Piedra DA, Rodríguez-Venegas E de la C, Hernández LQ. Valor diagnóstico del índice de Sokolow-Lyon en la hipertrofia ventricular izquierda. CorSalud. 2021; 13: 135-141.
14. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. 2002; 106: 3068-3072. Available in: https://doi.org/10.1161/01.cir.0000039105.49749.6f
15. Fonseca C. Diagnosis of heart failure in primary care. Heart Fail Rev. 2006; 11: 95-107. Available in: https://doi.org/10.1007/s10741-006-9481-0
16. McCullough PA, Sandberg KR. B-type natriuretic peptide and renal disease. Heart Fail Rev. 2003; 8: 355-358. Available in: https://doi.org/10.1023/a:1026195332025

Correspondence:
Silvia Palomo-Piñón, MD
E-mail: silvia-palomo@hotmail.com

CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105188

A review of non-pharmacological and pharmacological therapies to treat high blood pressure

Una revisión de las terapias no farmacológicas y farmacológicas para tratar la hipertensión arterial

Adolfo Chávez-Mendoza, MD,* Fabiola Pazos-Pérez, MD,‡ Abel Alberto Pavía-López, MD§

Keywords:
High blood pressure, pharmacological approaches, non-pharmacological interventions.

Palabras clave:
Hipertensión arterial, enfoques farmacológicos, intervenciones no farmacológicas.

ABSTRACT

Despite the wide availability of therapeutic options to treat high blood pressure (HBP) in market and healthcare systems, there is a low proportion of patients who achieve blood pressure goals. In this work, we review essential non-pharmaceutical measures, along with current and novel pharmacological approaches which have been recommended in the management of HBP. In summary, weight loss, increased physical activity, diminishing sodium and potassium using DASH and Mediterranean regimes, along with cessation of tobacco consumption, are widely proven non-pharmacological interventions that have demonstrated an impact in decreasing arterial blood pressure. Regarding pharmacological approaches, most of them have been focused on the renin-angiotensin-aldosterone system (RAAS), for which angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) stand for the most widely used antihypertensives, as well as being cost-effective strategies to decrease arterial blood pressure. Combining diverse antihypertensive medications has also demonstrated a good approach when the formulations are implemented within one-pill administration. Nevertheless, the diverse combination with other antihypertensive regimes needs to be individualized for the clinical characteristics of each patient. Finally, novel strategies are currently being studied to handle HBP in the future.

RESUMEN

A pesar de la amplia disponibilidad de opciones terapéuticas para tratar la hipertensión arterial (HTA) en el mercado y en los sistemas sanitarios, hay una baja proporción de pacientes que alcanzan los objetivos de presión arterial. En este trabajo se revisan las medidas no farmacéuticas esenciales, junto con los enfoques farmacológicos actuales y novedosos que se han recomendado en el tratamiento de la HTA. En resumen, la pérdida de peso, aumento de la actividad física, disminución del sodio y el potasio mediante los regímenes DASH y mediterráneo, junto con el cese del consumo de tabaco, son intervenciones no farmacológicas ampliamente probadas que han demostrado un impacto en la disminución de la presión arterial. En cuanto a los enfoques farmacológicos, la mayoría de ellos se han centrado en el sistema renina-angiotensina-aldosterona (SRAA), por lo que los inhibidores de la enzima convertidora de angiotensina (IECA) y los bloqueadores de los receptores de angiotensina (BRA) son los antihipertensivos más utilizados, además de ser estrategias rentables para disminuir la presión arterial. La combinación de diversos medicamentos antihipertensivos también ha demostrado ser un buen enfoque cuando las formulaciones se implementan dentro de la administración de una sola píldora. No obstante, la combinación diversa con otros regímenes antihipertensivos debe individualizarse en función de las características clínicas de cada paciente. Por último, se están estudiando nuevas estrategias para el manejo de la HTA en el futuro.

INTRODUCTION

During the last decades, healthcare systems worldwide have experienced a transition towards late medical care, which prioritize secondary or tertiary medical attention instead of primary care. Despite the wide availability of therapeutic options to treat high blood pressure (HBP) in the market and in healthcare systems, there is a low proportion of patients who

* Current President, Alliance for a Healthy Heart. Mexico, Member of GREHTA.
‡ Servicio de Nefrología, Hospital de Especialidades CMN Siglo XXI. CDMX, México, Miembro GREHTA.
§ Interventional Cardiologist, Centro Médico ABC, Sociedad Mexicana de Cardiología. México, Member of GREHTA.

How to cite: Chávez-Mendoza A, Pazos-Pérez F, Pavía-López AA. A review of non-pharmacological and pharmacological therapies to treat high blood pressure. Cardiovasc Metab Sci. 2022; 33 (s3): s223-s232. https://dx.doi.org/10.35366/105188

achieve therapeutic goals. Furthermore, HBP is further combined with cardiometabolic health diseases like diabetes and overweight, which further increase the risk for the onset of CVD. The Global Status Report 2014 (GSR-2014) has proposed an initiative to reduce the burden of cardiovascular disease (CVD) through the implementation of public health policies that sought to target four main objectives of manage HBP: 1) reduce the burden of alcohol and tobacco intake, 2) improve actions to promote physical activity, 3) reduce the food intake of sodium and 4) promote the early diagnosis of high-blood pressure in all healthcare settings.[1] Nevertheless, there is still a debate regarding what could be the long-term effects of these public health policies that prioritize non-pharmaceutical interventions. In this work, we review essential non-pharmaceutical measurements, along with pharmacological approaches that have been recommends in the management HBP in a primary care approach.

Non–pharmaceutical measures for high blood pressure

It has been widely proven that increased fat accumulation, a high intake of sodium (> 3 grams per day), potassium, fatty foods (more than 7% of total fat), use of tobacco, along with low physical activity are well-documented risk factors that end-up promoting a high-risk atherosclerotic profile (high level of LDL-C and low HDL-C). Therefore, most of the non-pharmaceutic therapeutic actions have been aimed towards reducing the previously mentioned risk factors. In *Table 1*, we present a summary of targeted interventions that have demonstrated a beneficial effect in decreasing blood pressure in adults, along with the literature that have supported these statements.

A well-documented intervention is the DASH (Dietary Approach to Stop Hypertension) diet, as it has been demonstrated that it could reduce 8 to 14 mmHg of SBP. The DASH

Table 1: Non-pharmaceutical measures for high blood pressure.

Interventions	Targeted goals	Estimated effect	Reference
Weight loss	Ideal body mass index between 18.5 and 25 kg/m^2 Net weight reduction of -5.1 kg (95% confidence interval [CI], -6.03 to -4.25) Individualize the use of medication and bariatric surgery	4.4 mmHg in SBP 3.6 mmHg in DPB	(32,33)
Abdominal circumference	< 94 cm on men < 88 cm on women		(7,34)
Physical activity	At least 30 minutes per day for 5 days in a week including isometric exercise	8.3 to 5.2 mmHg in SBP	(35)
Low sodium intake	< 5 g of salt per day Reduction of intake of the size of a table teaspoon (~3 g of salt)	2.0 to 4.0 mmHg in SBP	(36)
Consumption of food with potassium	A maximum intake of 90 mmol or 3,510 mg per day	Up to 11 mmHg in SPB	(37–39)
Mediterranean diet or DASH	High intake of fruits and vegetables, along with a low consumption of high calorie foods and low fat	Up to 11 mmHg in SPB	(2–4)
Coffee consumption	Protective effect with < 5 cups per day	5 to 15% reduction on CVD risk	(40)
Low tobacco consumption	Full suspension		
Low alcohol consumption	14 units per week in men 8 units per week in women 1 unite = 125 mL of wine and 250 mL of beer	~5.50 mmHg in SBP ~3.97 mmHg in SBP	(7,41–43)

regime implies in a reduction in carbohydrate consumption, and promoting an intake in whole grains, bird meat, fish, a low in fat intake and a consumption of nine to eleven fruit and vegetable per day. Furthermore, the DASH regime has shown an increased benefit within older adults. Another accepted and well-studied dietary regime is the Mediterranean diet, which is comprised of a high consumption of vegetables, fruits, olive oil, low-fat cheeses, sugar-free yoghurt, whole-bean cereals, a small portion of wine and a substitution of red meat ingestion with white-fish and chicken.[2-5]

All these recommendations have been posed as effective strategies to manage blood pressure in primary care settings. However, it is crucial to promote empowerment in each patient as an essential component in the application of these approaches. Edward Wagner and et al developed a model that sought to promote empowerment using a dual combination of self-monitoring and care alongside with a closer interaction with its healthcare provider.[6] The main purpose of the empowerment model is to implement efficient lifestyle changes that end-up reducing the impact of prevalent CVD risk factors. This perspective could be applicable to patients living with HBP, along in subjects that sought to prevent or delay the disease. Finally, according to the European Society of Hypertension, it is recommended that a follow-up assessment should be made every three months since the start of the initiation of lifestyle changes to reevaluate and perform modifications.[7]

Although these actions seek to promote simple strategies, it has been documented that the efficacy of non-pharmacological interventions may be restricted in vulnerable socioeconomic groups given to a low income and lower educational attainment.[8,9] Therefore, there is a need of research for simple and low-cost strategies that could benefit vulnerable communities, and in consequence, diminish the burden of high-blood pressure.

Overview of the pharmacological therapies to reduce high-blood pressure

Pathophysiological implications. Patients living with primary HBP are usually treated with a wide variety of pharmacological interventions that have their main therapeutic action via different pathophysiological mechanisms *(Figure 1)*. In *Table 2*, we summarize the mechanism of the most efficient commercially available antihypertensive drugs that decrease central venous pressure, systemic vascular resistance and improve cardiac output by diverse associated mechanism.

Renin-angiotensin-aldosterone system. The renin-angiotensin-aldosterone system has (RAAS) has a fundamental role in balancing blood pressure. The RAAS has been described as a sequence of organized biochemical reactions that helps maintain blood pressure homeostasis. After discovering its essential components, a century ago, the RAAS marked a whole chapter within the pathogenesis of HBP and led to an entire pharmacological research area for managing cardiometabolic diseases.

The kidneys are the only site where prorenin is metabolized into renin and then transported into the plasmatic circulation. Afterward, in the liver, renin metabolizes angiotensinogen to create angiotensin. Nevertheless, other sites where it has been described as capable of producing angiotensinogen are brain, kidney, heart, large arteries, and adipose tissue. Angiotensinogen is then proteolytically converted into angiotensin-II by a crucial enzyme named angiotensin-converting enzyme (ACE) in the lungs. Other sites where this step could be performed are blood vessels, kidneys, heart, and brain, which could metabolize angiotensin II independently of ACE (via chymase, carboxypeptidase cathepsin G, and plasminogen activator pathways). Angiotensin II then produces diverse physiological reactions driven by the widely spread type 1 (AT1) receptors rather than type 2 (AT2) within the body. The effects produced by the stimulation of AT1 and AT2 are shown in *Table 1*. Finally, angiotensin II triggers the release of aldosterone and vasopressin (antidiuretic hormone), which are produced by the adrenal and pituitary glands, respectively. Both aldosterone and vasopressin acts as sodium and water restrictors, leading to an increasing blood volume and blood pressure.[10]

Another critical system involved in the counterregulation of blood pressure is the renal

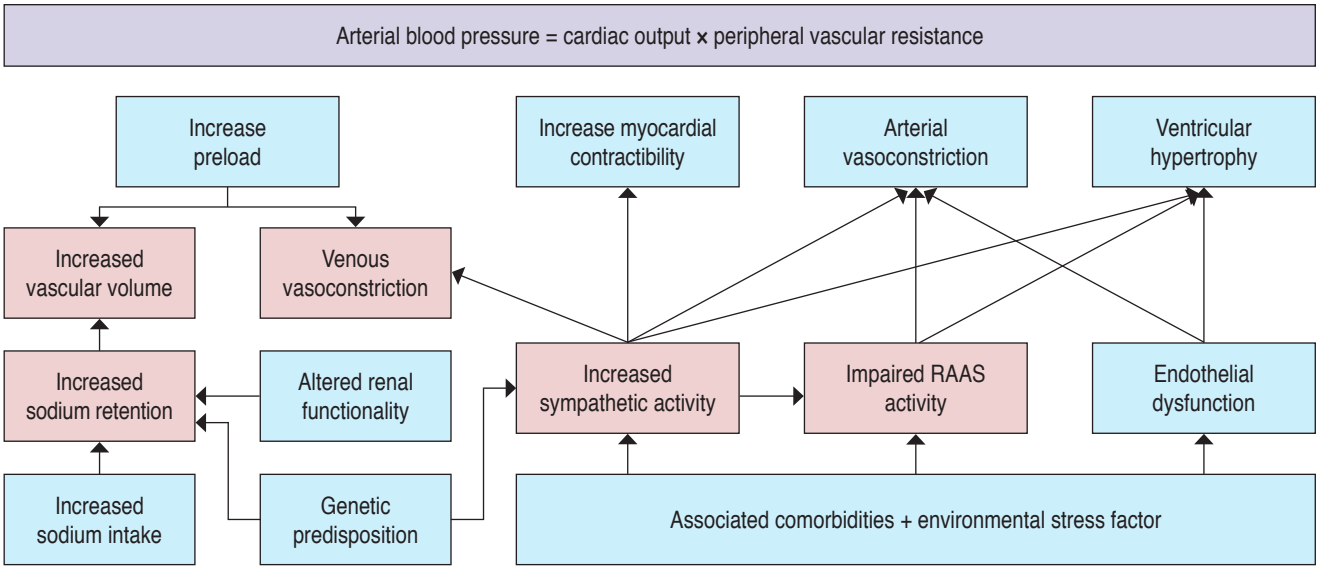


Figure 1: Brief pathophysiology of high blood pressure.

Table 2: Summary of the mechanism of action for the most efficient commercially available antihypertensive drugs.

Type	Mechanism of action	Final effects
Diuretics	Decrease blood volume through sodium and water excretion.	— Decrease in cardiac output and diminishing ventricular preload via Frank–Starling's mechanism. — Improvement on systemic vascular resistance.
Beta-blockers	Blocking the sympathetic system from the cardiovascular system.	— Decreasing heart rate, cardiac contractility, and stroke volume. — Useful in managing "hyperdynamic syndromes", characterized by an increase in the cerebral RAAS. — Decrease sympathetic stimulation that promote catecholamines cascade.
Non - dihydropyridine calcium channel blockers	Decreasing cardiac output through dropping heart rate and myocardial contractility	— Highly cardio selective pharmacotherapeutic action.
Dihydropyridine calcium channel blockers		— More selective for the systemic vasculature — Promotes a reduction in systemic vascular resistance.

kinin –kallikrein– prostaglandin system. The first steps are promoted by kinin and kallikrein secretion induced by mineralocorticoids receptors. The system promotes a reduction in the reabsorption of sodium in the ascending part of Henle's loop and promote the release of renal prostaglandins, hence, restricting vasodilatation of renal efferent arterioles and promoting sodium excretion. In people living with HBP, it has been described a decrease in the activity on the kinin –kallikrein– prostaglandin system. Nevertheless, this system continues to be an area of further research.[11]

Considerations in using angiotensin converting enzyme inhibitors. In 1970, the Brazilian pharmacologist Sergio H. Ferreira, discovered that the *Bothrops Jaraca*'s venom contained a peptide capable of inhibiting the action of Kinase II, an enzyme involved in the degradation of bradykine. He identified that

this peptide could be used for therapeutic use, thus, motivate him into synthetize captopril as the first ACEIs of its kind.[12] Nowadays, several ACEIs have been synthetized and have been positioned as the first line of action in diverse hypertensive related disorders, including heart failure with history of heart attack, diabetes, diastolic dysfunction, and within patients living with chronic kidney disease.[13]

Regarding combined therapies, it has been described that ACEIs are usually mixed with thiazides or loop diuretics as their joint effects prevent the synthesis of angiotensin II secondary to the secretion of renin associated to diuretic intake. Furthermore, the combination of ACEIs with calcium antagonists is also an effective approach, since both families block the stimulation of RAAS activity, especially from the dihydropyridine family. Other mechanisms that have been described as complementary mechanism of action for ACEIs are related to a decrease in the metabolism of angiotensin II from angiotensin I, a decrease in aldosterone secretion stimulated by angiotensin I, and a decrease in degradation of bradykinin. Likewise, ACEIs have been studied as cardioprotective agents in patients classified with high risk of a cardiovascular event.

A group of interest where ACEIs have been posed as essential pharmacological tools are in patients living with diabetes and HBP as it has proven that they could reduce renal albumin excretion. Furthermore, ACEIs have shown a consistent decrease in the progression on chronic kidney disease, along with a decrease in the risk of incident cerebrovascular and peripheral artery diseases, without necessarily impairing cerebral or peripheral blood flow.[13,14]

Regarding the limitations of using ACEIs, it has been described that hypotension is the main adverse effect reported during the first weeks of usage. However, its risk could decrease after using prolonged ACEIs (E.g., ramipril, perindopril and trandolapril) and reduce the dosage of any other simultaneously combined antihypertensive. Other commonly associated adverse effects related to the use of ACEIs include non-productive dry cough, isolated cases of angioedema and hypersensitivity to its components. A serious adverse effect is hyperkalemia, therefore, it is highly recommended that plasmatic potassium levels should be assessed before starting any ACEIs and should be periodically monitored in follow-up visits.[15,16] Finally, it is highly recommended that serum creatinine and glomerular filtration rate (GFR) should be measured before starting this therapy. Any impairment higher than 30% from baseline in either creatinine or GFR during the first weeks after starting whichever ACEIs or when making a dosage increase should be warranted as an immediate suspension of the medication.[13,15,16] Circumstances where the use of ACEIs is contraindicated are during pregnancy and lactation. Nevertheless, when the situation could limit its suspension or changing by any other approved antihypertensive, it should be closely monitored, and extreme precaution is warranted. Other situations that could limit its use are in HBP with vascular-renal origins. The situations where we conseil to use ACEIs with caution are listed in *Table 3*.

Considerations in using angiotensin receptor blockers. Since 1970, it has been an increasing trend in the development of angiotensin receptor blockers (ARBs) being the first compounds synthetized only for intravenous use. Nevertheless, in 1990 the first oral presentation of ARBs appeared for commercial use, in which Losartan was the first ARBs used to treat HBP. Afterwards, other ARSs were synthetized, such as valsartan, ibersartan, candersartan, telmirsartan, olmersartan, and others.

Similarly, with ACEI inhibitors, the ARBs act of the blockade of RAAS through specific antagonism in angiotensin II AT1 receptor. Diverse observational studies within patients living with diabetes have shown that ARBs may change or slow down the progression of renal disease along with an overall reduction in cardiovascular risk. Furthermore, it has been proposed that the dual combination of ACEI with ARBs could improve clinical results hypothesized by a greater RAAS blockade. Nevertheless, there is still debate whether this should be a systematic strategy for threatening HBP. Evidence from the COOPERATE (combination treatment of angiotensin-II preceptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease)

Table 3: Considerations for the individualization of high blood pressure treatment

Situations	Recommendations for antihypertensive treatment
Heart failure with reduced LVEF	ACEIs, ARBs, beta-blockers, thiazides, mineralocorticoid receptor inhibitor
Ischemic heart disease	ACEIs, ARBs, beta-blockers, mineralocorticoid receptor antagonist
Chronic kidney disease	ACEIs, ARBs
Atrial fibrillation	ACEIs, ARBs, and/or beta-blocker, non – dihydropyridine calcium antagonist
Contraindications	**Antihypertensive drug**
Angioedema	Avoid ACEIs
Heart failure	Avoid non – dihydropyridine calcium antagonists (E.g., verapamil, diltiazem)
Pregnancy	Avoid ACEIs, ARBs, or direct renin inhibitors
AV conduction block or extreme bradycardia	Do not use beta-blockers

and ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) studies have found contradictory results. Both studies demonstrated thar the combination of ACEI and ARBs failed to slow down the evolution of kidney failure. Even more, the same studies have reported some cases where there were significant impairments within renal function and increased risk of hyperkalemia.[17,18] These studies along with several experts' opinions have recommended their combined use only on those patients with proteinuria nephropathies or in those patients who could well-tolerate low-grade doses of both ACEIs and ARSs with strict supervision of proteinuria and renal functionality.

