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7th Brazilian Guideline of Arterial Hypertension

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Introduction

On behalf of the Brazilian Society of Cardiology, Brazilian Society of Hypertension and Brazilian Society of Nephrology, I present to you the 7th Brazilian Guideline of Arterial Hypertension, result of the joint work of an expert team of renowned professionals appointed by their respective medical societies.

The production of this new guideline was necessary to update the knowledge accumulated over the past years, considering the Brazilian reality and clinical practice. The guidance and recommendations contained in this document reflect the evidence of the effectiveness of the interventions. The present text does not deal specifically with cost-effectiveness analyses. The major objective of the medical societies and authors is to guide health professionals on the preventive measures and care for individuals with arterial hypertension, aiming at reducing the complications of arterial hypertension, considered the major risk factor for cardiovascular disease.

The following table was used as reference for the grades of recommendation and levels of evidence.

Grades of recommendation:

Class I: Conditions to which there is conclusive evidence or at least general consensus concerning the safety and usefulness/efficacy of the intervention;

Class II: Conditions to which there is conflicting evidence and/or disagreement of opinion concerning the safety and usefulness/efficacy of the intervention;

Class IIa: Evidence/opinion in favor of the intervention. Most experts agree;

Class IIb: Less well-established safety and usefulness/efficacy, without predominance of favorable opinions on the intervention;

Class III: Conditions to which there is evidence and/or consensus that the intervention is not useful/effective, and, in some cases, even harmful.

Levels of evidence:

Level A: Data derived from multiple consistent randomized controlled clinical trials, and/or a robust meta-analysis of randomized clinical trials;

Level B: Data derived from a less robust meta-analysis, one single randomized trial or non- randomized trials (observational);

Level C: Data derived from consensual expert opinion.

We hope the concepts expressed in this guideline can be widely spread to a better and more comprehensive care of individuals with arterial hypertension.

Marcus Vinícius Bolívar Malachias

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Abbreviations of the Brazilian Guideline of AH

ABI	Ankle-brachial index
ABPM	Ambulatory blood pressure monitoring
AC	Abdominal circumference
ACC	American College of Cardiology
ACEI	Angiotensin-converting-enzyme inhibitor
ACTH	Adrenocorticotropin
AH	Arterial hypertension
AHA	American Heart Association
AHI	Apnea-hypopnea index
AKI	Acute kidney injury
Aldo	Aldosterone
AMI	Acute myocardial infarction
APA	Aldosterone-producing adenoma
APE	Acute pulmonary edema
ARB	Angiotensin II receptor blocker
BB	Beta-blocker
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CAH	Chronic arterial hypertension
CbVD	Cerebrovascular diseases
CCB	Calcium-channel blocker
CDC	Centers for Disease Control and Prevention
CHF	Congestive heart failure
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CrCl	Creatinine clearance
CS	Cushing's syndrome
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
CVRF	Cardiovascular risk factor
DAH	Diastolic arterial hypertension
DBP	Diastolic blood pressure
DHA	Docosahexaenoic acid
DIU	Diuretic
DM	Diabetes mellitus
EPA	Eicosapentaenoic acid
GFR	Glomerular filtration rate
GH	Growth hormone
GRS	Global Risk Score
HbA1c	Glycated hemoglobin
HBPM	Home blood pressure monitoring
HC	Hypertensive crisis
HD	Hypertensive diseases
HDL-C	High-density lipoprotein cholesterol
HE	Hypertensive emergency
HF	Heart failure
HR	Heart rate
HU	Hypertensive urgency
ICU	Intensive care unit
IDF	International Diabetes Federation
IGF-1	Insulin-like growth factor 1
IHD	Ischemic heart diseases
IMT	Intima-media thickness
IPEMs	State Departments of Weights and Measures
ISH	Isolated systolic hypertension
IV	Intravenous
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
MH	Masked hypertension
MI	Myocardial infarction
MIBG	Metaiodobenzylguanidine
MRI	Magnetic resonance imaging
MS	Metabolic syndrome
NKF	National Kidney Foundation
NPT	Non-pharmacological treatment
OSAHS	*Obstructive sleep apnea-hypopnea syndrome*
PAD	Peripheral arterial disease
PE	Preeclampsia
PH	Prehypertension
PHA	Primary hyperaldosteronism
PHEO	Pheochromocytoma
PNS	Brazilian National Health Survey
POF	Survey on Family Income
PP	Pulse pressure
PRA	Plasma renin activity
PSNS	Parasympathetic nervous system
PTH	Parathormone
PVR	Peripheral vascular resistance
PWV	Pulse wave velocity
RAAS	Renin-angiotensin-aldosterone system
RAH	Resistant arterial hypertension
RBMLQ	Brazilian Legal Metrology and Quality Network
RF	Risk factor
RVAH	Renovascular arterial hypertension
SAH	Systemic arterial hypertension
SBP	Systolic blood pressure
SNP	Sodium nitroprusside
SNS	Sympathetic nervous system
SUS	Brazilian Unified Health Care System
TC	Total cholesterol
TIA	Transient ischemic attack
TOD	Target-organ damage
TSH	Thyroid stimulating hormone
UACR	Urine albumin/creatinine ratio
US	Ultrasonography
VIGITEL	Surveillance for Risk Factors and Protection Against Chronic Diseases via Telephone Inquiry
WCE	White-coat effect
WCH	White-coat hypertension