The main indications to implement ARBs are similar for ACEIs, although the beneficial effect is observe gradually compared to what it is expected from ACEIs, mainly due to an absence of action in bradykinins. Conversely for what happens in ACEIs, the decrease in blood pressure with the use of ARBs are usually not accompanied by a reflex tachycardia, dry cough, or angioedema. This makes ARBs are particularly good prescription option on patients that have presented a favorable response to ACEIs but were suspended due to their associated adverse effects. Finally, there has been described some sceneries where the ARBs have a higher benefit compared with ACEIs, which are cases of severe HBP with electrocardiographic evidence of left ventricular hypertrophy (E.g., LIFE trial).

Combination of antihypertensive therapies

It has been described that the use of monotherapy, even at optimal doses, could not be enough to achieve arterial pressure goals. The increasing disability of controlling arterial blood pressure using single antihypertensive regimes indicates a need to have novel therapeutic strategies. The European Society of Cardiology Working Group (ESCWG) emphasize the urgent necessity to change the current approaches since ESC guidelines have recommended more conservative blood pressure targets (≤ 130/80 mmHg in the general population and ≤ 140/90 for older adults), which makes a whole challenge to control blood pressure.[7,19,20]

Diverse clinical studies have suggested a need to combine antihypertensive regimes due to diverse clinical and non-clinical factors associated with the management of each patient. Nevertheless, the use of two pills could restrict or even limit the adherence and tolerance to the medication. Consequently, a novel approach to combine antihypertensive was found within combined pills that had a combination of two types of antihypertensive.

These novel approaches are then translated into a way to use fixed combination of single pills to improve efficacy and adherence in treatment. Most of the clinical trials that have been performed an evaluation to evaluate the effect of two antihypertensives have found improvements in blood pressure goals. In the ACCOMPLISH study, the dual combination

with an ACEIs and a calcium channel blocker proved superior to an ACEIs combination plus a thiazide diuretic to prevent primary CV complications. Nevertheless, the ASCOT study demonstrated that the combination of an ACEIs, BCC, and a beta-blocker or thiazide diuretic on the ASCOT study did not prove any superior efficacy. Exceptions to these findings were studied that sought a combination of diuretics, ARBs, or ACEIs plus a beta-blocker channel (BBC). Furthermore, a combination of a diuretic plus a BBC has proven to reduce cardiovascular complications. Nevertheless, the combinations of a diuretic with a BBC were associated with a higher incidence of diabetes than other combinations.[17,21,22]

Since 1999, the WHO proposed that the expected mean decrease in blood pressure levels using monotherapy ranges from 8 to 12 mmHg for systolic and 4 to 8 mmHg for diastolic pressure. Conversely, there is an expected average reduction of 12 to 22 mmHg for systolic and 7 to 12 mmHg for diastolic pressure for dual combination therapy. Finally, results from the PIANIST study showed that a triple combination therapy led to a maximum decrease in systolic and diastolic blood pressure of 45 mmHg and 21 mmHg, respectively.[23]

Overall an approach based on combined therapy could be an appropriate option to begin, whether systolic blood pressure levels is ≥ 150 mmHg or when there is a high cardiovascular risk level estimation. Calcium channel blockers or diuretics could complement the selection of RAAS inhibitors whether blood pressure goals are not achieved. A visual summary based on 2018 ESC recommendations is presented in *Figure 2*. This algorithm sought to make easier clinical decisions in all care settings.

New pharmacological strategies

In recent years, it has been demonstrated within animal models that prolonged activation of RAAS has diverse effects on the central nervous system, increasing peripheral vascular resistances and stimulating the secretion of arginine and vasopressin, which ultimately lead to impairments in blood pressure management. Aminopeptidase A (APA) is an enzyme responsible for the conversion of angiotensin II to angiotensin III, leading to a tonic stimulatory in blood pressure within mice models. Therefore, APA has been tagged as a candidate for HBP treatment. A recent compound in phase II studies named «RB150» has been proposed as a prodrug capable of inhibiting APA with encouraging results.

Another pharmacological target relies on endothelin-1 (ET-1), an endothelium-derived contractile factor released by vascular endothelial cells. It has been described that ET-1 is a potent vasoconstrictor and an essential regulator of vascular tension. ET-1 can bind

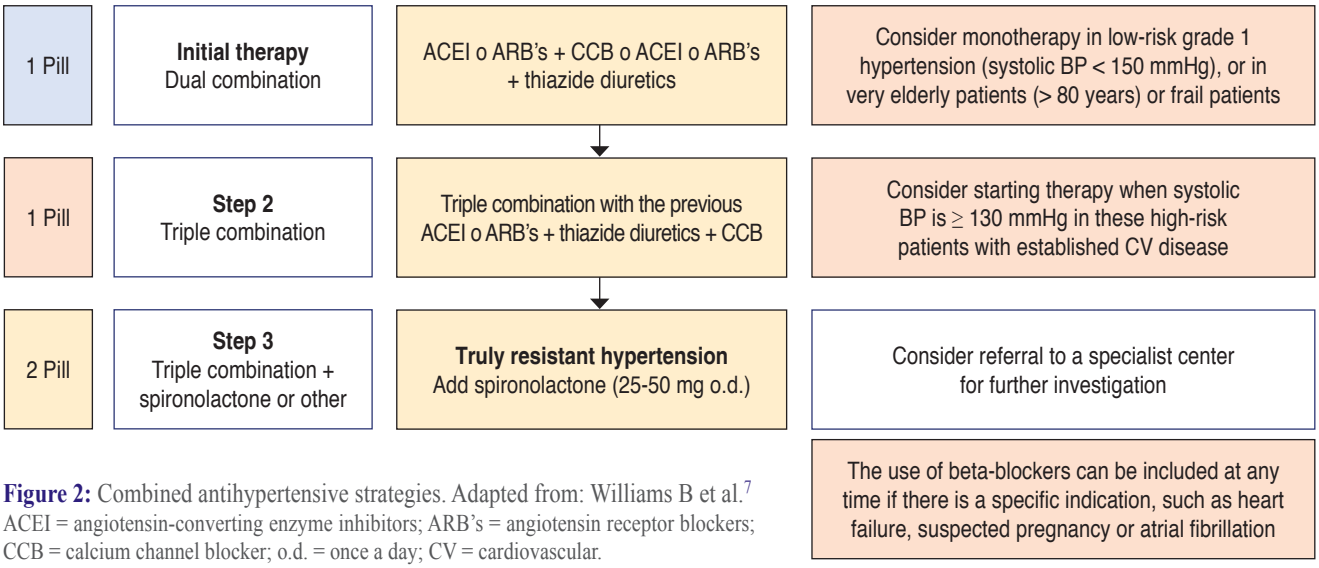


Figure 2: Combined antihypertensive strategies. Adapted from: Williams B et al.[7]
ACEI = angiotensin-converting enzyme inhibitors; ARB's = angiotensin receptor blockers; CCB = calcium channel blocker; o.d. = once a day; CV = cardiovascular.

with specific ET receptors, including ETAR and ETBR, promoting vascular vasoconstriction, cell proliferation, tissue fibrosis, and vascular endothelial injury, which are involved in the pathogenesis of HBP. ET-1 binding to ETBR can also activate endothelial cells by producing nitric oxide, therefore relaxing the vascular smooth muscle, and inhibiting vasoconstriction and cell proliferation. Hence, ETAR inhibition might be a novel pharmacological target for the treatment of HBP. In recent years, it has been developed diverse antagonists of ETR divided by their selective actions (E.g., darusentan and ambrisentan), non-selective (E.g., bosentan, and macitentan), a selective antagonist of ETBR, and dual antagonist of ETAR/EYBR (E.g., macitentan, and aprocintentan).

Is there any news on high blood pressure treatment? Nowadays, there has been better consistent evidence concerning cardiovascular risk decrease through reasonable blood pressure control and early initiation of dual therapy. This has shed light on novel pharmacological approaches, such as neuromodulations therapies. The objective of neuromodulations therapies is to improve downregulation on sympathetic outflow and improve blood pressure management. This approach is currently being studied in diverse ways of administration, such as oral pharmacological treatments (E.g., LCZ696, ARNI's) and direct interventionalists (E.g., catheter-mediated renal denervation). Other drugs, such as sodium-glucose cotransporter-2 (SGLT2) Inhibitors, have shown excellent benefits in other pathologies such as diabetes and heart failure. Therefore, current studies have been performed to explore their potential contribution to blood pressure management.

A particular physiopathological mechanism identified within HBP is related to the blood-brain barrier impairments. It has been described those disruptions within this system promote an autonomic dysfunction that causes an increase in blood pressure. Moreover, there is a phenomenon of secondary neuroinflammation and astroglia dysfunction hyperactivation of the RAAS, oxidative stress, and the release of inflammatory cytokines. The description of this pathway has led to the development of novel therapies targeting central nervous systems that can cross the blood-brain barrier.[24,25] For example, firibastat is a drug that lowers blood pressure by reducing vasopressin and cerebral Angiotensin III (NEW HOPE study).[26] Another drug capable of crossing the blood-brain barrier is Minocycline, which is currently being studied as an inhibitor of Microglia activation. Finally, aprocitentan is an antagonist of endothelin type A and type B receptor, which have shown to be a promising alternative given their results in phase II of the study against lisinopril (PRECISION Study).[27]

Finally, some promising therapies include vaccines that target alpha 1D adrenergic (ADRQβ-004) and angiotensin II (AngQb and AGMG0201) receptors.[28,29] Another currently being studied therapy is allopregnanolone, which selectively modulates the receptor for gamma-aminobutyric acid.[30] Other promising approaches are related to natriuretic peptide receptor agonists, vasopressin antagonists, vasoactive intestinal peptide analogs, dopamine beta-hydroxylase inhibitors, and others.[31-43]

CONCLUSION

The comprehensive understanding of the RAAS has led to the manufacture of diverse antihypertensive strategies focused on developing pharmacological agents capable of inhibiting the production or blocking the action of RAAS components. The creation of renin inhibitors, ACE inhibitors (ACEIs), selective and non-selective angiotensin II receptor blockers, β-adrenergic receptor blockers, and inhibitors of the activity and synthesis of aldosterone, among others have revolutionized the way we manage cardiovascular and renal diseases. Further investigations will continue to identify new elements of the RAAS that will help clinicians to improve our understanding of its functioning and the possibility of developing new therapies that will be more selective and efficient. In the meantime, the RAAS will continue to be the center of our attention for many years to come.

REFERENCES

1. World Health Organization. Global status report on noncommunicable diseases 2014. Geneva: World Health Organization; 2014.

2. Doménech M, Roman P, Lapetra J, García de la Corte FJ, Sala-Vila A, de la Torre R et al. Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids: one-year randomized, clinical trial. Hypertension. 2014; 64: 69-76. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.113.03353
3. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr. 2010; 92: 1189-1196. Available in: https://doi.org/10.3945/ajcn.2010.29673
4. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 1997; 336: 1117-1124. Available in: https://doi.org/10.1056/NEJM199704173361601
5. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008; 358: 1887-1898. Available in: https://doi.org/10.1056/NEJMoa0801369
6. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the chronic care model in the new millennium. Health Aff (Millwood). 2009; 28: 75-85. Available in: https://doi.org/10.1377/hlthaff.28.1.75
7. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39: 3021-3104. Available in: https://doi.org/10.1093/eurheartj/ehy339
8. Schargrodsky H, Hernández-Hernández R, Champagne BM, Silva H, Vinueza R, Silva Aycaguer LC et al. CARMELA: assessment of cardiovascular risk in seven Latin American cities. Am J Med. 2008; 121: 58-65. Available in: https://doi.org/10.1016/j.amjmed.2007.08.038
9. Teo K, Chow CK, Vaz M, Rangarajan S, Yusuf S, PURE Investigators-Writing Group. The Prospective Urban Rural Epidemiology (PURE) study: examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries. Am Heart J. 2009; 158: 1-7.e1. Available in: https://doi.org/10.1016/j.ahj.2009.04.019
10. Benavente D, Mrcp CDC, Ferro CJ. Principales componentes del sistema renina-angiotensina-aldosterona: historia, modulación farmacológica e impacto clínico. Rev Med Clin Conde. 2010; 21: 516-529. Disponible en: https://doi.org/10.1016/S0716-8640(10)70567-8
11. Gao Q, Xu L, Cai J. New drug targets for hypertension: a literature review. Biochim Biophys Acta Mol Basis Dis. 2021; 1867: 166037. Available in: https://doi.org/10.1016/j.bbadis.2020.166037
12. Vane JR. The history of inhibitors of angiotensin converting enzyme. J Physiol Pharmacol. 1999; 50: 489-498.
13. Piepho RW. Overview of the angiotensin-converting-enzyme inhibitors. Am J Health Syst Pharm. 2000; 57 Suppl 1: S3-S7. Available in: https://doi.org/10.1093/ajhp/57.suppl_1.S3
14. Regulski M, Regulska K, Stanisz BJ, Murias M, Gieremek P, Wzgarda A et al. Chemistry and pharmacology of Angiotensin-converting enzyme inhibitors. Curr Pharm Des. 2015; 21: 1764-1775. Available in: https://doi.org/10.2174/1381612820666141112160013
15. Ghatage T, Goyal SG, Dhar A, Bhat A. Novel therapeutics for the treatment of hypertension and its associated complications: peptide- and nonpeptide-based strategies. Hypertens Res. 2021; 44: 740-755. Available in: https://doi.org/10.1038/s41440-021-00643-z
16. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-converting enzyme inhibitors in hypertension: to use or not to use? J Am Coll Cardiol. 2018; 71: 1474-1482. Available in: https://doi.org/10.1016/j.jacc.2018.01.058
17. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008; 358: 2560-2572. Available in: https://doi.org/10.1056/NEJMoa0802987
18. Sleight P. The ONTARGET/TRANSCEND Trial Programme: baseline data. Acta Diabetol. 2005; 42 Suppl 1: S50-S56. Available in: https://doi.org/10.1007/s00592-005-0181-3
19. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D et al. 2020 international society of hypertension global hypertension practice guidelines. Hypertension. 2020; 75: 1334-1357. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.120.15026
20. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018; 71: e13-115. Available in: https://doi.org/10.1161/HYP.0000000000000065
21. Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014; 384: 591-598. Available in: https://doi.org/10.1016/S0140-6736(14)61212-5
22. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008; 359: 2417-2428. Available in: https://doi.org/10.1056/NEJMoa0806182
23. Tóth K, PIANIST Investigators. Antihypertensive efficacy of triple combination perindopril/indapamide plus amlodipine in high-risk hypertensives: results of the PIANIST study (Perindopril-Indapamide plus AmlodipiNe in high rISk hyperTensive patients). Am J Cardiovasc Drugs. 2014; 14: 137-145. Available in: https://doi.org/10.1007/s40256-014-0067-2
24. Stewart MH, Lavie CJ, Ventura HO. Future pharmacological therapy in hypertension. Curr Opin Cardiol. 2018; 33: 408-415. Available in: https://doi.org/10.1097/HCO.0000000000000529
25. Haspula D, Clark MA. Neuroinflammation and sympathetic overactivity: mechanisms and implications

in hypertension. Auton Neurosci. 2018; 210: 10-17. Available in: https://doi.org/10.1016/j.autneu.2018.01.002
26. Llorens-Cortes C, Touyz RM. Evolution of a new class of antihypertensive drugs: targeting the brain renin-angiotensin system. Hypertension 2020; 75: 6-15. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.119.12675
27. Verweij P, Danaietash P, Flamion B, Ménard J, Bellet M. Randomized dose-response study of the new dual endothelin receptor antagonist aprocitentan in hypertension. Hypertension. 2020; 75: 956-965. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.119.14504
28. Li C, Yan X, Wu D, Zhang K, Liang X, Pan Y et al. Vaccine targeted alpha 1D-adrenergic receptor for hypertension. Hypertension. 2019; 74: 1551-1562. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.119.13700
29. Nakagami H, Morishita R. Recent advances in therapeutic vaccines to treat hypertension. Hypertension. 2018; 72: 1031-1036. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.118.11084
30. Singh RR, McArdle ZM, Iudica M, Easton LK, Booth LC, May CN et al. Sustained decrease in blood pressure and reduced anatomical and functional reinnervation of renal nerves in hypertensive sheep 30 months after catheter-based renal denervation. Hypertension. 2019; 73: 718-727. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.118.12250
31. Oparil S, Schmieder RE. New approaches in the treatment of hypertension. Circulation Research. 2015; 116: 1074-1095. Available in: https://doi.org/10.1161/CIRCRESAHA.116.303603
32. Jordan J, Toplak H, Grassi G, Yumuk V, Kotsis V, Engeli S et al. Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension: obesity and heart failure. J Hypertens. 2016; 34: 1678-1688. Available in: https://doi.org/10.1097/HJH.0000000000001013
33. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension. 2003; 42: 878-884. Available in: https://doi.org/10.1161/01.HYP.0000094221.86888.AE
34. López-Jaramillo P, Sánchez RA, Diaz M, Cobos L, Bryce A, Parra Carrillo JZ et al. Latin American consensus on hypertension in patients with diabetes type 2 and metabolic syndrome. J Hypertens. 2013; 31: 223-238. Available in: https://doi.org/10.1097/HJH.0b013e32835c5444.
35. Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical activity on mortality in patients with high blood pressure: a systematic review. J Hypertens. 2012; 30: 1277-1288. Available in: https://doi.org/10.1097/HJH.0b013e3283544669
36. Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. Cochrane Database Syst Rev. 2011; CD004022. Available in: https://doi.org/10.1002/14651858.CD004022.pub3
37. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med. 2014; 371: 612-623. Available in: https://doi.org/10.1056/NEJMoa1311889
38. Gu D, Zhao Q, Chen J, Chen JC, Huang J, Bazzano LA et al. Reproducibility of blood pressure responses to dietary sodium and potassium interventions: the GenSalt study. Hypertension. 2013; 62: 499-505. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.113.01034.
39. Guideline: potassium intake for adults and children. World Health Organization; 2012.
40. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation. 2014; 129: 643-659. Available in: https://doi.org/10.1161/CIRCULATIONAHA.113.005925
41. Roerecke M, Kaczorowski J, Tobe SW, Gmel G, Hasan OSM, Rehm J. The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. Lancet Public Health. 2017; 2: e108-e120. Available in: https://doi.org/10.1016/S2468-2667(17)30003-8
42. Xin X, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension. 2001; 38: 1112-1117. Available in: https://doi.org/10.1161/hy1101.093424
43. Cushman WC, Cutler JA, Hanna E, Bingham SF, Follmann D, Harford T et al. Prevention and treatment of hypertension study (PATHS): effects of an alcohol treatment program on blood pressure. Arch Intern Med. 1998; 158: 1197-1207. Available in: https://doi.org/10.1001/archinte.158.11.1197

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: The authors declare that they have no conflict of interests.

Correspondence:
Adolfo Chávez-Mendoza, MD
E-mail: dr.adolfochavez@gmail.com

CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105189

Impact of alternative therapies in the treatment of resistant systemic arterial hypertension

Impacto de las terapias alternativas en el tratamiento de la hipertensión arterial sistémica resistente

Enrique Díaz-y-Díaz, MD, FACC* Juan José Parcero-Valdés, MD, FACC, FSCAI‡

Keywords:
Resistant arterial hypertension, renal denervation, baroreceptor stimulation therapy.

Palabras clave:
Hipertensión arterial resistente, denervación renal, terapia de estimulación de barorreceptores.

ABSTRACT

Resistant arterial hypertension has been defined as a condition where a patient is being treated with an antihypertensive regimen with ≥ 4 drugs or ≥ 3 drugs that include a diuretic and still has blood pressure figures ≥ 140/90 mmHg. Given that the prevalence of resistant arterial hypertension is high, clinicians should be aware of its potential risk of not handling this condition. This review aims to discuss contributors and clinical recommendations to help clinicians better understand and treat resistant arterial hypertension within all care settings. We also demonstrate data from randomized placebo-controlled trials and conclude that renal denervation significantly reduces ambulatory and office blood pressure. Moreover, it was similar between patients on and off background antihypertensive medications. Furthermore, a novel therapy named baroreceptor stimulation therapy has shown promising data in both experimental and clinical experiments to handle resistant arterial hypertension. Both approaches may be highly relevant in patients who are intolerant to medications.