Chapter 1 - Concept, Epidemiology and Primary Prevention

Concept

Arterial hypertension (AH) is a multifactorial clinical condition characterized by sustained elevation of blood pressure (BP) levels ≥ 140 and/or 90 mm Hg. It is often associated with metabolic disorders, functional and/or structural changes in target organs, being worsened by the presence of other risk factors (RF), such as dyslipidemia, abdominal obesity, glucose intolerance and diabetes mellitus (DM).[1,2] It is independently associated with events such as sudden death, stroke, acute myocardial infarction (AMI), heart failure (HF), peripheral arterial disease (PAD) and fatal and non-fatal chronic kidney disease (CKD).[1-4]

Medical and social impact of arterial hypertension

North American data from 2015 revealed the presence of AH in 69% of patients on their first episode of AMI, in 77% of those with stroke, in 75% of those with HF and in 60% of those with PAD.[5] Arterial hypertension accounts for 45% of the cardiac deaths and for 51% of the deaths due to stroke.[6]

Arterial hypertension and cardiovascular disease in Brazil

In Brazil, AH affects 32.5% (36 million) of the adults, over 60% of the elderly, contributing direct or indirectly to 50% of the deaths due to cardiovascular disease (CVD).[7] Along with DM, its complications (cardiac, renal and stroke) have high impact on loss of work productivity and on family income, estimated as US$ 4.18 billion from 2006 to 2015.[8]

In 2013 there were 1,138,670 deaths, 339,672 of which (29.8%) due to CVD, the major cause of death in Brazil (Figure 1).

The mortality rates have decreased over the years, except for the hypertensive diseases (HD), which increased from 2002 to 2009, showing a reduction trend since 2010. The HD rates in that period ranged from 39/100,000 inhabitants (2000) to 42/100,000 inhabitants. Ischemic heart diseases (IHD) dropped from 120.4/100,000 inhabitants (2000) to 92/100,000 inhabitants (2013), cerebrovascular diseases (CbVD), from 137.7/100,000 inhabitants (2000) to 89/100,000 inhabitants (2013), and congestive HF (CHF), from 47.7/100,000 inhabitants (2000) to 24.3/100,000 inhabitants (2013)[9] (Figure 2).

In addition, CVD account for the high frequency of hospitalizations, with high socioeconomic costs. Data from the Hospital Information System of the Brazilian Unified Public Health System point to a significant reduction in the hospitalization trend due to AH, from 98.1/100,000 inhabitants (2000) to 44.2/100,000 inhabitants (2013).

Historical hospitalization rates due to CVD by region are shown in Figure 3, with a reduction for HD and stability or reduction trend for stroke, despite the increase in hospitalizations due to IHD.

Prevalence of arterial hypertension

The prevalence of HA in Brazil varies according to the population studied and the assessment method (Table 1).

In the meta-analysis by Picon et al., the 40 cross-sectional and cohort studies included showed a reduction trend in AH prevalence in the last three decades, from 36.1% to 31.0%.[10] A study with 15,103 government employees from six Brazilian capitals has reported a 35.8% AH prevalence, with predominance of men (40.1% vs 32.2%).[11]

Data from VIGITEL (2006 to 2014) indicate that the self-reported AH prevalence among individuals aged 18 years and over, living in the capitals, ranged from 23% to 25%, respectively, with no difference in the period assessed, not even regarding sex. The self-reported AH prevalence varied among adults according to age groups as follows: 18 - 29 years, 2.8%; 30 - 59 years, 20.6%; 60 - 64

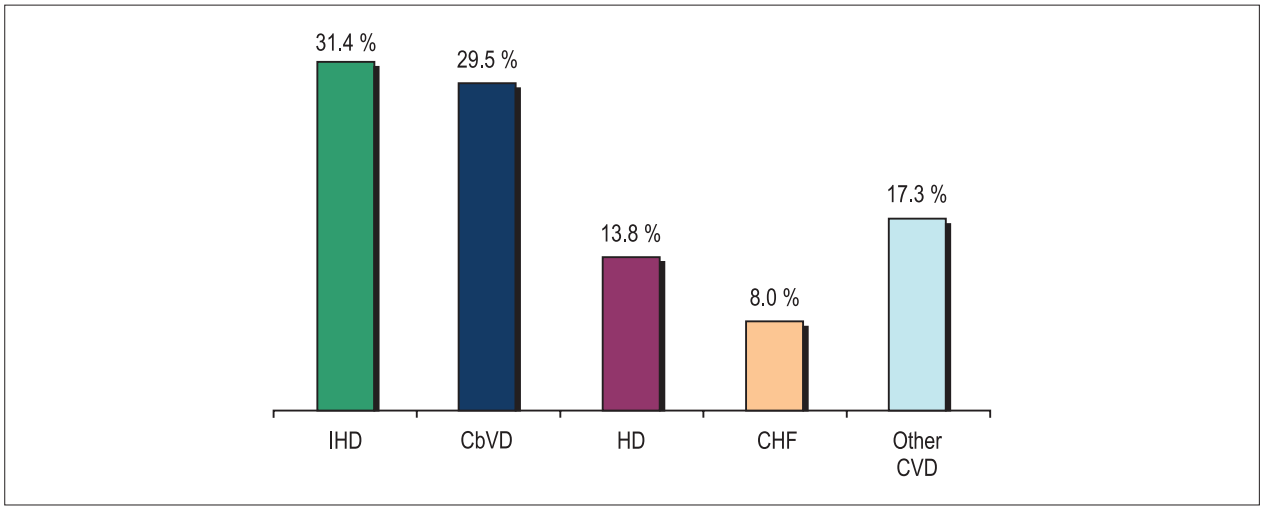

Figure 1 – *Mortality rate in Brazil due to cardiovascular diseases (CVD) and distribution according to cause in 2013. IHD: ischemic heart disease; CbVD: cerebrovascular disease; HD: hypertensive disease; CHF: congestive heart failure.*