RESUMEN

La hipertensión arterial resistente se ha definido como una condición en la que un paciente está siendo tratado con un régimen antihipertensivo con ≥ 4 fármacos o ≥ 3 fármacos que incluyen un diurético y todavía tiene cifras de presión arterial ≥ 140/90 mmHg. Dado que la prevalencia de la hipertensión arterial resistente es alta, los clínicos deben ser conscientes de su riesgo potencial de no manejar esta condición. Esta revisión tiene como objetivo discutir las contribuciones y las recomendaciones clínicas para ayudar a los clínicos a entender y tratar mejor la hipertensión arterial resistente dentro de todos los entornos de atención. También se muestran datos de ensayos aleatorios controlados con placebo y se concluye que la denervación renal reduce significativamente la presión arterial ambulatoria y en el consultorio. Además, fue similar entre los pacientes que tomaban o no medicamentos antihipertensivos de fondo. Asimismo, un nuevo tratamiento denominado terapia de estimulación de barorreceptores ha mostrado datos prometedores tanto en experimentos como en la clínica para manejar la hipertensión arterial resistente. Ambos enfoques pueden ser muy relevantes en pacientes que no toleran la medicación.

INTRODUCTION

Systemic arterial hypertension is the number one risk factor for mortality worldwide. The burden of the disease relies on its contribution to cardiovascular morbidity and mortality. Nevertheless, resistant arterial hypertension stands for a highly risk condition that could exacerbate diverse complications and outcomes of the disease. According to international guidelines, resistant arterial hypertension has been defined as a condition where a patient is being treated with an antihypertensive regimen with ≥ 4 drugs or ≥ 3 drugs that include a diuretic and still has blood pressure figures ≥ 140/90 mmHg.[1] Usually, patients classified with resistant arterial hypertension trend to had target organ lesions, hence, it is highly recommended to perform an immediate referral with a trained specialist of to a qualified clinical center that could deal with the optimal management of the disease. Moreover, it has

* División de Cardiología. UMAE Hospital de Cardiología del Centro Médico Nacional Siglo XXI, IMSS. Ciudad de México, Miembro de GREHTA.
‡ Director of North Medical Center for Heart Studies, Tijuana, Baja California, Member of GREHTA.

How to cite: Díaz-y-Díaz E, Parcero-Valdés JJ. Impact of alternative therapies in the treatment of resistant systemic arterial hypertension. Cardiovasc Metab Sci. 2022; 33 (s3): s233-s237. https://dx.doi.org/10.35366/105189

been shown that patients living with persistent arterial hypertension trend to have an adverse cardiovascular risk profile. A recent report from Daugherty et al. declared that patients with resistant hypertension display a 47% increase in cardiovascular events compared with patients without this condition.[2] Therefore, persistent arterial hypertension is a condition that should be promptly detected and in consequence, appropriately treated to prevent associated complications to the disease. In this review, we discuss the epidemiology, contributors and clinical recommendations that could help clinicians to better understand and treat resistant arterial hypertension within all care settings.

Prevalence of resistant arterial hypertension. Although resistant arterial hypertension is a condition that has been associated with mixed factors related to therapeutic and clinical management, diverse epidemiological reports have pointed out that its prevalence is properly high. According to the American National Health and Nutrition Surveys (NHANES) from 2008, the estimated prevalence of adults that classified with resistant arterial hypertension was of 12.8%.[3] A similar prevalence has been reported in the 2011 Spanish Registry of Ambulatory Blood Pressure, where 14.8% of its participants were classified with resistant arterial hypertension.[4] Moreover, results from ASCOT, ALLHAT and ACCOMPLISH studies reported an estimated prevalence of resistant arterial hypertension of 25% up to 35% on threatened patients.[5] These epidemiological reports shown that the estimated prevalence of patients that had resistant arterial hypertension criteria ranges from 15 to 35%.

Contributors of resistant arterial hypertension. The contributors to resistant arterial hypertension highlight a therapeutic non-compliance within two main axes: fail in appropriated pharmacotherapy and lack of appropriate non-pharmacological measures. Both conditions could be further combined with secondary commodities that aggravate arterial hypertension, such as obstructive sleep apnea or renal artery stenosis. Hence, it is endorsed that the first actions to perform within resistant arterial hypertension is to assess adequate therapeutic compliance and then, rule-out secondary causes of arterial hypertension. Additionally, a high percentage of these patients will require a combined multi-antihypertensive regime, some of which are understudied drugs in randomized clinical trials. In this context, spironolactone is a recent promising antihypertensive that has been studied to treat resistant arterial hypertension due to primary and secondary causes. A randomized clinical trial performed in 2015 revealed that spironolactone succeeded in decreasing blood pressure within patients living with resistant arterial hypertension.[6] Since then, spironolactone has been considered a potential pharmacological approach to treat the disease.[7]

INTERVENTIONAL TREATMENT OF RESISTANT HYPERTENSION: RENAL SYMPATHETIC DENERVATION

Potential benefits of renal denervation. For several decades, increased hyperactivity within the sympathetic nervous system has been described as the leading cause of the physiopathology of resistant arterial hypertension.[8] Therefore, renal sympathetic denervation has been studied as an approach to handle the disease. The method consists of a minimally invasive percutaneous intervention based on the ablation of afferent and efferent renal nerves using a catheterism approach through arterial access (E.g., right femoral artery). The technique is based on forming a low dose of radiofrequency or ultrasonographic energy within the adventitia of the renal artery to create a thermic ablation, interrupting large portions of the nervous system fibers. Alternative ways to accomplish renal nerve ablation include applying nerve agents, cryotherapy, or brachytherapy, which are currently under clinical investigation.

Conversely, for what happened with similar techniques that failed to improve outcomes (E.g., lumbar sympathectomy), renal sympathetic denervation has consistently improved blood pressure control by decreasing renal adrenergic nerve stimulation. Furthermore, this procedure have shown pleiotropic benefits in improving glycemic levels, sleep apnea, arrhythmias, and oxidative stress since other cardiometabolic conditions such as congestive heart failure,

atrial fibrillation, sleep-disordered breathing, and diabetes mellitus are also found within these patients.[9,10] Nevertheless, the efficacy of renal denervation has been the subject of broad discussions. Pragmatic and observational studies showed a completely different effect on lowering blood pressure than those observed in early clinical trials.[11,12] Moreover, a recent placebo-controlled clinical trial using ultrasonographic renal denervation failed to give increased benefit against conventional triple antihypertensive treatment in patients with resistant arterial hypertension.[13]

Efficacy of renal denervation. To elucidate the controversies, a recent published meta-analysis of randomized, blinded, placebo-controlled clinical trials sought to assess the overall effect of renal denervation compared with concomitant antihypertensives in patient living with resistant arterial hypertension.[14] The main endpoints of the selected studied were changes in 24-hour ambulatory systolic blood pressure or changes in office measure diastolic blood pressure compared to baseline. The authors found seven clinical trials that randomized 1,368 patients (782 in renal denervation and 586 to placebo) during a mean time follow-up of 4.5 months.[13,15-20] We summarize the main findings of the meta-analysis as follows:

1. Renal denervation achieved a statistically significant reduction of 3.61 and 1.85 mmHg of ambulatory systolic and diastolic blood pressure, respectively.
2. Renal denervation was associated with a decrease of 5.86 and 3.65 mmHg office systolic and diastolic blood pressure.
3. The overall benefit was consistent in both patients taking baseline antihypertensive medications and those naïve-treated subjects.

The authors concluded that there is consistent evidence that renal denervation is a useful strategy to handle resistant arterial hypertension demonstrated by randomized clinical trials. Furthermore, it could be a useful alternative rather than increasing the number of medications in patients who are already taking three or more antihypertensives. The results from this study could lead to further research to even consider renal denervation as first-line therapy for naïve-treatment patients living with arterial hypertension. Limitations to be mentioned from this metanalysis is the inclusion of two trials that were conducted in patients without concomitant antihypertensives, and five trials that were performed with concomitant antihypertensives. Additionally, the short duration of all the clinical trials still is unable to assess the long-term benefits of denervation or even the adverse effects related to this technique, which could only be assess using long-term blinding. The latter point has been only tested in animal models, but the long-term effects of renal denervation on humans continuous to be an area of further research.[21] Nevertheless, there are still limitations regarding randomized clinical trials as these studies makes impractical the long-term follow up and the real-life assessment of cost-effectiveness of renal denervation. Some authors have mentioned that within subjects ≥ 60 years of age with a 13.2% initial 10-year predicted risk of cardiovascular disease, it would be a cost-effective strategy.[22] Finally, it is unknown whether renal denervation is superior to aggressive antihypertensive schemes with spironolactone, which will need to be further assess with clinical trials.

Final considerations of renal denervation. The evidence from all the previously mentioned randomized placebo-controlled clinical trials makes us conclude that renal denervation has consistently shown to provide a significant reduction of both ambulatory and office blood pressure. Although the crude benefit is of 4 to 2 mmHg, it has been proven to be similar between patients with a background of use of antihypertensives. Therefore, it has been mentioned that the real beneficiaries of renal denervation would be those patients that could be adequately manage with oral antihypertensives of which may be completely intolerant to the adverse effects caused by the medication. Within these cases, renal denervation could be the last resource to reduce all-cause mortality and mayor cardiovascular events similarly to what has been demonstrated for conventional antihypertensive approaches.[23,24]

STIMULATION OF CAROTID BARORECEPTORS FOR THE TREATMENT OF REFRACTORY HYPERTENSION

Baroreceptor stimulation therapy (BAT) has been described as an invasive approach to managing resistant arterial hypertension in patients in whom conventional and even invasive treatments have failed to control blood pressure. The BAT is based on the activation of carotid baroreceptors through an implant that modulates autonomic activity; hence, its capacity to reduce blood pressure. A recent meta-analysis of seven observational and two randomized clinical trials found a significant reduction in systolic blood pressure after applying ventricular stimulation therapy in carotid baroreceptors. The study found a reduction of 36 mmHg (30-42 mmHg) systolic blood pressure.[25] Another meta-analysis demonstrated a significant reduction of 21 mmHg (17-26 mmHg) and 38 mmHg (30-46 mmHg) of systolic blood pressure at short-term (1-6 months) and long-term (> 12 months) effects, respectively.[26] Although both meta-analyses suggest BAT's beneficial effect on blood pressure management, the results should be interpreted with great care. The current evidence from controlled clinical trials is scarce. Therefore, there is a need for further research in this area. Nevertheless, these results provide promising evidence for continuing performing experimental and clinical trials to evaluate the long-term benefit of BAT further.

CONCLUSIONS AND TAKE A HOME MESSAGES

Renal sympathetic denervation offers the most consistent and robust evidence to be considered an alternative to handle resistant arterial hypertension. Overall, renal sympathetic denervation offers a consistent reduction in blood pressure for at least three years with a good safety profile and infrequent need for reintervention. However, the is still unknown evidence whether it could be superior to aldosterone antagonists as the first choice in resistant arterial hypertension. Renal sympathetic denervation may be considered whether the use of aldosterone antagonists is impossible. Further research is needed regarding novel therapies that could be implemented to reduce the cardiovascular risk profile in patient who are intolerant to traditional antihypertensive medications.

REFERENCES

1. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39: 3021-3104. Available in: https://doi.org/10.1093/eurheartj/ehy339
2. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. 2012; 125: 1635-1642. Available in: https://doi.org/10.1161/CIRCULATIONAHA.111.068064
3. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension. 2011; 57: 1076-1080. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.111.170308.
4. De la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011; 57: 898-902. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.110.168948
5. Pimenta E, Calhoun DA. Resistant hypertension: incidence, prevalence, and prognosis. Circulation. 2012; 125: 1594-1596. Available in: https://doi.org/10.1161/CIRCULATIONAHA.112.097345
6. Williams B, MacDonald TM, Caulfield M, Cruickshank JK, McInnes G, Sever P et al. Prevention and treatment of hypertension with algorithm-based therapy (PATHWAY) number 2: protocol for a randomised crossover trial to determine optimal treatment for drug-resistant hypertension. BMJ Open. 2015; 5: e008951. Available in: https://doi.org/10.1136/bmjopen-2015-008951
7. Díaz y Díaz E. Hipertensión arterial sistémica resistente; el papel de la denervación renal. Cardiología y Medicina Vascular. Actualidades. Editorial Alfil; n.d.
8. Grassi G. Assessment of sympathetic cardiovascular drive in human hypertension: achievements and perspectives. Hypertension. 2009; 54: 690-697. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.108.119883
9. Leong KTG, Walton A, Krum H. Renal sympathetic denervation for the treatment of refractory hypertension. Annu Rev Med. 2014; 65: 349-365. Available in: https://doi.org/10.1146/annurev-med-051812-145353
10. Witkowski A, Prejbisz A, Florczak E, Kadziela J, Sliwinski P, Bielen P et al. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. Hypertension. 2011; 58: 559-565. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.111.173799
11. Howard JP, Nowbar AN, Francis DP. Size of blood pressure reduction from renal denervation: insights from meta-analysis of antihypertensive drug trials of 4,121 patients with focus on trial design: the CONVERGE

report. Heart. 2013; 99: 1579-1587. Available in: https://doi.org/10.1136/heartjnl-2013-304238
12. Ahmad Y, Kane C, Arnold AD, Cook CM, Keene D, Shun-Shin M et al. Randomized blinded placebo-controlled trials of renal sympathetic denervation for hypertension: a meta-analysis. Cardiovasc Revasc Med. 2022; 34: 112-118. Available in: https://doi.org/10.1016/j.carrev.2021.01.031
13. Azizi M, Sanghvi K, Saxena M, Gosse P, Reilly JP, Levy T et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. Lancet. 2021; 397: 2476-2486. Available in: https://doi.org/10.1016/S0140-6736(21)00788-1
14. Ahmad Y, Francis DP, Bhatt DL, Howard JP. Renal denervation for hypertension: a systematic review and meta-analysis of randomized, blinded, placebo-controlled trials. JACC Cardiovasc Interv. 2021; 14: 2614-2624. Available in: https://doi.org/10.1016/j.jcin.2021.09.020.
15. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet. 2018; 391: 2335-2345. Available in: https://doi.org/10.1016/S0140-6736(18)31082-1
16. Bohm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. Lancet. 2020; 395: 1444-1451. Available in: https://doi.org/10.1016/S0140-6736(20)30554-7
17. Desch S, Okon T, Heinemann D, Kulle K, Rohnert K, Sonnabend M et al. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. Hypertension. 2015; 65: 1202-1208. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.115.05283
18. Mathiassen ON, Vase H, Bech JN, Christensen KL, Buus NH, Schroeder AP et al. Renal denervation in treatment-resistant essential hypertension. A randomized, SHAM-controlled, double-blinded 24-h blood pressure-based trial. J Hypertens. 2016; 34: 1639-1647. Available in: https://doi.org/10.1097/HJH.0000000000000977
19. Kandzari DE, Bohm M, Mahfoud F, Townsend RR, Weber MA, Pocock S et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet. 2018; 391: 2346-2355. Available in: https://doi.org/10.1016/S0140-6736(18)30951-6
20. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014; 370: 1393-1401. Available in: https://doi.org/10.1056/NEJMoa1402670
21. Singh RR, McArdle ZM, Iudica M, Easton LK, Booth LC, May CN et al. Sustained decrease in blood pressure and reduced anatomical and functional reinnervation of renal nerves in hypertensive sheep 30 months after catheter-based renal denervation. Hypertension. 2019; 73: 718-727. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.118.12250
22. Chowdhury EK, Reid CM, Zomer E, Kelly DJ, Liew D. Cost-effectiveness of renal denervation therapy for treatment-resistant hypertension: a best case scenario. Am J Hypertens. 2018; 31: 1156-1163. Available in: https://doi.org/10.1093/ajh/hpy108
23. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016; 387: 957-967. Available in: https://doi.org/10.1016/S0140-6736(15)01225-8
24. Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. Lancet. 2021; 397: 1625-1636. Available in: https://doi.org/10.1016/S0140-6736(21)00590-0
25. Wallbach M, Koziolek MJ. Baroreceptors in the carotid and hypertension-systematic review and meta-analysis of the effects of baroreflex activation therapy on blood pressure. Nephrol Dial Transplant. 2018; 33: 1485-1493. Available in: https://doi.org/10.1093/ndt/gfx279
26. Chunbin W, Fu S, Jing H. Efficacy and safety of baroreflex activation therapy for treatment of resistant hypertension: a systematic review and meta-analysis. Clin Exp Hypertens. 2018; 40: 501-508. Available in: https://doi.org/10.1080/10641963.2016.1273943

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: The authors declare that they have no conflict of interests.

Correspondence:
Enrique Díaz-y-Díaz, MD, FACC
E-mail: enriquedyd@prodigy.net.mx

CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105190

Management of high blood pressure during all-trimesters of pregnancy

Tratamiento de la hipertensión arterial durante todos los trimestres del embarazo

Ana G Múnera-Echeverri, FACC, FSIAC,* Edith Ruiz-Gastelum, FeSISIAC, FACC‡

Keywords:
High blood pressure, pregnancy, cardiovascular risk.

Palabras clave:
Hipertensión arterial, embarazo, riesgo cardiovascular.

ABSTRACT

High blood pressure (HBP) disorders of pregnancy are one of the leading causes of morbidity during pregnancy along with maternal-fetal mortality in developing countries. In this work, we discuss the physiopathology, diagnostic assessment, and treatment and prevention strategies focused on diminishing the burden of hypertensive disorders of pregnancy at all-care levels. Most of the current guidelines encourage to perform an adequate assessment in every woman living with chronic HBP prior to pregnancy. Preeclampsia stands for a multisystemic, multifactorial, dynamic, and progressive disease that could appear at any gestation week. Furthermore, an adequate assessment of any hypertensive disorder of pregnancy is needed to prevent acute and long-term complications related these diseases. Pharmacological management should be based on clinical manifestations at the moment of evaluation. All woman with hypertensive disorder during pregnancy had an increased cardiovascular risk, therefore, continuous follow-up management is highly recommended.

RESUMEN

Los trastornos de hipertensión arterial (HTA) en el embarazo son una de las principales causas de morbilidad durante el mismo, junto con la mortalidad materno-fetal en los países en desarrollo. En este trabajo se analiza la fisiopatología, la evaluación diagnóstica y las estrategias de tratamiento y prevención enfocadas a disminuir la carga de los trastornos hipertensivos del embarazo en todos los niveles asistenciales. La mayoría de las directrices actuales animan a realizar una evaluación adecuada en todas las mujeres que viven con HTA crónica antes del embarazo. La preeclampsia es una enfermedad multisistémica, multifactorial, dinámica y progresiva que puede aparecer en cualquier semana de gestación. Además, es necesario realizar una evaluación adecuada de cualquier trastorno hipertensivo del embarazo para prevenir las complicaciones agudas y a largo plazo relacionadas con estas enfermedades. El tratamiento farmacológico debe basarse en las manifestaciones clínicas en el momento de la evaluación. Todas las mujeres con trastorno hipertensivo durante el embarazo tienen un mayor riesgo cardiovascular, por lo que se recomienda un seguimiento continuo.

INTRODUCTION

High blood pressure (HBP) disorders of pregnancy are one of the leading causes of morbidity during pregnancy and maternal and fetal mortality in developing countries. Its estimated incidence during pregnancy is 7.5%, and it further increased up to 15.3% within women coursing its first pregnancy or with chronic health comorbidities, such as obesity, diabetes, and metabolic syndrome.[1,2] The European Society of Cardiology (ESC), the American College of Cardiology (ACC), and the American College of Ginecobsetry (ACOG) agreed that a standardized definition of HBP during pregnancy is a measured blood pressure ≥ 140/90 mmHg.[3-5] The proposed threshold is higher than the one proposed by the ACC and American Heart Association (AHA) to diagnose stage 1 HBP (≥ 130/80 mmHg), which has been demonstrated to be an optimal cut-off value to reduce the incidence of cardiovascular disease at long-term follow-up.[4] This work discusses the physiopathology, diagnostic assessment, and treatment and prevention strategies focused on diminishing the burden of hypertensive disorders of pregnancy at all-care levels.

* Medellín Luz Castro de Gutiérrez General Hospital. Colombian Society of Cardiology and Cardiovascular Surgery, Member of GREHTA.
‡ Coordinadora de clínica de hipertensión y riesgo cardiovascular en ISSSTESON (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado de Sonora), Miembro GREHTA.

How to cite: Múnera-Echeverri AG, Ruiz-Gastelum E. Management of high blood pressure during all-trimesters of pregnancy. Cardiovasc Metab Sci. 2022; 33 (s3): s238-s243. https://dx.doi.org/10.35366/105190

Physiopathology of hypertensive disorders of pregnancy

There have been described mixed physiological changes within the cardiovascular system during pregnancy, including a decrease in systemic vascular and increased plasmatic and cardiac volume output. Moreover, other physiological metabolic changes during pregnancy include increased insulin resistance, hypercoagulative state, and increased serum cholesterol and triglycerides production. Other changes that have been described related to the cardiovascular system include an increase in 50% renal and glomerular filtration rate. All these changes lead to a rise in blood pressure within each trimester of pregnancy and an augmented risk of hypertensive disorders of pregnancy.[1,2]

There has been a hypothesis to elucidate the real physiopathology of hypertensive disorders of pregnancy. The most accepted theories mention that an abnormal cytotrophoblast invasion within spiral arteries decreases utero-placenta blood perfusion. Thus, leading to an inflammatory cascade in a chain reaction, with a disrupted balance of angiogenic factors, plaquetary aggregation, and overall endothelial dysfunction.[1,6] Nevertheless, there are still unknown genetic, metabolic, and physiological pathways that need further study. Classification of hypertensive disorders of pregnancy are presented in *Table 1*.

Assessment of blood pressure during pregnancy

An adequate blood pressure assessment in the early stages of pregnancy is fundamental. Before the measurement is taken, the patient must be perfectly calmed and ideally situated in a comfortable chair. The sphygmomanometer must be certified and calibrated according to the user manual before any assessment. Therefore, the clinician or healthcare professional must proceed to assess the blood pressure. In case there are extreme measurements (systolic $\geq$ 160 or $\geq$ 110 mmHg diastolic), the whole procedure must be repeated after 15 minutes. Finally, all women should perform a self-measured blood pressure assessment within patients with previous HBP diagnoses or whether the patient had inadequate pregnancy control. Furthermore, self-monitory could mitigate the «white-coat» effect during clinical visits.

Prevention of preeclampsia

It has been described that in women with a healthy lifestyle before pregnancy have a decreased risk of hypertensive disorders during pregnancy. Therefore, all women without evident contraindications should be encouraged to perform any type of exercise routine and be guided to change their diet patterns to achieve their ideal body weight composition even before pregnancy. Additionally, dietary recommendations include folic acid and calcium supplementation. Whether in women who have been already identified with preeclampsia or with two moderate risk factors, it is then recommended to prescribe a 100-1,500 mg acetylsalicylic acid dose during nights starting at the 12-16 week up to the 36 weeks of gestation.

Assessment on previous high blood pressure

Based on the current evidence, we encouraged that all women living with HBP needs to be submitted to a prompt medical evaluation with the objective to identify target-organ damage, need of additional clinical assessment, promote life-style changes, and give appropriate counseling about chronic HBP impairments during pregnancy. Additionally, this group need to be assessed regarding hazardous pharmacological regimes such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), renin-based and anti-aldosterone antihypertensives.[5,7] It is highly recommended that both a complete medical history and physical examination, along with target-organ assessment and biochemical evaluation should be made in every woman prior to pregnancy and at the diagnosis of pregnancy. Finally, for women with significant changes in blood pressure, or which arrived with signs of preeclampsia, it is mandatory to had a biochemical evaluation to exclude target-organ damage and a further evaluation on the fetal condition with an obstetric echocardiography with umbilical Doppler assessment.[2,5,8] Clinical risk factors are presented in *Table 2*.

Table 1: Classification of high blood pressure disorders.*

Disorder	Definition
Before pregnancy or < 20 weeks of gestation	
Chronic arterial high blood pressure	Detected high blood pressure before pregnancy or before 20 weeks of gestation
Essential	Arterial high blood pressure unknown cause
Secondary arterial high blood pressure	Arterial high blood pressure due to secondary cause
«White-coat» high blood pressure	SBP > 140 and/or DBP > 90 measured in the office/hospital, and pressure < 135/85 using ABPM or MPAC
Masked arterial high blood pressure	BP < 140/90 in the office/hospital and > 135/85 outside the office/hospital
≥ 20 weeks of gestation	
Gestational high blood pressure	*De novo* high blood pressure > 20 weeks' gestation in the absence of proteinuria and PE
Transient gestational high blood pressure	Arterial high blood pressure after 20 weeks of gestation, which disappears in subsequent shots of the BP
Pre-eclampsia *de novo*	PE *(de novo)* is gestational high blood pressure accompanied by one or more of the following conditions: — Proteinuria: protein/creatinine ratio (PrCr) in a urine sample > 30 mg/mmol, or albumin/creatinine (ACR) > 8 mg/mmol, or > 300 mg in 24-hour urine, or > 2+ in urine on dipstick if other tests are not available — Target organ dysfunction: • Neurological complications (eclampsia, headache, stroke, altered state of consciousness, scotomata) • Pulmonary edema • Hematological compromise: Hemolysis, platelets < 150,000) • Renal compromise: Creatinine > 1 mg/dL • Liver compromise (transaminases > 40 IU/L) with or without epigastric or right upper quadrant pain — Utero-placental dysfunction (abruption, fetal growth restriction, altered umbilical artery Doppler, fetal death
Pre-eclampsia with chronic high blood pressure	Women with chronic high blood pressure who develop proteinuria, maternal organ dysfunction or utero-placental dysfunction

*International Society for the Study of Hypertension in Pregnancy (ISSHP) classification.
SBP = systolic blood pressure, DBP = diastolic arterial pressure, ABPM = ambulatory blood pressure monitoring, HBPM = home blood pressure monitoring, PE = pre-eclampsia, BP = blood pressure.
Modified from: American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics.[7]

Management of high blood pressure during pregnancy

Management should be guided based on clinical and severity manifestations for any hypertensive disorders during pregnancy. It its highly recommended that all patients diagnosed with gestational HBP or with preeclampsia needs to be hospitalized. This recommendation guarantees a prompt evaluation of the fetal condition, an adequate stabilization of blood pressure and the creation of an appropriate follow-up clinical management.[2,5]

Different clinical societies have proposed different blood pressure thresholds to begin pharmacological treatment. The ACOG encourages to begin antihypertensive therapy whether clinicians identify persistent blood pressure over ≥ 160/110 mmHg. Moreover, the ACOG mentions that an ideal blood pressure goal is a systolic blood pressure between 120 to 160 mmHg while having a diastolic

blood pressure between 80 to 110 mmHg within coexistent comorbidities.[7] Conversely, diverse clinical societies, including the ESC have recommended to begin pharmacological management to every pregnant woman with blood pressure > 140/90 mmHg.[6,8,9] Furthermore, the same ESC encourages to treat every immediately every woman with the previously mentioned threshold and with gestational HBP, chronic HBP, preeclampsia or with evidence of target-organ damage. The accepted goals proposed by diverse societies is a blood pressure < 130/80 mmHg.[1,6,8-10] The International Society for the Study of Hypertension in Pregnancy (ISSHP) specifies that an ideal goal, regardless of systolic blood pressure, is a diastolic blood pressure < 85 mmHg.[11]

It has been reported that non-severe presentations of hypertensive disorders during pregnancy could be treated with first line oral pharmacological approaches, such as labetalol, nifedipine and methyldopa.[2,11,12] Conversely, women with urgent hypertensive crisis (defines as systolic blood pressure > 160 mmHg or diastolic blood pressure > 110 mmHg) should be immediately treated and maintained with intravenous antihypertensives enlisted in *Table 3*.[5,8,11] The optimal goal within urgent hypertensive crisis is grounded on a blood pressure < 150/100 mmHg without triggering secondary hypotension or compromising utero-placenta blood perfusion. Finally, the ESC has recommended the use of use of nitroglycerin in cases with secondary edema due to preeclampsia, and in a last resourse, the use of sodium nitroprusside. Nevertheless, it should be monitored given the risk of fetal cyanuric intoxication.[2]

A cost-benefit should be performed between the risk of preterm labor and the maternal integrity to continue with pregnancy. It has been mentioned that within cases below the 34th gestational week, delivery should be guided in a close in-hospital surveillance setting to implement corticosteroids to accelerate fetal lung maturation along with an integral medical evaluation. The same recommendations are encouraged within cases between the 34th-37th gestational week.[5,6,12] Finally, immediate labor should be started in cases with severe neurological manifestations, uncontrolled HBP with ≥ 3 antihypertensives, incident pulmonary edema, progressive thrombocytopenia, transfusion requirements, abnormal creatinine, increased liver enzymes, or a severe fetal compromise.[11]

Management at delivery

All women should be advised regarding signs and symptoms of preeclampsia. Additionally,

Table 2: Clinical risk factors for PE.

	High risk factors	Moderate risk factor
Previous history	Previous preeclampsia	Placental abruption fetal growth restriction fetal death family history of PE (first degree)
Demography	BMI before pregnancy > 30 kg/m^2	Maternal age > 35 years Black race Low socioeconomic status
Previous medical conditions	Chronic high blood pressure Mellitus diabetes Chronic kidney disease Antiphospholipid syndrome	
Current gestation	Assisted reproductive therapy Multiple pregnancy	Nulliparity

PE = preeclampsia, BMI = body mass index, SLE = systemic lupus erythematosus.
Modified from: Braunthal S et al.[1] American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics.[7]

Table 3: Antihypertensive treatment for urgent control in severe arterial hypertension.

Medication	Dose	Comment	Onset of action (minutes)
Labetalol	10-20 mg IV, followed by 20-80 mg every 10-30 minutes to a maximum cumulative dose of 300 mg, or 1-2 mg/min IV infusion	Avoid in women with asthma, myocardial disease, decompensated heart failure, advanced heart block, and bradycardia	1-2
Hydralazine	5 mg IV or IM, then 5-10 mg IV every 20-40 minutes up to a maximum cumulative dose of 20 mg, or infusion of 0.5-10 mg/hour	Higher or more frequent doses are associated with maternal hypotension, headache, and abnormal fetal heart rate tracing	10-20
Oral nifedipine (immediate release)	10-20 mg PO, repeat in 20 minutes, if necessary, then 10-20 mg every 2-6 hours, maximum daily dose 180 mg	Reflex tachycardia and headache as secondary effects	5-10

IM = intramuscular; IV = intravenous; PO = orally.

women living with hypertensive disorders during pregnancy and with uncontrolled blood pressure require close surveillance between 3-7 days. During the postpartum period, contraindicated medications like AICE inhibitors could be restarted. Advise of adverse effects of antihypertensives during lactation should be warranted. Finally, methyldopa should be avoided at postpartum due to the risk of depression and sedation.[3,11,12]

Follow-up and cardiovascular risk: fourth trimester (lifetime)

After childbirth, a «fourth trimester» begins. This term refers to the rest of the woman's life after pregnancy.[13] Women with a history of hypertensive disorders during pregnancy have 4% increased risk of gestational HBP or at least 15% more risk of preeclampsia in future pregnancies. The ISSHP recommends:

1. Three months after delivery, all women should be assessed with blood pressure measurements, urinalysis, and biochemical evaluation.
2. Six months after delivery, all women should also be reassessed whether possible.
3. Continuous assessment of cardiovascular risk throughout all life should be made in all women.
4. After any hypertensive disorders of pregnancy, all women and their children should adopt healthy lifestyles. These includes a healthy diet, regular exercise, ideal weight, no exposure to tobacco or smoke, and a blood pressure < 120/80 mmHg.[11]

REFERENCES

1. Braunthal S, Brateanu A. Hypertension in pregnancy: Pathophysiology and treatment. SAGE Open Med. 2019; 7: 2050312119843700. Available in: https://doi.org/10.1177/2050312119843700
2. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cífková R, De Bonis M et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy: The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). European Heart Journal. 2018; 39: 3165-3241. Available in: https://doi.org/10.1093/eurheartj/ehy340
3. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). European Heart Journal. 2018; 39: 3021-3104. Available in: https://doi.org/10.1093/eurheartj/ehy339
4. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force

on Clinical Practice Guidelines. Hypertension. 2018; 71: e13-115. Available in: https://doi.org/10.1161/HYP.0000000000000065
5. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020; 135: e237-260. Available in: https://doi.org/10.1097/AOG.0000000000003891
6. Hypertension in pregnancy: diagnosis and management. London: National Institute for Health and Care Excellence (NICE); 2019.
7. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 203: chronic hypertension in pregnancy. Obstet Gynecol. 2019; 133: e26-50. Available in: https://doi.org/10.1097/AOG.0000000000003020.
8. Butalia S, Audibert F, Coté A-M, Firoz T, Logan AG, Magee LA et al. Hypertension Canada's 2018 Guidelines for the Management of Hypertension in Pregnancy. Can J Cardiol. 2018; 34: 526-531. Available in: https://doi.org/10.1016/j.cjca.2018.02.021.
9. WHO recommendations: Drug treatment for severe hypertension in pregnancy. Geneva: World Health Organization; 2018.
10. Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K et al. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. Can J Cardiol. 2016; 32: 569-588. Available in: https://doi.org/10.1016/j.cjca.2016.02.066
11. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2022; 27: 148-169. Available in: https://doi.org/10.1016/j.preghy.2021.09.008.
12. Múnera-Echeverri AG, Muñoz-Ortiz E, Ibarra-Burgos JA. Hipertensión arterial y embarazo. Revista Colombiana de Cardiología. 2021; 28: 3-13. Available in: https://doi.org/10.24875/rccar.m21000002
13. Castro Conde A, Goya M, Delgado Marín JL, Martínez Sánchez N, Pallarés Carratalá V, Obaya JC et al. Recomendaciones de seguimiento a partir del "cuarto trimestre" de mujeres con complicaciones vasculares y metabólicas durante el embarazo. Documento de consenso de la SEC, SEMERGEN, semFYC y SEGO. REC: Cardio Clinics. 2020; 55: 38-46. Available in: https://doi.org/10.1016/j.rccl.2019.10.004

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: The authors declare that they have no conflict of interests.

Correspondence:
Ana G Múnera-Echeverri, FACC, FSIAC
E-mail: anagm@une.net.co

CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105191

Management of high blood pressure in older-adults: aging, senescence and ageism

Gestión de la hipertensión arterial en adultos mayores: envejecimiento, senescencia y edadismo

Luis Alcocer, MD, MsPH*

Keywords:
High blood pressure, older adults, aging, ageism, hypertensive treatment.

Palabras clave:
Hipertensión arterial, adultos mayores, envejecimiento, edadismo, tratamiento hipertensivo.

ABSTRACT

The gradual increase of blood pressure related to aging is a consenting phenomenon. Furthermore, the onset of high blood pressure (HBP) becomes an important health concern for older adults given the diverse challenges in treatment and management. Effective treatment could substantially impact quality of life. In this review, we describe the pathophysiologic pathways in which blood pressure could be influenced by aging processes, how we could better characterize the disease and how to give an initial approach in management within older adults. Giving an appropriate antihypertensive treatment must be focused on lowering mmHg as its advantageous properties are similar across all ages; however, in absolute terms, the acquired benefits are greater in older individuals than in young people. Current data suggests that antihypertensive medication should not be rejected, altered, or terminated only because of advanced age. While this may appear reasonable, ageism is an important social determinant to initiate antihypertensive, since it restricts its access solely because of advanced age. Clinical efforts should be performed to optimize strategies to improve blood pressure in older adults.

RESUMEN

El aumento gradual de la presión arterial relacionado con el envejecimiento es un fenómeno consentido. Además, la aparición de la hipertensión arterial (HTA) se convierte en un importante problema de salud para los adultos mayores, dados los diversos retos que plantea su tratamiento y gestión. Un tratamiento eficaz podría influir sustancialmente en la calidad de vida. En esta revisión describimos las vías fisiopatológicas en las que la presión arterial podría verse influida por los procesos de envejecimiento, cómo podríamos caracterizar mejor la enfermedad y cómo dar un enfoque inicial en el manejo dentro de los adultos mayores. La administración de un tratamiento antihipertensivo adecuado debe centrarse en la disminución de los mmHg, ya que sus propiedades ventajosas son similares en todas las edades; sin embargo, en términos absolutos, los beneficios adquiridos son mayores en los individuos de edad avanzada que en los jóvenes. Los datos actuales sugieren que la medicación antihipertensiva no debe ser rechazada, modificada o interrumpida sólo por la edad avanzada. Aunque esto puede parecer razonable, el edadismo es un determinante social importante para iniciar la antihipertensiva, ya que restringe su acceso sólo por la edad avanzada. Se deben realizar esfuerzos clínicos para optimizar las estrategias para mejorar la presión arterial en los adultos mayores.

* Master in Cardiovascular Theory, Certified Hypertensiologist. President of the Interamerican Society of Hypertension. Emeritus Academic of the Mexican Academy of Surgery. Emeritus Honorary Member of the Mexican Society of Cardiology. Distinguished Professor: GREHTA, AMPAC, and ANCAM. Mexico, Member of GREHTA.

INTRODUCTION

The dramatic increase in life expectancy along with a decrease trend in global birth rates recorded in recent years, had conditioned aging worldwide. There has been a significant demographic growth within population aged 60 years and older.[1] Along with the shift in aging, there has been an epidemiological transition where globally it has been experienced a downward of Chronic Communicable Diseases (CCD) and an increase for up to 80% of the global burden disease attributable to Chronic non-Communicable Diseases (CnCD), particularly cardiovascular diseases (CVD).[2] Therefore, there is an increasing need to study, comprehend and treat CVD risk factors in older adults. High blood pressure

How to cite: Alcocer L. Management of high blood pressure in older-adults: aging, senescence and ageism. Cardiovasc Metab Sci. 2022; 33 (s3): s244-s249. https://dx.doi.org/10.35366/105191

(HBP) (defined as a blood pressure > 140/90 mmHg) continues to be a highly growing health problem in older adults due to its high reported prevalence between 30 to 80%. Moreover, its impact within older population impairs life expectancy and quality of life, leading to recent public health policies that sought to prioritize its appropriate management. Despite all the efforts, HBP continues to be highly underrated condition as it usually misinterpreted as a progressive elevation of systolic blood pressure related to aging. This misrelated conception could explain why elderly population does not receive an adequate management. It has been reported that older population usually does not receive sufficient treatment, or does not achieve treatment goals, therefore, reducing quality of live. It is imperative to avoid diverse complications related to HBP in the elderly, such as acute cerebrovascular diseases.[3] Here, we described the pathophysiologic pathways in which blood pressure could be influenced by aging processes, how we could better characterize the disease and how to give an initial approach in management within this population.

Ageism

Ageism is the term that has been adopted worldwide when older adults does not appropriately receive all the potential benefits of an adequate antihypertensive treatment due to age-conditioned inequities in health care attention. Ageism has been closely related to social discrimination within vulnerable and socially disadvantaged groups. For contextualizing the effect, it is worldly to mention some of the conditionings of discrimination. Commonly, adult self-identify with each other as belonging to the same group due to diverse social and cultural characteristics (E.g., gender, nationality, ethnic group, age, social status, education, economy, political preferences) that constitutes their main social core. The need of self-identification or belonging to a social group has been widely studied as a phenomenon across all ages. This condition is also noticeable in older adults, regardless their economic status. Older adults still need for a comprehensive social support network comprised of close-relatives, friends, or trusted persons. Nevertheless, this phenomena of self-identity within a social group could induce to exclude or even discriminate individuals who do not share common characteristics. Discrimination extends beyond simple cognitive or emotive domains to become a dangerous way of coexisting, implying that anyone who is not a member of a social group faces lesser standards.