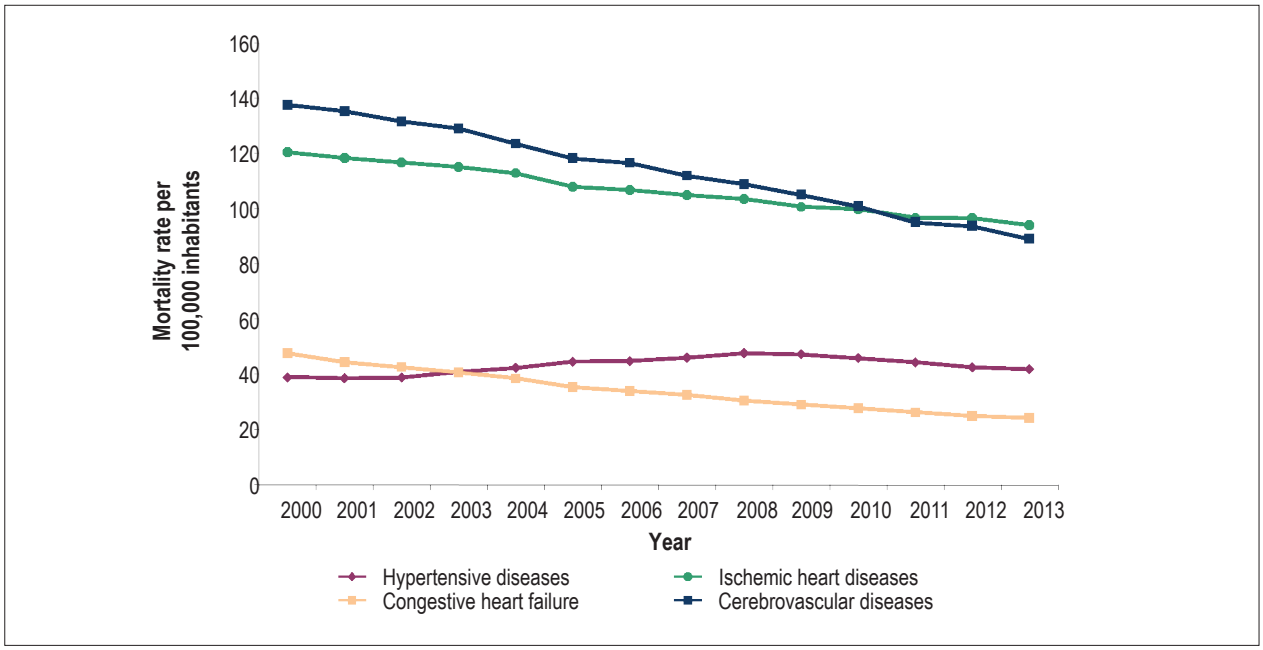

Figure 2 – *Mortality rate in Brazil due to CVD from 2000 to 2013. Source: Information System on Mortality. Health Surveillance Secretariat, Brazilian Ministry of Health.*