Historical context of ageism

Historically, a sense of belonging to a group has been used to promote positive features (E.g., coherence and teamwork), but it has also been used to promote discrimination encouraging wars, enslavement, exploitation, and even annihilation. The attempts to fight discrimination could be found within the French Revolution in 1794 which was a direct precedent to eradicate slavery and stated in the Declaration of the Human Rights and the Citizens. The fight against discrimination continued with the foundation of the feminism movement in New York in 1848; although, social inequalities for women have not yet been fully achieved in diverse features, such as health care. Regardless all the efforts that have been made since 1794, there are still well-known discriminatory behaviors, such as racism, machismo, homophobia and in recent years, ageism.[4] Nevertheless, ageism often is more common and even unnoticed than racism or gender discrimination.[5]

Definition of «old age»

Older age has been arbitrary defined with diverse thresholds related to life-expectancy within each country. Elderly has been defined as adults who exceeds 60 years in low-and middle-income countries and 65 years within high-income countries. However, recent guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) mentions that older adults should be considered subjects between 65 to 79 years and ancient as subjects > 80 years old.[6,7] Within this concept, it was wrongly accepted that every adult, given its advanced

age, should have receive antihypertensive treatment with decreased intensity. Instead, a more comprehensive and expertise approach is that every clinical decision should be based on the senescence of older adults. Senescence happens at different speeds in different people and is usually non-synchronous on tissues, and systems. Therefore, senescence could be a more useful concept for clinicians as the condition that determines the type of treatment prescribed. Nevertheless, some authors questioned this approach. The HYVET trial, a landmark study in elderly hypertensive patients, does not seem to support the concept of senescence, although they declare to not include frail patients.

Senescence is closely related to fragility with diverse criteria required to classify and define it. However, for daily clinical practice and to simplify its application in older person living with HBP, fragile is defined with at least two of following five criteria: 1) over 80 years of age, 2) unfeasibility to live independently, 3) frequent falls, 4) advanced cognitive impairment, 5) diseases that substantially limit hope and or quality of life.[8] For decision-making purposes, the consensus of the European Society of Hypertension-European Union Geriatric Medicine Society defines frailty as: «a person who live in nursing homes or who need daily assistance for their basic activities» which could represent up to 35% of adults > 80 years.[9]

Aging and blood pressure levels

Although diastolic blood pressure does not necessarily increase with age, systolic blood pressure does increase with aging. Although it has been observed that the average systolic and diastolic blood pressure is higher in men than in women, within women under 55 years, the systolic pressure exceeds discreetly compared to men. In Mexico, as demonstrated by the MMM19-Mexico study, the sex differences are more accentuated in men compared to women within increased ages.[10] The progressive elevation of systolic and diastolic blood pressure happens at different speeds according to everyone. HBP could be considered as an aging process due to progressively increases in blood pressure. We could illustrate this example within a 40-year-old person with systolic pressures of 160 mmHg that could have the same blood pressure as a 60-year-old adult. Nevertheless, it should not be interpreted that the gradual increase in blood pressure is related to aging and therefore be considered as a «normal» condition that does not require treatment. This inaccurate interpretation should raise alarm as all patients with high blood pressure reflects a higher risk of adverse cardiovascular outcomes.

Characteristics of high blood pressure in the elderly

Aging could modify antihypertensive strategies according to diverse conditions physiological conditions.

Increased vascular stiffness: with aging, there is a progressive stiffness due to structural impairments within middle layers at elastic arteries, a modification in vascular collagens, a phenomenon of interstitial fibrosis, and calcification within elastin fibers. Overall, increased vascular stiffness causes that distribution vessels become less distensible which forces the systolic pressure to increase. Consequently, this leads to an increase resistance in ventricular load displayed through an increased pulse wave and peripheral arterioles speed and a stronger rebound wave. The rebound wave conditions a further increase in systolic pressure within the final portion of the systolic cycle (systolic augmentation).[11] These phenomena generate hazardous damage for the arterial system, heart, and kidneys in older adults. Increased vascular stiffness makes a more turbulent blood flow and, consequently, promotes a reduction in organ perfusion and coronary flow; therefore, the heart's metabolism and oxygen consumption increase. In this supplement, you can read a more comprehensive explanation of this phenomenon called AVA (accelerated vascular aging).

Variability: the variability of blood pressure increases in older adults. It has been recognized that higher variability is an independent cardiovascular risk factor. There are diverse types of variability: cardiac bets, circadian rhythm, seasonal changes, and many others, which goes beyond the scope of this work.

Postural hypotension: autonomic dysregulation is a widespread phenomenon in older adults. This condition is highly prevalent in users of specific antihypertensives or in patients with diabetic neuropathy. A particular consequence of neuropathies is losing the sympathetic reflex, which raises blood pressure when standing up. Postural hypotension has been recognized as an essential conditioner of syncope in the older population and an independent risk factor for falls and cardiovascular complications.

Accelerated progression of kidney damage: renal function decreases as age increases: aging decreases glomeruli and glomerular filtration rate. In older adults, HBP stimulates impairments within renal functionality due to glomerulosclerosis, interstitial renal fibrosis, and microvascular damage (adverse remodeling of the kidney). Furthermore, there are deficiencies within the sodium/potassium-adenosine triphosphate membrane pump that causes an increase in intracellular sodium and ultimately lead to volume retention. These conditions are further worsened by secondary hyperkalemia due to a progressive decrease in renal tubular mass caused by microvascular damage related to aging.

Accelerated progression of cognitive decline: dementia is a significant concern within the elderly population with a huge personal, family, and social cost. The process of cognitive decline is related to aging, but uncontrolled high blood pressure and dyslipidemia are one of the most important modifiable risk factors for vascular dementia and Alzheimer's disease. Paradoxically, blood pressure drops after the onset of dementia. The presence of a no-night pattern of no decrease in outpatient blood pressure monitoring (ABPM) is associated with nearly three times the risk for cognitive impairment.[12]

High prevalence of secondary high blood pressure: secondary HBP should always be considered in older adults. Some situations to consider are when a patient has an abrupt hypertensive onset, is measured with severe high blood pressure or is having refractive antihypertensive treatment. It has been estimated that the prevalence of HBP in older adults is higher than general population. Studies made in autopsies revelated that up to 50% had renal arterial stenosis which is a main cause of secondary HBP. HBP related to another type of steroid is more frequent in the elderly; for example, glucocorticoids used in the elderly to treat rheumatic diseases could increase systolic blood pressure by 15 mmHg.[13] Furthermore, the prevalence of peripheral arterial disease could be up to 35 to 54%, 39% within patients with prior arterial occlusion of the lower limbs, and 38% in those suffering from an aortic aneurysm. All these conditions accelerate kidney damage along with the morbidity and mortality due to an accentuated risk for ischemic heart disease.[14]

Obstructive night apnea: could be considered as a cause of secondary HBP. Approximately 30% of hypertensive patients have this condition, and its frequency duplicates by every ten years of age.[15]

Thyroid disorders: the prevalence of hypothyroidism and hyperthyroidism within older patients living with HBP could be up to 3.8 and 3.6%, respectively. Conversely, primary aldosteronism is relatively rare condition observed within this population, with an estimated prevalence of 1% up to 11%.[16]

How to prescribe the treatment of high blood pressure in older adults: a summary of current recommendations

Overall, older adults without fragility should receive the same treatment indicated for any adult. Age alone is not more considered an accepted criteria to deny an older patient a antihypertensive treatment. The recent evidence has proven that adequate antihypertensive treatment decreases the risk for acute and chronic complications and improve quality of life. The treatment for non-fragile older patient follows the same recommendations posed for all adults:

1. The cut-off points for diagnosing high blood pressure are the same for as the rest of adults.
2. Prudent lifestyle modifications are considered as the first line coadjutant treatment along with antihypertensive management.

According to current guidelines, the first step to achieve are changes in lifestyle; however, in the older subjects, this is a challenge. Traditional changes (E.g., weight loss, low-sodium diet, exercise) are usually not easy to achieve and sometimes even contraindicated. Therefore, the first step of treatment is usually combined with antihypertensive management and with reasonable recommendations to modify lifestyle habits. According to the NICE guidelines, it is recommended that adult-aged 55 years should start with antihypertensive monotherapy using calcium antagonists. As a second option, a diuretic or a blocker of the renin-angiotensin system is recommended. However, there are still diverse gaps in the literature that encourage to accept that these antihypertensive could be more useful or safer within this population.

Age has been also described as an important modifier of the pharmacokinetic of antihypertensive medications. There are significant differences of absorption, distribution, renal or hepatic metabolism, decrease in receptors and major interaction with other drugs. These physiological changes observed in adults forced Canadian Hypertension Guidelines to withdrew diverse recommendations for old adults in 2017.[17] The fear that an intensive antihypertensive regime could increase the number of falls in the elderly is a frequent concern; however, the sprint study demonstrated that no significant differences were observed in patients submitted to intensive regimes.[18]

Take home messages

Antihypertensive treatment within older adults without significant impairments begins with fixed combinations based on blocker of the renin-angiotensin system. It has been suggested that an angiotensin conversion enzyme inhibitor or an angiotensin receptor blocker (A) in combination with a calcium antagonist (C) or a diuretic (D), could be an appropriate management considering the potential pharmacokinetic differences in older adults. If blood pressure goals are not achieved, the second step consists of the use of a triple combination of the three fundamental pharmacological classes (ACD). According to the ESC/ESH-2018 and ACC/AHA 2017 guidelines, frailty, stands for one of the few current indications to start antihypertensive monotherapy treatment. Using this approach, monotherapy should be stated using small doses in patients with reasonable life expectancy.[6,7] Compared to previous 2017 hypertension guidelines, different criteria were used to diagnose HBP, to initiate antihypertensive treatment, and recommended goals. According to the ACC/AHA 2017 guidelines, the goals in older adults were < 130/80 mmHg, which is the same threshold for general population. The most recent ESC/ESH 2018 guidelines mentioned that the goals would be a systolic blood pressure between 130-139 mmHg and a diastolic blood pressure of 70-79 mmHg. As with other adults, the non-frail elderly must reach pressure goals within three months. Because all the current evidence, we consider that the risk of not treating an older adult without threatened life conditions creates a high burden on quality of life, for we encourage to implement correct antihypertensive strategies.

REFERENCES

1. Omran AR. Epidemiologic transition in the United States: the health factor in population change. Popul Bull. 1977; 32: 1-42.
2. World Health Organization. Global status report on noncommunicable diseases 2014. Geneva: World Health Organization; 2014.
3. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013; 310: 959-968. Available in: https://doi.org/10.1001/jama.2013.184182
4. Butler RN. Age-ism: another form of bigotry. Gerontologist. 1969; 9: 243-246. Available in: https://doi.org/10.1093/geront/9.4_part_1.243
5. Nosek BA, Banaji MR, Greenwald AG. Harvesting implicit group attitudes and beliefs from a demonstration website. 2016. Available in: https://doi.org/10.31234/osf.io/fe8yr
6. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39: 3021-104. Available in: https://doi.org/10.1093/eurheartj/ehy339
7. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of

Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018; 71: e13-e115. Available in: https://doi.org/10.1161/HYP.0000000000000065
8. Warwick J, Falaschetti E, Rockwood K, Mitnitski A, Thijs L, Beckett N et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the hypertension in the very elderly trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. BMC Med. 2015; 13: 78. Available in: https://doi.org/10.1186/s12916-015-0328-1
9. Benetos A, Bulpitt CJ, Petrovic M, Ungar A, Agabiti Rosei E, Cherubini A et al. An expert opinion from the European Society of Hypertension-European Union Geriatric Medicine Society Working Group on the Management of Hypertension in Very Old, Frail Subjects. Hypertension. 2016; 67 (5): 820-825. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.115.07020
10. Alcocer L, Rosas M, Estrada A, Ruiz-Gastelum E, Pombo EJ, Cardona EG et al. May measurement month 2019: an analysis of blood pressure screening results from Mexico. Eur Heart J Suppl J Eur Soc Cardiol. 2021; 23: B104-B106. Available in: https://doi.org/10.1093/eurheartj/suab026
11. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol. 2007; 50 (1): 1-13. Available in: https://doi.org/10.1016/j.jacc.2006.12.050
12. Guo H, Tabara Y, Igase M, Yamamoto M, Ochi N, Kido T et al. Abnormal nocturnal blood pressure profile is associated with mild cognitive impairment in the elderly: the J-SHIPP study. Hypertens Res. 2010; 33 (1): 32-36. Available in: https://doi.org/10.1038/hr.2009.172
13. Mosso L, Carvajal C, González A, Barraza A, Avila F, Montero J et al. Primary aldosteronism and hypertensive disease. Hypertension. 2003; 42 (2): 161-165. Available in: https://doi.org/10.1161/01.HYP.0000079505.25750.11
14. Hansen KJ, Edwards MS, Craven TE, Cherr GS, Jackson SA, Appel RG et al. Prevalence of renovascular disease in the elderly: a population-based study. J Vasc Surg. 2002; 36: 443-451. Available in: https://doi.org/10.1067/mva.2002.127351
15. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol. 2008; 52 (8): 686-717. Available in: https://doi.org/10.1016/j.jacc.2008.05.002
16. Streeten DH, Anderson GH, Howland T, Chiang R, Smulyan H. Effects of thyroid function on blood pressure. Recognition of hypothyroid hypertension. Hypertens Dallas Tex. 1988; 11: 78-83. Available in: https://doi.org/10.1161/01.hyp.11.1.78
17. Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K et al. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. Can J Cardiol. 2016; 32: 569-588. Available in: https://doi.org/10.1016/j.cjca.2016.02.066
18. SPRINT Research Group, Wright JT, Williamson JD, Whelton PK, Snyder JK, Sink KM et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015; 373: 2103-2116. Available in: https://doi.org/10.1056/NEJMoa1511939

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The author received no specific funding for this work.

Conflict of interest/financial disclosure: The author declare that they have no conflict of interests.

Correspondence:
Luis Alcocer Díaz-Barreiro, MD
E-mail: alcocerdb@gmail.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105192

Systemic high blood pressure associated with psychosocial factors in Mexico: a multidimensional approach

Hipertensión arterial sistémica asociada a factores psicosociales en México: un enfoque multidimensional

Enrique B Gómez-Álvarez, MD,* Andrea A Núñez-Ruiz‡

Keywords:
High blood pressure, psychosocial factors, blood pressure control.

Palabras clave:
Hipertensión arterial, factores psicosociales, control de la presión arterial.

ABSTRACT

High blood pressure (HBP) continues to be one of the most prevalent diseases worldwide. Psychosocial work factors have proven to be a modifiable risk factor related to cardiovascular disease. Here, we discuss how psychosocial factors are related to a negative impact on HBP. Diverse authors consider that excessive workload, low decision-making capacity, and low social support contribute to adverse working elements. These factors have been highlighted due to the COVID-19 pandemic, in which there has been an increased job strain and reduced work/life balance, which were particularly accentuated for women that are home providers and caregivers. The implementation of protective measurements at the institutional and individual levels should be implemented to reduce the negative impact of HBP and, consequently, reduce the burden of cardiovascular risk in all workers.

RESUMEN

La hipertensión arterial (HTA) sigue siendo una de las enfermedades más prevalentes en todo el mundo. Los factores psicosociales del trabajo han demostrado ser un factor de riesgo modificable relacionado con las enfermedades cardiovasculares. Aquí se analiza cómo los factores psicosociales están relacionados con un impacto negativo en la HTA. Diversos autores consideran que la excesiva carga de trabajo, la baja capacidad de decisión y el escaso apoyo social contribuyen a los elementos laborales adversos. Estos factores se han puesto de manifiesto debido a la pandemia de COVID-19, en la que se ha producido un aumento de la tensión laboral y una reducción del equilibrio entre el trabajo y la vida privada, que se acentuaron especialmente en el caso de las mujeres que son proveedoras y cuidadoras del hogar. Es necesario implementar medidas de protección a nivel institucional e individual para reducir el impacto negativo de la HTA y, en consecuencia, reducir la carga de riesgo cardiovascular en todos los trabajadores.

INTRODUCTION

High blood pressure (HBP) continues to be a major cause of premature deaths worldwide. Globally, it has been estimated that approximately 1,400 million people between 30-79 years old lives with HBP. From this population, it has been estimated that 14% is under blood pressure goals. Regardless the decreasing trend of prevalence from the last two decades in high-income countries, it has been reported that up to 2/3 of all adults living with HBP currently belongs to low-and-middle income countries.[1] This alarming estimation suggest that HBP is a chronic degenerative disease related to low-income and poverty.[2] Concerning Mexico, recent epidemiological reports have estimated that the prevalence of HBP is high, particularly in borderline states. Results from the 2019 National Health and Nutrition Surveys, revealed that Sonora (24.6%) and Campeche (26.1%) are the most affected

* Jefe del Servicio de Cardiología CMN 20 de Noviembre, ISSSTE, CDMX, Miembro GREHTA.
‡ Adscrito Cardiología CMN 20 de Noviembre ISSSTE, CDMX, Miembro GREHTA.

How to cite: Gómez-Álvarez EB, Núñez-Ruiz AA. Systemic high blood pressure associated with psychosocial factors in Mexico: a multidimensional approach. Cardiovasc Metab Sci. 2022; 33 (s3): s250-s253. https://dx.doi.org/10.35366/105192

states, followed by Chihuahua, Coahuila and Veracruz.[3] All this evidence suggest that psychosocial factors are of high relevance when studying the epidemiology of HBP, particularly those focused on socioeconomical and working conditions. In this work, we discuss the psychosocial factors are negative to related HBP.

OVERVIEW OF PSYCHOSOCIAL FACTORS MODELS

Psychosocial factors are defined as certain conditions related to working status that could impair the performance and health of individuals. In 2018, it was approved the Mexican Official Norm Number 35 (*NOM -035-STPS-2018*) which is related to psychosocial risk factors related to working status.[4] Furthermore, the same document state preventive and control regulations that should be implemented within each Mexican working center. The main framework of psychosocial factors is based on the works published by Karasek in 1979. He based his model on a demand/control aspect based on psychological demands and the power of decisions driven by to improve community. He also mentioned that increased working demands without necessarily accessing to better economic opportunities drive to person towards an increased risk of health impairments. In 1988, Johnson and Hall include that social support network is a fundamental contributor towards psychosocial factors related to health, making it a tridimensional model *(Figure 1)*.[5]

EVIDENCE RELATED TO HIGH BLOOD PRESSURE

According to recent epidemiological evidence, it has been posed that psychosocial factors could be considered as modifiable cardiovascular risk factors. Evidence from a metanalysis performed in 2013 by Babu GR et al, shown within case-control and cohort studies a relationship between increased working periods and a significant risk to develop HBP. Nevertheless, the same authors recognize diverse limitations that should warn the interpretation of their results.[6] Another recent study performed by Faruque et al described a positive relationship of excessive working hours with increased systolic and diastolic blood pressure levels, along with an increased incidence of HBP.[7] These evidence suggest that psychosocial factors could be a significant barrier to achieve a reduction of cardiovascular diseases within adult population.[8]

In Mexico, it has been mentioned that our country has a significant overburden

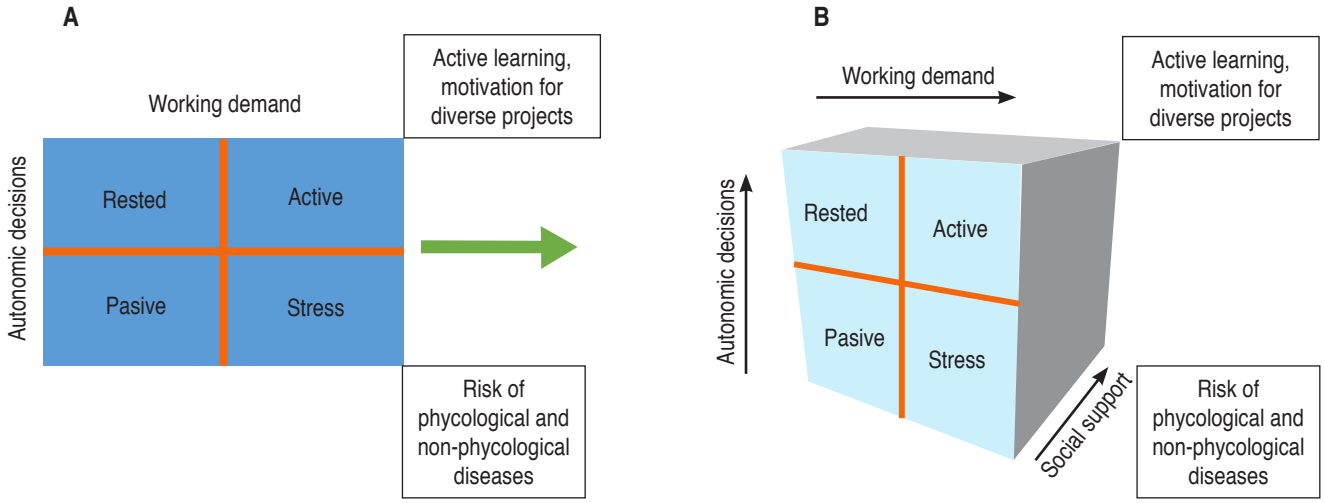


Figure 1: Relationship between psychological demands, control, and social support. Adapted from: Chiang Vega et al.[15]

attributable to excessive working hours. Recent reports shown that approximately 80% of the productive economic sector in Mexico works more than 40 hours per week without having sufficient economical remuneration. According to the Organization for Economic Co-operation and Development (OECD), Mexico has been classified as the country with the highest annual working hours (2,124 hrs. per year) but still stands as one of the country with the lowest economical remuneration.[9]

PSYCHOSOCIAL FACTORS, WORK AND SEX DIFFERENCES

Since 1950, subjects with personality trail type A (competitive, highly motivated, ambitious, and aggressive) have increased risk of incident cardiovascular disease. Nevertheless, evidence from the last decade revealed that subjects with personality trail type D (negative affective, inhibition, social reclusion, and introverts) had higher risk for overall cardiovascular complications. This evidence suggests that negative emotional factors and certain personality trails have become of increased relevance within cardiovascular research.[10]

Conversely, it has been mentioned that housework was a cardiovascular protective factor. In the past, it was assumed that women who were positioned at workplaces would have an increased cardiovascular risk factors like observed in men. Nowadays, we known that women who have both home and workplace responsibilities are psychosocial related factors that could promote increased health impairment compared to male counterparts.[11]

PSYCHOSOCIAL FACTORS RELATED TO COVID-19 PANDEMIC

Migration from rural to urban population, as well as structural poverty and less access to health services, are well-documented sociodemographic determinants for the management of HBP. It has been recorded that subjects with economic deficiencies have 70% less antihypertensive treatment for blood pressure compared with people with access to medical services.[12] These structural deficiencies have been accentuated within the COVID-19 pandemic.

The COVID-19 pandemic has been a tagged as a global crisis for healthcare systems, but also represents a loss in economic and health stability for many countries. Furthermore, COVID-19 brought changes in labor dynamics by promoting work-at-home *(home-office)*. Nevertheless, one of the biggest challenges has been establishing an appropriate work/life balance while maintaining an adequate productivity. In a study performed by Tejero et al revealed that the most important psychosocial factors related to home-office were: Poor psychological separation from work, decreased transportation to, employers not respecting schedules and holding meetings outside working hours. A second and negative domain was described and was related to the lack of interaction between co-workers as it has been mentioned that relationships within an office is beneficial social support. Overall, the author concluded that *home-office* produced: lower productivity, longer working hours, higher stress, sleep disturbances and less social interaction.[13]

ACTIONS TO REDUCE THE IMPACT OF PSYCHOSOCIAL FACTORS AT WORK AND IMPROVE QUALITY OF LIFE

The actions to improve working conditions and have demonstrated to have the greatest impact are those implemented at an institutional level (organizational level, middle and senior management) compared to those implemented at individual levels.[14] The Mexican Official Norm Number 35 mentions that within each institutional, the following strategies should be implemented: prevention of psychosocial risk factors, prevention of workplace violence and promotion of a favorable organizational environment. At an individual level, the factors that have the greatest impact are related to a positive leadership, sense of belonging to the company, psychological detachment from work, stable working hours and rewards within the work.[4]

CONCLUSION

Mexico is the country with the longest working hours and the lowest monetary compensation.

A job with flexibility, decision-making capacity of the employees, as well as rewards for a better activity performed are key tools not only for better productivity and work performance, but also reduce psychosocial risk factors for HBP and cardiovascular complications. It is important to implement these policies within middle and upper institutional management, which will improve health and quality of life of all workers. Sociodemographic inequalities and gender gaps are highly established in our country. It is important to implement specific measures to reduce double workload in women who are mothers to further reduce their cardiovascular risk.

REFERENCES

1. Guideline for the pharmacological treatment of hypertension in adults. Geneva: World Health Organization; 2021.
2. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nat Rev Cardiol. 2021; 18: 785-802. Available in: https://doi.org/10.1038/s41569-021-00559-8
3. Encuesta nacional de salud y nutrición 2018-19. Resultados nacionales. Inst Nac Salud Pública n.d. [Accessed March 15, 2022] Disponible en: https://www.insp.mx/produccion-editorial/novedades-editoriales/ensanut-2018-nacionales
4. Secretaria de Gobernación. NORMA Oficial Mexicana NOM-035-STPS-2018, Factores de riesgo psicosocial en el trabajo-Identificación, análisis y prevención. n.d.
5. Cruz-Serrano NI, Briones-Aranda A, Sarmiento V del RB, Meza MDT-, León-González JM. Los factores de riesgo cardiovascular en población indígena y mestiza en Chiapas. RESPYN Rev Salud Pública Nutr. 2021; 20: 31-46 Disponible en: https://doi.org/10.29105/respyn20.4-4.
6. Babu GR, Jotheeswaran AT, Mahapatra T, Mahapatra S, Kumar A, Detels R et al. Is hypertension associated with job strain? A meta-analysis of observational studies. Occup Environ Med. 2014; 71: 220-227. Available in: https://doi.org/10.1136/oemed-2013-101396
7. Faruque MO, Framke E, Sørensen JK, Madsen IEH, Rugulies R, Vonk JM et al. Psychosocial work factors and blood pressure among 63 800 employees from The Netherlands in the Lifelines Cohort Study. J Epidemiol Community Health. 2022; 76: 60-66. Available in: https://doi.org/10.1136/jech-2021-216678.
8. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, et al. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. JAMA. 2002; 288: 1882-1888. Available in: https://doi.org/10.1001/jama.288.15.1882
9. OECD. Country statistical profile: Mexico 2021/2. Paris: Organisation for Economic Co-operation and Development; 2021.
10. Sahoo S, Padhy SK, Padhee B, Singla N, Sarkar S. Role of personality in cardiovascular diseases: an issue that needs to be focused too! Indian Heart J. 2018; 70 Suppl 3: S471-477. Available in: https://doi.org/10.1016/j.ihj.2018.11.003.
11. Ruiz-López P, Pullas-Tapia P, Parra-Parra C-A, Zamora-Sánchez R. La doble presencia en las trabajadoras femeninas: equilibrio entre el trabajo y la vida familiar. Rev Comun SEECI. 2018: 33-51.
12. Campos-Nonato I, Hernández-Barrera L, Flores-Coria A, Gómez-Álvarez E, Barquera S. [Prevalence, diagnosis and control of hypertension in Mexican adults with vulnerable condition. Results of the Ensanut 100k]. Salud Publica Mex. 2019; 61: 888-897. Available in: https://doi.org/10.21149/10574
13. Tejero LMS, Seva RR, Fadrilan-Camacho VFF. Factors associated with work-life balance and productivity before and during work from home. J Occup Environ Med. 2021; 63: 1065-1072. Available in: https://doi.org/10.1097/JOM.0000000000002377
14. Hulls PM, Richmond RC, Martin RM, Chavez-Ugalde Y, de Vocht F. Workplace interventions that aim to improve employee health and well-being in male-dominated industries: a systematic review. Occup Environ Med. 2022; 79: 77-87. Available in: https://doi.org/10.1136/oemed-2020-107314
15. Chiang VM, Gómez FN, Sigoña IM. Factores Psicosociales, *stress* y su relación con el desempeño: comparación entre centros de salud. Salud trab. 2013; 21: 111-128.

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: The authors declare that they have no conflict of interests.

Correspondence:
Enrique B Gómez-Álvarez, MD
E-mail: egomezal@icloud.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105193

High blood pressure and telemedicine: past, present and future

Hipertensión arterial y telemedicina: pasado, presente y futuro

Humberto Álvarez-López, MD*

Keywords:
Telemedicine, arteria hypertension, ethical aspects.

Palabras clave:
Telemedicina, hipertensión arterial, aspectos éticos.

ABSTRACT

In a contemporary world accelerated by the COVID-19 pandemic, telemedicine has become an excellent option to offer remote consultations to control chronic degenerative diseases of high prevalence, such as hypertension, diabetes, and dyslipidemias. This review discusses precedents, ethical and legal aspects, and their current implementations towards managing high blood pressure (HBP). Although there are several reasons and clear benefits for implementing telemedicine, there are legal, ethical, and practical limitations and poor knowledge of its application within healthcare professionals. Appropriate ethical practice and an adequate legal framework within telemedicine will bypass all considerable risks related to quality, safety, and continuity of care associated with this practice. Regarding practical aspects, physician's clinical judgment is fundamental to know if it is possible to give medical consultation through telemedicine according to every patient's health requirement. Through diverse electronic and technological tools, the physicians could guarantee an appropriate medical consultation and handle follow-up visits. In general medicine, it could be possible that telemedicine would help to reduce the burden of care for patients with chronic diseases, decrease bureaucratic procedures, and support physicians practicing in isolated areas.

RESUMEN

En un mundo contemporáneo acelerado por la pandemia del COVID-19, la telemedicina se ha convertido en una excelente opción para ofrecer consultas a distancia para controlar enfermedades crónico-degenerativas de alta prevalencia, como la hipertensión, la diabetes y las dislipidemias. En esta revisión se analizan los precedentes, los aspectos éticos y legales, y sus implementaciones actuales para el control de la hipertensión arterial (HTA). Aunque existen varias razones y claros beneficios para la implementación de la telemedicina, existen limitaciones legales, éticas y prácticas, así como un escaso conocimiento de su aplicación por parte de los profesionales sanitarios. Una práctica ética apropiada y un marco legal adecuado dentro de la telemedicina evitarán todos los riesgos considerables relacionados con la calidad, la seguridad y la continuidad de la atención asociada a esta práctica. En cuanto a los aspectos prácticos, el juicio clínico del médico es fundamental para saber si es posible dar una consulta médica a través de la telemedicina de acuerdo con los requisitos de salud de cada paciente. A través de diversas herramientas electrónicas y tecnológicas, los médicos podrían garantizar una consulta médica adecuada y gestionar las visitas de seguimiento. En el ámbito de la medicina general, es posible que la telemedicina ayude a reducir la carga asistencial de los pacientes con enfermedades crónicas, a disminuir los trámites burocráticos y a apoyar a los médicos que ejercen en zonas aisladas.

INTRODUCTION

The World Health Organization (WHO) defines *telemedicine* as «the delivery of health care services, where distance is a critical factor, by all health-care professionals using information and communication technologies for the exchange of valid information for the diagnosis, treatment, and prevention of disease and injuries, research and evaluation, and for the continuing education of health-care providers, all in the interests of advancing the health of individuals and their communities».[1] In a contemporary world accelerated by the COVID-19 pandemic, telemedicine has become an excellent option to offer remote

* Member of the Group of Experts in Arterial Hypertension (GREHTA) Mexico, Member of the National Association of Cardiologists of Mexico (ANCAM), Member of the Mexican Society of Cardiology, Delegate in Jalisco of the Medical Association of the Hospital de Cardiología A.C., Former President of the College of Cardiologists of Jalisco, Hospital de Especialidades Puerta de Hierro Andares, Zapopan, Jalisco, Mexico.

How to cite: Álvarez-López H. High blood pressure and telemedicine: past, present and future. Cardiovasc Metab Sci. 2022; 33 (s3): s254-s258. https://dx.doi.org/10.35366/105193

consultations to control chronic degenerative diseases of high prevalence, such high blood pressure (HBP), diabetes, and dyslipidemias. Furthermore, telemedicine has been postured as a novel strategy to increase the percentages of adequate treatment and pharmacological management to reduce cardiovascular morbidity and mortality. This review discusses precedents, ethical and legal aspects, and their current implementations towards managing HBP.

Telemedicine background

According to the definition of telemedicine, remote medical care has been implemented for centuries for giving medical consultations using diverse technological tools. In 1879, the first recorded history of a remote consultation was given between a physician and a patient by telephone. In 1915, besides telephone, it was also possible to give medical consultation and clinical advice on ships across seas by radio frequencies. In recent decades, with the widespread use of the internet, there has been an increasing trend of access for telemedicine worldwide. Nevertheless, its massive implementation was accelerated in 2020 during the COVID-19 pandemic. This worldwide crisis accentuated the need for accessible healthcare access for everyone regardless of social distance restrictions or socioeconomic circumstances.[2] Although there are several reasons and clear benefits for implementing telemedicine, there are legal, ethical, and practical limitations and poor knowledge of its application within healthcare professionals. These conditions have been described as restrictions to systematically apply telemedicine as a strategy for all care levels summarizes the current advantages and disadvantages of using telemedicine *(Table 1)*.

Telemedicine: ethical and legal aspects

Telemedicine has considerable possibilities that could benefit uncountable adults living with chronic degenerative diseases, such as patients living with HBP. Nevertheless, its implementation also poses diverse ethical and legal challenges related to a medical-patient relationship. Appropriate ethical practice and an adequate legal framework within telemedicine will bypass all considerable risks related to quality, safety, and continuity of care associated with this practice.

It has been mentioned that the ethical aspects related to telemedicine should be identical to conventional medicine. The main objective of both practices is to prevent potential injuries that could happen to both patients and physicians. The medical-patient relationship is based on trust and mutual respect

Table 1: Remote Monitoring and Telemedicine

Advantages	Disadvantages
1. Save time 2. Save money 3. Increased control of degenerative chronic diseases (T2DM, HTN) 4. Greater coverage and accessibility 5. No transfer required 6. Lower risk of accidents, contagion, etc., 7. Increased coverage at remote sites 8. Especially useful in the elderly with limited mobility and patients with transfer problems 9. Reduction of absenteeism 10. Patient can upload data to the platform and doctor can make therapeutic modifications remotely achieving higher percentages of control in HTA, DM2, etc	1. Lack of acceptance from doctors and patients 2. Cannot be applied to all diseases 3. Requires technological equipment and internet access 4. Not all patients could be able to handle electronic devices. 5. Limited physical examination

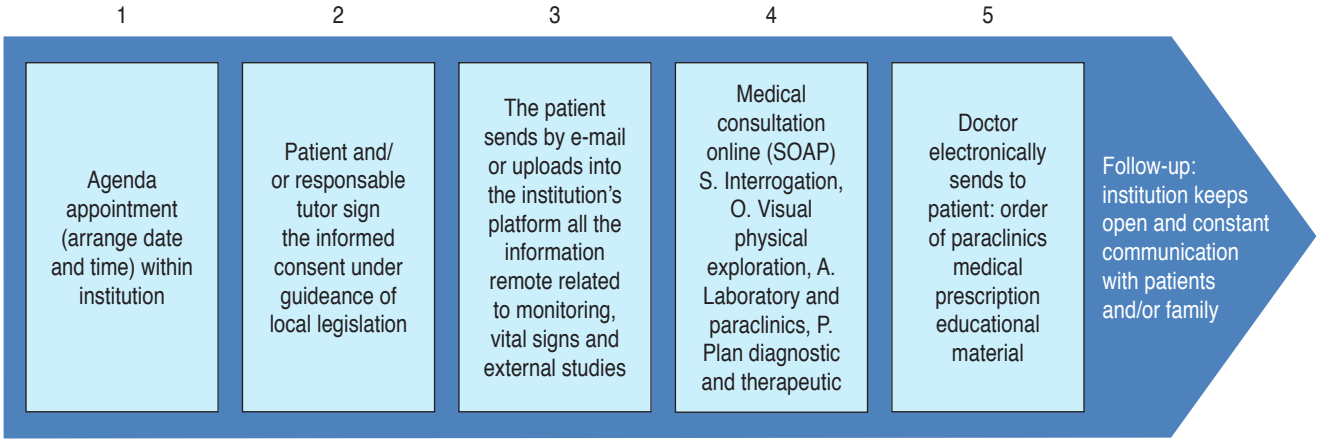


Figure 1: Suggested process of telemedicine for the control of high blood pressure in public medicine.

for both cases. Furthermore, it is necessary to guarantee privacy and confidentiality of all the clinical information using adequate data protection systems. This practice seeks to comply with the current regulatory and legal aspects from international, national, and regional institutions. We can rely on the guidelines set out in the Declaration of the World Medical Association (WMA) on the Ethics of Telemedicine. This declaration was adopted in the 58th General Assembly of the WMA in Copenhagen, Denmark, in October 2007 and subsequently amended in the 69th General Assembly of the WMA in Reykjavik, Iceland, in October 2018. Nevertheless, there are currently no international laws regulating telemedicine for most countries, including Mexico. During the COVID-19 pandemic, telemedicine's legal implications accelerated without a current positioning by any authority. However, it has been recognized that privacy and security standards practices are needed to guarantee appropriate security protocols. Like the American HIPAA *protocol (Health Insurance Portability and Accountability Act).*[2,3]

Telemedicine in high blood pressure

In this review, we will not analyze all the studies that have been published related to telemedicine implemented in the management of HBP.[4-7] Sufficiently is to mention that there have been multiple publications that show the potential benefits of telemedicine over the usual clinical consultations for several years. The use of telemedicine for the management of HBP provides more significant reductions in systolic and diastolic blood pressure and twice the number of patients that will reach blood pressure goals compared with traditional clinical visits. Recently the American Heart Association (AHA) has published a positioning related to telemedicine for controlling HBP.[8]

Telemedicine: practical aspects

The physician's clinical judgment is fundamental to know if it is possible to give medical consultation through telemedicine according to every patient's health requirement. The administrative staff who assist each physician must ensure that all patients and relatives have: a stable internet connection, electronic devices with connectivity (cell phones, computers, electronic tablets) and that they can handle them properly.

Physicians will need to use different platforms to conduct the video consultation that complies with HIPAA regulations to guarantee privacy. Some platforms could be the following: a) Zoom (healthcare version), b) Google G Suite, c) Microsoft Teams, d) Skype, e) WhatsApp. The last one itself does not amend to HIPAA compliant; however,

it is very accessible and has call and text functions. Its enterprise version is relatively more secure, but it still does not comply with all HIPAA regulations and, therefore, can only be used for healthcare practices that do not use sensitive patient data.

Although telemedicine can be applied for all patients living with HBP for the first consultation, it will depend on each patient for the subsequent or «already known» in person by the doctor. For these cases, the physical examination has already been performed and is only intended for follow-up care to evaluate adequate management of HBP and other cardiovascular risk factors.

The physician must provide each consultation within a suitable, private, and quiet place, with the appropriate lighting to show his face and generate trust in every patient. The camera should be pointed at eye level and a one-arm distance from the camera. It is also encouraged that a pre-established executive or assistant order a follow-up visit to achieve quality in medical care, which is very similar to when a face-to-face visit is granted. As shown in *(Figures 1 and 2)*, the consultation must be scheduled appropriately to connect the patient and a family member. At the time of the scheduled appointment, the patients and their relatives must sign an electronic informed consent understanding the advantages and limitations of telemedicine are specified. Likewise, the patient or close relative must send electronically to the physician the vital signs measurements that were taken at home (blood pressure, heart rate, temperature, oxygen saturation, weight, glucometer, etc.). The physician may access the clinical record platform with integrated remote monitoring, laboratory tests, X-rays, or cabinet studies that the patient has, whether appropriate. The physician must also send the electronic link with the date and time for the connection.

For preventing the patient does not comply with the scheduled appointment, «no-show» policies must be established. This means that the consultation must be paid for at least one hour before the scheduled appointment (electronic transferring or payment within convenience stores such as OXXO, PayPal, Mercado Pago, Stripe, and other platforms that have already been integrated within several electronic clinical records). It is advisable to send a personal reminder of the appointment with a text message 5 minutes before the consultation to avoid making the video call when family members or patients are not yet ready to receive it. At the time of the telemedicine consultation, the doctor must document all the information in the

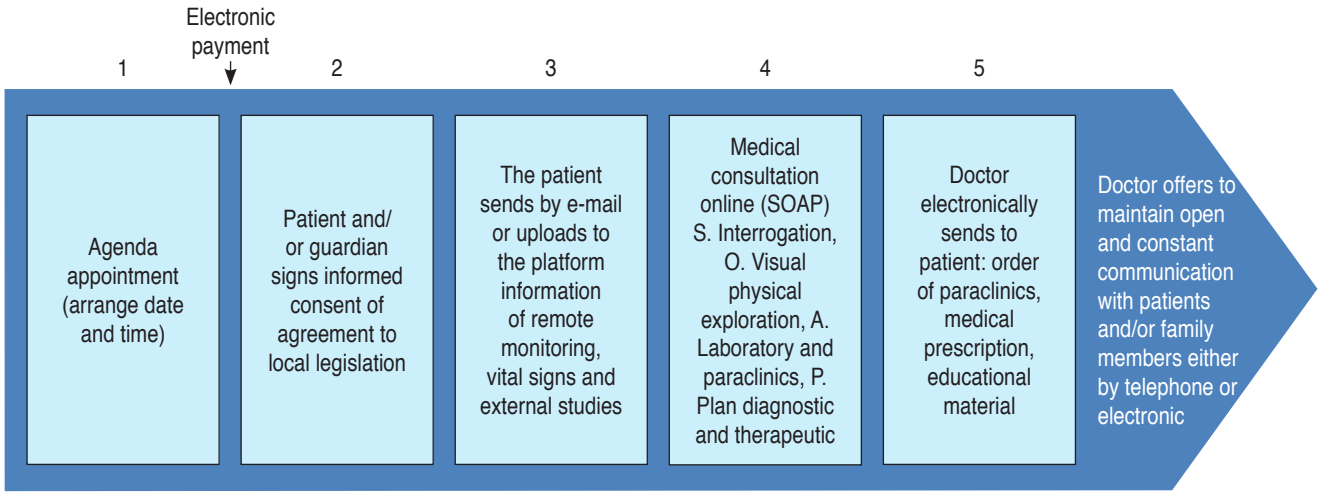


Figure 2: Suggested telemedicine process for high blood pressure control in private medicine.

electronic clinical record, including symptoms and signs, visual, physical examination perceived through the devices, paraclinical tests, and provide a digital prescription and lifestyle recommendations. At the end of the consultation, the doctor will make closing and will schedule a follow-up appointment either in person or by telemedicine, also will send the electronic prescription and laboratory tests to be carried out. He may also send written educational material, infographics, videos, or any information that can be considered helpful in educating the patient's disease. Finally, let the patient know that doctor-patient communication will always be open through different electronic channels to solve doubts, treatment adjustments, medical emergencies, or any communication. It is important to mention that this can be concluded by a telephone call in case of technical problems with the video call.

CONCLUSION

In the field of hypertension, telemedicine is an opportunity to achieve higher blood pressure control rates. Through remote monitoring, any physician could access home blood-pressure parameters and will be able to assemble various therapeutic changes that each patient requires. In general medicine, it will be possible to reduce the burden of care for patients with chronic diseases, reduce bureaucratic procedures, and support physicians practicing in an isolated area. Telemedicine is an excellent alternative to traditional medical practice but in no way replaces it. This practice is expected to grow significantly in the future.

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: The authors declare that they have no conflict of interests.

REFERENCES

1. Ryu S. Telemedicine: Opportunities and Developments in Member States: Report on the Second Global Survey on eHealth 2009 (Global Observatory for eHealth Series, Volume 2). Healthc Inform Res. 2012; 18: 153-5. Available in: https://doi.org/10.4258/hir.2012.18.2.153.
2. Pfizer. Guía de telemedicina 2021.
3. World Medical Association. WMA - The World Medical Association-Declaración de la AMM sobre las Responsabilidades y Normas Eticas en la Utilizacion de la Telemedicina 2017. [Accessed March 26, 2022] Available in: https://www.wma.net/es/policies-post/declaracion-de-la-amm-sobre-las-responsabilidades-y-normas-eticas-en-la-utilizacion-de-la-telemedicina/
4. Pellegrini D, Torlasco C, Ochoa JE, Parati G. Contribution of telemedicine and information technology to hypertension control. Hypertens Res Off J Jpn Soc Hypertens. 2020; 43: 621-628. Available in: https://doi.org/10.1038/s41440-020-0422-4
5. Wang J-G, Li Y, Chia Y-C, Cheng H-M, Minh HV, Siddique S, et al. Telemedicine in the management of hypertension: Evolving technological platforms for blood pressure telemonitoring. J Clin Hypertens Greenwich Conn. 2021; 23: 435-439. Available in: https://doi.org/10.1111/jch.14194
6. Li R, Liang N, Bu F, Hesketh T. The effectiveness of self-management of hypertension in adults using mobile health: systematic review and meta-analysis. JMIR MHealth UHealth. 2020; 8: e17776. Available in: https://doi.org/10.2196/17776
7. McManus RJ, Mant J, Franssen M, Nickless A, Schwartz C, Hodgkinson J, et al. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial. Lancet Lond Engl. 2018; 391: 949-959. Available in: https://doi.org/10.1016/S0140-6736(18)30309-X
8. Omboni S, McManus RJ, Bosworth HB, Chappell LC, Green BB, Kario K, et al. Evidence and recommendations on the use of telemedicine for the management of arterial hypertension: an international expert position paper. Hypertens Dallas Tex 1979. 2020; 76: 1368-1383. Available in: https://doi.org/10.1161/HYPERTENSIONAHA.120.15873

Correspondence:
Humberto Álvarez-López, MD
E-mail: beto66_mx@yahoo.com

Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 33 Suppl. 3
July-September 2022

doi: 10.35366/105194

The mexican health-care system and high blood pressure

El sistema de salud mexicano y la hipertensión arterial

Gabriela Borrayo-Sánchez, MD*

Keywords:
High blood pressure, intervention, healthcare systems.

Palabras clave:
Hipertensión arterial, intervención, sistemas sanitarios.

ABSTRACT

High blood pressure (HBP) is the most prevalent risk factor in the Mexican population. The Mexican Social Security Institute (IMSS) has more than 69 million recorded affiliated populations. HBP is the second most important disease that financially impacts the IMSS. It has been estimated that the cost to treat HBP is 52,284 million Mexican pesos, which is only exceeded by diabetes and cancer. HBP represents a financial burden and reinforces the need to focus on promoting healthy lifestyles, prevention, timely detection, and treatment adherence. Some studies have shown costly-effective interventions, especially when standardization of treatment protocols, risk-based treatments, and task sharing with healthcare providers. The Comprehensive Care Protocol is one of the first strategies for health services in Mexico that includes evidence-based, multidisciplinary activities within all care settings, particularly the primary one for the treatment of HBP, which is discussed in length in this paper.

RESUMEN

La hipertensión arterial (HTA) es el factor de riesgo más prevalente en la población mexicana. El Instituto Mexicano del Seguro Social (IMSS) tiene más de 69 millones de afiliados registrados. La HTA es la segunda enfermedad que más impacta financieramente al IMSS. Se ha estimado que el costo para tratar la HTA es de 52,284 millones de pesos mexicanos, sólo superado por la diabetes y el cáncer. La HTA representa una carga financiera y refuerza la necesidad de enfocarse en la promoción de estilos de vida saludables, la prevención, la detección oportuna y la adherencia al tratamiento. Algunos estudios han mostrado intervenciones costo-efectivas, especialmente cuando se estandarizan los protocolos de tratamiento, los tratamientos basados en el riesgo y el reparto de tareas con los proveedores de salud. El Protocolo de Atención Integral es una de las primeras estrategias para los servicios de salud en México que incluye actividades multidisciplinarias basadas en la evidencia dentro de todos los ámbitos de atención, particularmente el primario para el tratamiento de la HTA, que se discute ampliamente en este documento.

INTRODUCTION

High blood pressure (HBP) is the most prevalent risk factor in the Mexican population. Approximately 1/3 of the Mexican population older than 20 years of age have this condition. Furthermore, its frequency is greater than 50% when a subject had an acute coronary syndrome. Cardiovascular diseases (CVD) have been the leading cause of death for 20 years. In 2020, according to information from the National Institute of Statistics and Geography (INEGI), there was estimated excess mortality of 43%, where more than 218,000 deaths were attributable to cardiovascular causes. This impressive burden represents 62 thousand more than in 2019, exceeding the deaths observed for COVID-19.[1]

It has been estimated that more than 1.04 billion people live with the disease. The highest prevalence of HBP is reported in low-to-middle-income countries.[2] In Latin America, the prevalence of HBP is 44% (ranging between 17.7 to 52.5%), of which only 53.3%

* Former President of National Association of Cardiologists of Mexico (ANCAM), Member of GREHTA.

How to cite: Borrayo-Sánchez G. The mexican health-care system and high blood pressure. Cardiovasc Metab Sci. 2022; 33 (s3): s259-s265. https://dx.doi.org/10.35366/105194

receive treatment and 37.6% had blood pressure goals (< 140/90 mmHg). Moreover, better arterial pressure control has been reported within urban populations compared to rural communities (39.6 vs 32.4%). Of all the patients living with the disease, only 36.4% use two or more antihypertensive drugs.[3]

The Mexican Social Security Institute (IMSS) has more than 69 million recorded affiliated populations. This represents 54% of the national population estimated by the National Council of Population for 2021, as the number of adults requiring health services has consistently increased *(Figure 1)*. The IMSS has reported a population older than 20 years of 37,515,011, of which 7,749,578 have a previous medical diagnosis of HBP, which represents an estimated prevalence of 20.7%. 59.3% are women in this group, and 40.7% are men *(Table 1)*.

HBP is the second most important disease that financially impacts the IMSS. It has been estimated that the cost to treat HBP is 52,284 million Mexican pesos, which is only exceeded by diabetes mellitus (96,823 million pesos) and cancer (19,951 million pesos). Therefore, it represents a financial burden and reinforces the need to focus on promoting healthy lifestyles, prevention, timely detection, and treatment adherence. Some studies have shown costly-effective interventions, especially when standardization of treatment protocols, risk-based treatments, and task sharing with healthcare providers.[4,5]

Comprehensive Care Protocol for systemic high blood pressure

The IMSS standardizes and systematizes care for all its patients living with HBP with the Comprehensive Care Protocol (PAI; abbreviation in Spanish). This protocol includes multidisciplinary activities that are integrated into all care levels. Particularly at primary care levels, it focuses on strengthening all healthcare workers' preventive strategies. Furthermore, there is the active participation of medical personnel, nursing, nutrition, social work, psychology, dentistry, and medical assistants, who specifically carry out promotion actions and identify risk factors for hypertensive-related complications in all people aged 20.

The Comprehensive Care Protocol for HBP highlights evidence-based activities related to adequate blood pressure measurement at clinical visits and home and ambulatory blood pressure monitors (ABPM). This strategy also seeks to replace dual or triple combination therapies using a single pill approach and promote non-pharmacological strategies.

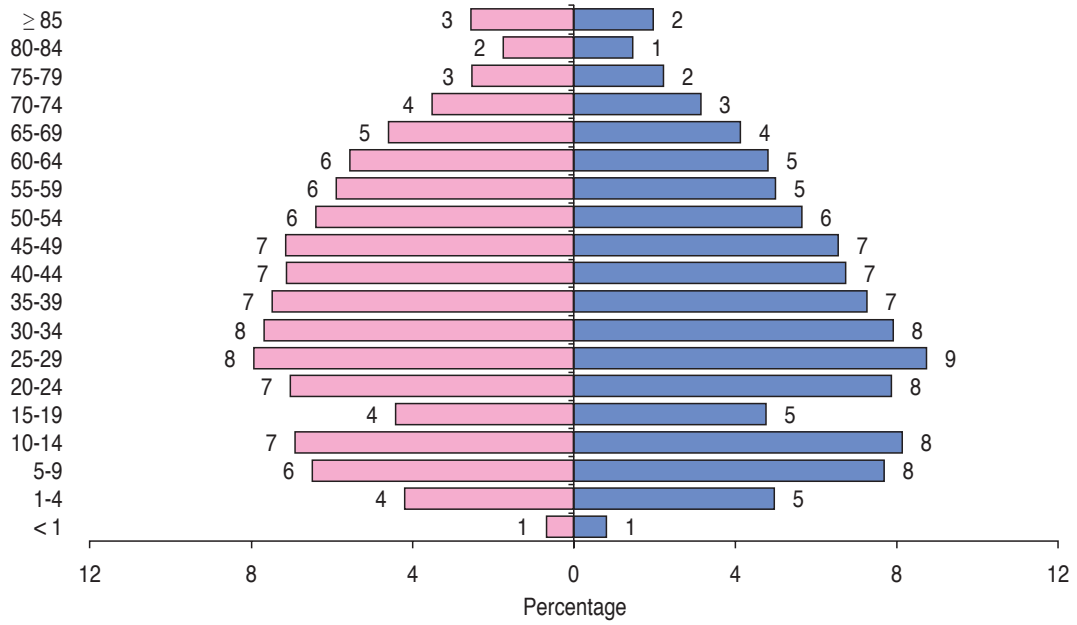


Figure 1: Population pyramid (CONAPO) showing an increase in the adult population.

Table 1: Census of IMSS beneficiaries aged 20 years and over living with high blood pressure.

Arterial hypertension	Women ≥ 20	Men ≥ 20	All ≥ 20	Overall population ≥ 20	Prevalence arterial hypertension in adults ≥ 20 (%)
Guerrero	66,905	46,044	112,949	452,665	25.0
Sonora	169,696	115,440	285,136	1'164,573	24.5
Veracruz Sur	110,982	73,969	184,951	762,151	24.3
Sinaloa	169,534	114,088	283,622	1'190,676	23.8
Chihuahua	224,223	146,778	371,001	1'587,467	23.4
Nayarit	46,701	34,298	80,999	347,700	23.3
Durango	76,931	50,417	127,348	549,887	23.2
Veracruz Norte	150,598	97,117	247,715	1'082,140	22.9
Baja California	198,248	138,729	336,977	1'474,358	22.9
Yucatán	102,620	71,376	173,996	765,690	22.7
Aguascalientes	72,024	51,607	123,631	559,346	22.1
CDMX Norte	219,955	142,651	362,606	1'652,412	21.9
Morelos	69,719	48,754	118,473	545,356	21.7
Michoacán	125,091	86,835	211,926	984,364	21.5
Tamaulipas	174,359	117,885	292,244	1'364,719	21.4
Coahuila	194,700	134,770	329,470	1'556,046	21.2
Baja California Sur	34,781	27,766	62,547	301,081	20.8
National	4'595,160	3'154,418	7'749,578	37'515,011	20.7
CDMX Sur	297,475	192,210	489,685	2'376,236	20.6
Zacatecas	47,188	33,107	80,295	392,495	20.5
México Oriente	382,424	253,306	635,730	3'120,091	20.4
San Luis Potosí	99,467	70,076	169,543	833,197	20.3
Jalisco	367,832	263,449	631,281	3'165,263	19.9
Hidalgo	66,219	47,150	113,369	569,125	19.9
Campeche	26,968	20,102	47,070	236,566	19.9
Colima	31,952	24,814	56,766	289,052	19.6
Nuevo León	298,733	215,820	514,553	2'678,386	19.2
Guanajuato	191,926	133,850	325,776	1'701,254	19.1
Tabasco	43,047	31,572	74,619	415,638	18.0
Puebla	127,067	85,584	212,651	1'190,244	17.9
Chiapas	52,636	36,444	89,080	508,995	17.5
México Poniente	160,519	107,375	267,894	1'537,644	17.4
Oaxaca	40,017	29,137	69,154	435,355	15.9
Tlaxcala	26,075	18,359	44,434	279,792	15.9
Querétaro	80,207	58,194	138,401	877,723	15.8
Quintana Roo	48,341	35,345	83,686	567,324	14.8

Additionally, the model seeks to empower every patient, focusing on improving self-control, self-care, promoting lifestyle changes, and closer interaction with healthcare providers.[6] Furthermore, this method to treat HBP is also based on a matrix model in which healthcare experts from the three levels of care coordinate and participate for the benefit of patients. The level of demand of the activities was classified according to the scientific evidence

as Essential (activities derived from clinical trials, meta-analyses, systematic reviews, and international and national guidelines), Optional (activities that can be chosen among several with the same effectiveness the resource is not available) and Evitable (activities that are not useful/effective and in some cases can be harmful) *(Figure 2)*.

Graphic representation of the level of demand of the activities		
I	**O**	**E**
Indispensable	Optional	Evitable
Essential action or activity. It is mandatory observance	Action or activity that can be chosen among several with the same effectiveness	Actions or activities that are not useful/effective and in some cases can be harmful

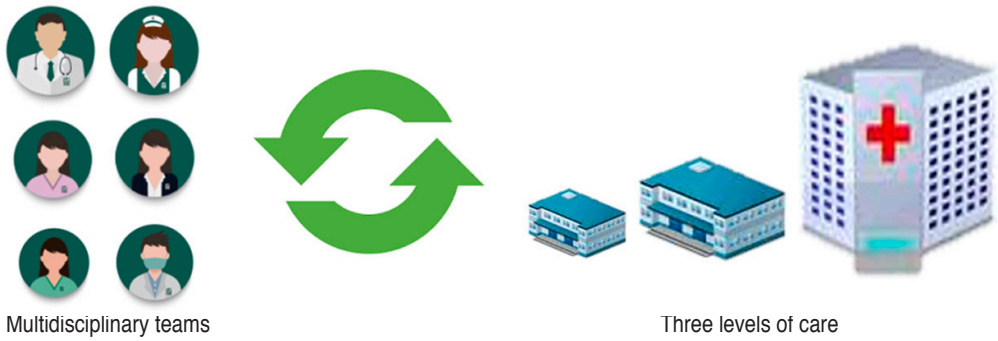
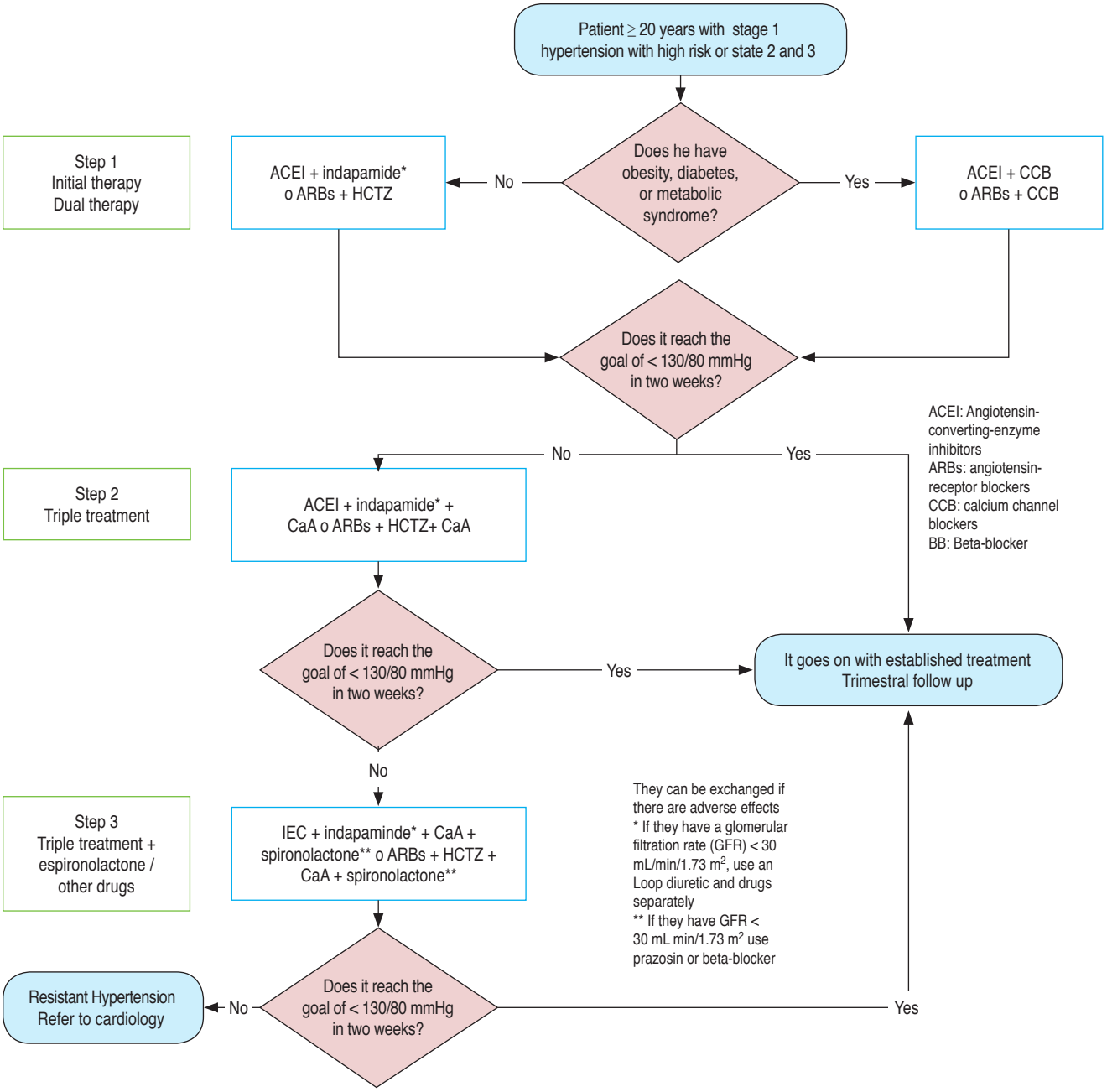


Figure 2:

The High Blood Pressure Comprehensive Care Protocol includes multidisciplinary team activities at the three levels of care.

Table 2: Risk stratification in patients with high blood pressure.

Risk factors + end-organ damage either with symptoms or without symptoms	Normal blood pressure or within limits (≥ 130/85 and < 140/90 mmHg)	Level 1 (≥ 140/90 and < 160/100 mmHg)	Level 2 (≥ 160/100 and < 180/110 mmHg)	Level 3 (≥ 180/110 mmHg)
Without risk factors	Low-risk	Low-risk	Moderate-risk	High-risk
≥ 1 or 2 risk factors	Low-risk	Moderate-risk	Moderate to high risk	High-risk
≥ 3 risk factors	Moderate-risk	Moderate to high risk	High-risk	High-risk to very-high risk
End-organ damage	Moderate to high risk	High-risk	High-risk	Very-high risk
Previous CVD or kidney impairments + T2D	Very-high risk	Very-high risk	Very-high risk	Very-high risk



Recommendations for the prescription of antihypertensives

1. Monotherapy must be tried only on patients with level HAS and low risk, or in special cases like fragile adults, patient hypersensitive to dual therapy, or pregnant women.
2. The first and second step should be tried with combined drugs in one single pill.
3. The general goal is < 130/80 mmHg but no less than 110/70 mmHg.
4. Always take into account the calculated glomerular filtration rate to appropriately indicate the corresponding diuretic.
5. In step 3, spironolactone should be added to triple therapy, if the goal of BP control is not achieved, after taking tests to assess renal function and/or risk of hyperkalemia. If there is a contraindication to spironolactone, prazosin or a beta-blocker can be considered.
6. The main cause of resistant hypertension is pseudo resistance, that is basically because of the lack of adherence in taking medication and also the lack of adherence to non-pharmacological treatment, which is crucial.

Figure 3: Step by Step Treatment algorithm for patients with high blood pressure.

Risk stratification is highly relevant within the Comprehensive Care Protocol. This approach is based on risk estimations that emphasize target organ damage, the number of risk factors, the presence of established cardiovascular and renal disease, and prevalent diabetes mellitus. The risk stratification also considers the degree of HBP to implement dual or triple antihypertensive treatments *(Table 2)*. The final objective of this approach is to implement diverse actions to promote healthy lifestyle habits, prioritize primary prevention, make a prompt diagnosis, and assure an adequate classification and stratification of cardiovascular risk.[7-9]

Finally, the Comprehensive Care Protocol for HBP attaches to the most relevant modifications proposed in the European and American HBP guidelines that prioritize dual antihypertensive therapies with Angiotensin-II Receptor Antagonists (ARA2) or Angiotensin Enzyme Inhibitors (ACEI) plus an antagonist of calcium (CaA). In particular cases, an optimal strategy would be using a triple therapy using ARA2/ACE inhibitors plus CaA plus first-line thiazide diuretic in patients without blood pressure goals (< 130/80 mmHg). It is essential to mention that monotherapy is always encouraged in mild HBP, low cardiovascular risk in older adults with faility or pregnant women *(Figure 3)*.[8,10,11]

Summary of essential activities in medicine

1. Promotes and participates in health promotion.
2. Promotes primary prevention in patients at risk of HBP.
3. Appropriately measures blood pressure in all health-care units.
4. It adequately stratifies cardiovascular risk in patients with HBP into low, medium, and high risk to establish pharmacological and non-pharmacological treatment goals according to the stratification.
5. Detects and treats comorbidities associated with cardiovascular risk.
6. Intentionally looks for target organ damage.
7. Use combined first-line therapies (Use step 1, step 2, step 3 of this protocol) in all hypertensive patients of medium/high risk and reserve monotherapy for cases of mild SAH or very sensitive patients or frail patients.
8. Promotes the use of Home Blood Pressure Monitoring and the use of the logbook.
9. Provides appropriate follow-up of the patient with HBP to guarantee the achievement of goals in the short, medium and long term.
10. Indicates Ambulatory Blood Pressure Monitoring in cases of diagnostic doubt or difficult control.
11. Detects and sends to the corresponding level the cases of major hypertensive emergencies with repercussions on the target organ.
12. Detects possible cases of secondary HBP and sends to the corresponding level with all the basic studies including ABPM or MDPA.
13. Detect cases of true resistance and send to third level, which will proceed according to the case.
14. Receive training in HBP, at least once a year
15. Various

CONCLUSIONS

The Comprehensive Care Protocol is one of the first strategies for health services in Mexico that includes evidence-based, multidisciplinary activities within all care settings, particularly the primary one. Additionally, this approach gets the benefit that all three care levels are highly coordinated to give standardize, preventive, diagnostic, and therapeutic approaches. In the latter, emphasis is placed on dual and triple therapy as the first line according to cardiovascular risk with the use of «one-single» pill approach, allocating monotherapy to low-risk patients, frail, and pregnant women. Non-pharmacological strategies are a fundamental part of the Comprehensive Care Protocol, as these should be emphasized along with the patient contribution, self-care, and empowerment to prevent hypertensive-related complications.

REFERENCES

1. Geografía (INEGI) IN de E y. Mortalidad. Regist Adm Vitales Natal Matrim 1994. [Accessed January 5, 2022] Available in: https://www.inegi.org.mx/temas/mortalidad/
2. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K et al. Global disparities of hypertension

prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation. 2016; 134: 441-450. Available in: https://doi.org/10.1161/CIRCULATIONAHA.115.018912
3. Lamelas P, Diaz R, Orlandini A, Avezum A, Oliveira G, Mattos A et al. Prevalence, awareness, treatment and control of hypertension in rural and urban communities in Latin American countries. J Hypertens. 2019; 37: 1813-1821. Available in: https://doi.org/10.1097/HJH.0000000000002108
4. Hipertensión Arterial n.d. [Accesado Marzo 31, 2022] Available in: http://www.imss.gob.mx/salud-en-linea/hipertension-arterial
5. Kostova D, Spencer G, Moran AE, Cobb LK, Husain MJ, Datta BK et al. The cost-effectiveness of hypertension management in low-income and middle-income countries: a review. BMJ Glob Health. 2020; 5: e002213. Available in: https://doi.org/10.1136/bmjgh-2019-002213
6. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. Circulation 2019; 140: e596-646. Available in: https://doi.org/10.1161/CIR.0000000000000678
7. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013; 309: 71-82. Available in: https://doi.org/10.1001/jama.2012.113905
8. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertens Dallas Tex 1979. 2018; 71: 1269-1324. Available in: https://doi.org/10.1161/HYP.0000000000000066
9. Gibbons GH, Harold JG, Jessup M, Robertson RM, Oetgen WJ. The next steps in developing clinical practice guidelines for prevention. J Am Coll Cardiol. 2013; 62: 1399-1400. Available in: https://doi.org/10.1016/j.jacc.2013.08.004.
10. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D et al. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens. 2020; 38: 982-1004. Available in: https://doi.org/10.1097/HJH.0000000000002453.
11. Mounier-Vehier C, Nasserdine P, Madika A-L. Stratification of cardiovascular risk in women: Optimize the medical care. Presse Medicale Paris Fr 1983. 2019; 48: 1249-1256. Available in: https://doi.org/10.1016/j.lpm.2019.09.049

Author contributions: Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Funding: The authors received no specific funding for this work.

Conflict of interest/financial disclosure: The authors declare that they have no conflict of interests.

Correspondence:
Gabriela Borrayo-Sánchez, MD
E-mail: gborrayos@yahoo.com.mx

The *Cardiovascular and Metabolic Science* (before *Revista Mexicana de Cardiología)* is the official entity of the National Association of Cardiologists of Mexico, the Society of Interventional Cardiology of Mexico, the National Association of Cardiologists of the Medical Center La Raza AC, the National Association of Cardiologists Serving State Workers AC, the Mexican Association for the prevention of Atherosclerosis and its complications AC, the Mexican Society of Preventive Cardiology, the Alliance for a Healthy Heart, the Mexican Society of Cardiac Pacing and Electrophysiology, Medical Association of the Hospital of Cardiology Medical Center S. XXI. The Journal is currently indexed in several databases, including Scielo, Free Medical Journals, Latindex, BVS, and Google Scholar, among other. Its scopes include original papers related to disease heart, blood vessels and related health sciences. The Journal publishes original research articles (experimental investigation) both clinical and preclinical, epidemiological papers, review topics, clinical case, corners of science, editorials (usually by invitation), letters to the editor and news of various associations. In order to be accepted, all manuscripts are initially evaluated by at least two peer reviewers and finally sanctioned by the Editorial Committee. The Journal accepts, in general terms, the stated guidelines by the International Committee of Medical Journal Editors. Manuscripts should be prepared according to the Requirements of Uniforms for Submission of Manuscripts to Biomedical Journals. The updated version is available at: www.icmje.org.

All submissions should be made on line at the Journal's site. New users must first create an account. Once logged in, submission should be made via the Author Center. If you experience any problem with your submission, please contact the editors at revmexcardiol@gmail.com

Submitted manuscripts should not be under review in any other journal. Moreover, all submissions must include full disclosure of all relationships that could be viewed as presenting a potential conflict of interest. If there are no conflicts of interest, authors should state that there are none.

Accepted papers will be owned by the Journal and may not be published (either whole or partial) elsewhere without written permission of the publisher.

Checklist

Check when each section has been duly completed in accordance with specified. Papers will not be accepted for a review if they do not include any (s) of the points previously mentioned.

General aspects

( ) Articles must be submitted electronically.
( ) Manuscripts should be written in English.
( ) The item must be written with a minimum font size 10 double space (28 x 21 cm), with margins of 2.5 cm on each side. The words in another language must be submitted Italicized. Avoid the use of «he, she, they, we» could be exchanged for nouns (doctor (s), patient (s), client (s), whenever possible, to seek gender neutrality.
( ) The text should be presented as follows: 1) page title, 2) abstracts and key words, 3) introduction, 4) materials/patients and methods; 5) results, 6) discussion, 7) conclusions, 8) acknowledgments, 9) references, 10) appendices, 11) text

boxes, 12) figure captions. Each section will begin in different sheet. The format can be altered in review articles, clinical case, corners of science, if considered necessary.

( ) All authors should have made intellectual participation in the manuscript (conception or design of the work, taking responsibility for the data acquisition and analysis, and conclusions). Authors should revise the CRediT 'Contributor Roles Taxonomy' to detail authors' contributions (https://credit.niso.org/).

( ) Send a description of the roles of each author through the Author Center Web. Considering the type of article to publish (original research articles, clinical and preclinical, multicenter studies, epidemiological papers, review topics), the number of authors depends on the type of study, topic complexity, number of participating centers and sample size.

( ) No more than five authors in corners of science.

( ) List the name, address, telephone number and e-mail of three suggested reviewers who are not members of your workgroup, so they can be considered as potential peer-evaluation candidates.

Text

Title page

( ) Includes: a) title with a maximum of 15 words, b) name(s) of the authors in the order in which will be published; if the paternal and maternal surnames are recorded, linked them with a hyphen, c) degrees of the authors, d) affiliations and institution(s) where was the work performed, e) complete address, telephone, fax and e-mail address of the corresponding author.

Abstract

( ) Both in English and Spanish; with a maximum of 250 words. Structured according to the order of information in the text: 1) Introduction, 2) objectives, 3) material and methods, 4) results and 5) conclusions.

( ) 3-5 Key words.

Text

( ) Divided into subtitles that facilitate the reading: 1) introduction, 2) objectives, 3) material and methods, 4) results, 5) discussion, 6) conclusions.

( ) The names, initials or numbers of the patients studied record should be omitted.

( ) Abbreviations are accepted, but must be preceded for what they mean the first time that they are cited, according to the international units of measurement.

( ) Medicines, drugs and chemicals should be called by its generic name, dosage and route of administration, indicating the international nomenclature.

( ) The statistical methods used should be described at the end of the material and methods section.

Acknowledgements

( ) Acknowledgements should be considerate to scientific assistance, contributors to the acquisition of funding, figures or illustrations acquisition, general supervision, writing assistance, technical editing, administrative support, language editing, or proofreading.

( ) The acknowledgments and details on supports, drug (s) and team (s) provided (s) should be cited before the references.

References

( ) Vancouver style citation is required. (https://guides.lib.monash.edu/citing-referencing/vancouver).

( ) Identified in the text with Arabic numbers and superindex in progressive order of appearance.

( ) Personal communications and unpublished data will be cited unnumbered in a footnote.

Examples of journal articles:

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

Six or more authors

San-Luis R, Munayer J, Aldana T, et al. Venous connection total anomalous pulmonary. Five years of experience. Rev Mex Cardiol 1995; 6: 109-16.

Books

Myerowitz PD. Heart transplantation. New York: Futura Publishing; 1987: 20-31.

Book chapters

Hardesty R, Griffi th B. Combined heart-lung trans plantation. In: Myerowitz PD. Heart transplantation. New York: Futura Publishing; 1987: 125-140.

Tables

( ) None.

( ) Yes.

Quantity (with letters): _____

( ) The authors declare that all tables in the manuscript are entirely original and do not require reprint permission.
( ) The information provided is not repeated in the text or in Figures. Maximum allowed is the 50 percent plus one of the text sheet.
( ) They are headed by the title and marked progressively with Arabic numbers according to their appearance in the text.
( ) The title of each table alone explains its contents and allows correlate with limited text.

Figures

( ) None.

( ) Yes.

Quantity (with letters): _____

( ) The authors declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.
( ) Are considered as photographs, drawings, graphics and schemes. The drawings must be designed by professionals. Maximum allowed is the 50 percent plus one of the text sheet.
( ) The information provided is not repeated in the text or tables.
( ) Are identified progressively with Arabic numbers according to the order of appearance in the text, remember that the counting includes the fotographs, drawings, graphs and diagrams.
( ) Separately attached in JPEG format.

The titles and explanations are presented separately

( ) Photographs that enables the people´s identification are accompanied by consent letters.
( ) Color illustrations are accepted and thus will appear online, but if authors wanted to be published in color of the printed version, must cover the proportional cost of printing.

Figure captions

Quantity (with letter): _____

( ) They are marked with Arabic numberd according to the overall sequence corresponding to them.

Ethical aspects

( ) The humans procedures must conform with the Ethical Standards of the Declaration of Helsinki of 1975 and the 1989 amendments to the agreement about ; issued by the Ministry of Health, published on January 26 1982 and the Scientific Committee and Ethics institution where they where first performed.
( ) Animal experiments conform to the rules the National Research Council and the institution where it was performed.
( ) Any other situation that may be of interest must be notified in writing to publishers.

Transfer of Copyright

Article title:

Author (s):

Author contributions:

The authors certify that the above-mentioned article is original work and has not previously been published except in abstract form; all tables, illustrations, and figures in the manuscript are entirely original and do not require reprint permission. Once accepted for publication in the *Cardiovascular and Metabolic Science*, copyright will be transferred to the latter. They also state that it has not been sent simultaneously for publication in another journal. The authors agree that, if necessary, this article would be included in the electronic media that the editors of the *Cardiovascular and Metabolic Science* consider appropriate.

The authors report that the order in which their names are mentioned in the article have been agreed between them and is a product of the proportion in which they participated in the elaboration of the work.

Signature of all authors

Location and date:

Bibliotecas e Índices en los que ha sido registrada e indizada la Revista Cardiovascular and Metabolic Science

Medigraphic, literatura biomédica
http://www.medigraphic.org.mx

Free Medical Journals
http://www.freemedicaljournals.com/f.php?f=es

Biblioteca de la Universidad de Regensburg, Alemania
http://www.bibliothek.uni-regensburg.de/ezeit/fl.phtml?notation=WW-YZ&bibid=ZBMED&colors=3&frames=&toc=&ssg=

Biblioteca de la Universidad Federal de Sao Paulo, Brasil
http://www.unifesp.br/dis/bibliotecas/revistas.htm

Biblioteca del Instituto de Investigaciones Biomédicas, UNAM
http://www.revbiomedicas.unam.mx/_biblioteca/revistas.html

Universidad de Laussane, Suiza
http://www2.unil.ch/perunil/pu2/

Biblioteca de la Universidad Norte de Paraná, Brasil
http://www.unopar.br/bibli01/biologicas_periodicos.htm

LATINDEX. Sistema Regional de Información en Línea para Revistas Científicas de América Latina, el Caribe, España y Portugal
http://www.latindex.unam.mx/

Biblioteca Virtual en Salud (BVS, Brasil)
http://portal.revistas.bvs.br

Biblioteca del Instituto de Biotecnología, UNAM
http://www.biblioteca.ibt.unam.mx/revistas.php

Asociación Italiana de Bibliotecas (AIB)
http://www.aib.it/aib/commiss/cnur/peb/peba.htm3

Biblioteca Médica Estatal del Ministerio de Patrimonio y Cultura, Italia
http://bms.beniculturali.it/ejnls/index.php

Fundación Ginebrina para la Formación y la Investigación Médica, Suiza
http://www.gfmer.ch/Medical_journals/Revistas_medicas_acceso_libre.htm

PERIODICA (Índice de Revistas Latinoamericanas en Ciencias) UNAM
http://periodica.unam.mx

Google Académico
http://scholar.google.com.mx/

Wissenschaftszentrum Berlin für Sozialforschung, Berlin WZB
http://rzblx1.uni-regensburg.de/ezeit/detail.phtml?bibid=WZB&colors=3&lang=de

Virtuelle Bibliothek Universität des Saarlandes, German
http://rzblx1.uni-regensburg.de/ezeit/search.phtml?bibid=SULB&colors=7&lang=de

University of South Australia. Library Catalogue
http://search.library.unisa.edu.au/az/a

Biblioteca electrónica de la Universidad de Heidelberg, Alemania
http://rzblx1.uni-regensburg.de/ezeit/search.phtml?bibid=UBHE&colors=3&lang=de

Biblioteca de la Universidad de Bielefeld, Alemania
https://www.digibib.net/jumpto?D_SERVICE=TEMPLATE&D_SUBSERVICE=EZB_BROWSE&DP_COLORS=7&DP_BIBID=UBBIE&DP_PAGE=search&LOCATION=361

Department of Library Services, Christian Medical College - Vellore
http://dodd.cmcvellore.ac.in/ftext/free%20e-journalR.htm

Mercyhurst University. Hammermill Library. Erie, Pennsylvania
http://services.trueserials.com/CJDB/MERCYHURST/browse

Memorial University of Newfoundland, Canada
http://www.library.mun.ca/copyright/index_new.php?showAll=1&page=1

Journals for free
http://www.journals4free.com/

Google Books
http://www.google.com.mx/books?id=w0GaAAAAIAAJ&lr=&hl=en&redir_esc=y

Research Institute of Molecular Pathology (IMP)/ Institute of Molecular Biotechnology (IMBA) Electronic Journals Library, Viena, Austria
http://cores.imp.ac.at/max-perutz-library/journals/details/?tx_ezbfe_pi3%5Bjournal_id%5D=15597&cHash=ce986bc3bc6d621dbca9ddbfea98424b

Scielo México
http://www.scielo.org.mx

OMRON

Omron

Innovación Tecnológica

para el monitoreo remoto del paciente hipertenso

Bluetooth®

HEM-9200T
Monitor de presión arterial de brazo

Centro de Atención Telefónica:
800 277 2509/55 5901 4300

Visítenos en:
www.omronhealthcare.la/mx
/OmronLA/ /Omronla

TECNOLOGÍA DE
OMRON HEALTHCARE
EN JAPÓN