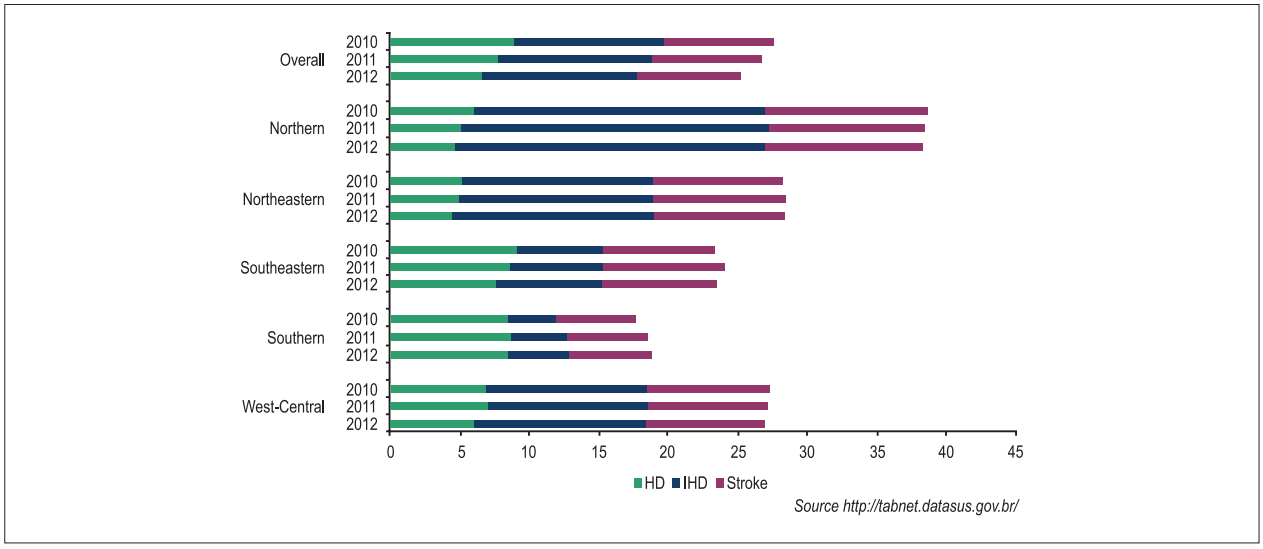

Figure 3 – *Hospitalization rate in Brazil per 100,000 inhabitants, per geopolitical region, from 2010 to 2012.*

Table 1 – Prevalence of AH according to different approaches

Source	BP	n	General (%)	Men	Women
Picon et al.[10*]	Measured	17,085	28.7 (26.2-31.4)	27.3 (22.5-32.8)	27.7 (23.7-32.0)
Scala et al.[7]	Measured		21.9-46.6	-	-
VIGITEL, 2014**	Self-reported via telephone	40,853	25.0		
PNS, 2013**	Self-reported	62,986	21.4	18.1	21.0
PNS, 2014**	Measured	59,402	22.3	25.3	19.5

*BP: blood pressure. *Meta-analysis; studies from the 2000 decade. **Note: Self-declared hypertensives under treatment were not considered hypertensive in the VIGITEL and PNS surveys.*

years, 44.4%; 65 - 74 years, 52.7%; and ≥ 75 years, 55%. The Southeastern region showed the highest self-reported AH prevalence (23.3%), followed by the Southern (22.9%) and West-Central (21.2%) regions. The Northeastern and Northern regions had the lowest rates, 19.4% and 14.5%, respectively.[12]

In 2014, the Brazilian National Health Survey (PNS) measured the BP of selected dwellers from drawn residences, using calibrated digital semi-automated devices. Three BP measurements were taken at two-minute intervals, considering the mean of the last two measurements, inserted in *smartphone*. The overall prevalence of BP ≥140/90 mm Hg was 22.3%, with predominance among men (25.3% *vs* 19.5%), ranging from 26.7% in Rio de Janeiro to 13.2% in Amazonas, with predominance in the urban area as compared to the rural one (21.7% *vs* 19.8%).

Knowledge, treatment and control

A review[7] has shown a wide variation of BP knowledge (22% to 77%), treatment (11.4% to 77.5%) and control (10.1% to 35.5%) rates, depending on the population studied (Table 2).

Prehypertension

Prehypertension (PH) is characterized by systolic BP (SBP) between 121 and 139 and/or diastolic BP (DBP) between 81 and 89 mm Hg.[13] The world prevalence of PH has ranged from 21% to 37,7% in population-based studies, except for Iran (52.1%) (Figure 4).[14]

Prehypertension associates with a higher risk of developing AH[15,16] and cardiac abnormalities.[17] Approximately one third of the cardiovascular (CV) events attributed to BP elevation occur in individuals with PH.[18] Meta-analyses of the incidence of CVD, IHD and stroke in prehypertensive individuals have shown a higher risk among those with BP levels between 130 and 139 or 85 and 89 mm Hg than among those with BP levels between 120 and 129 or 80 and 84 mm Hg (Figure 5).[14]

The clinical implication of that epidemiological evidence is that the BP of prehypertensive individuals should be monitored closely, because a significant proportion of them will develop AH and its complications.[2]

Risk factors for arterial hypertension

Age

There is a direct and linear association between aging and AH prevalence related to the increase: i) in life expectancy of the Brazilian population, currently 74.9 years; ii) in the elderly population ≥ 60 years in the past decade (2000 to 2010), from 6.7% to 10.8%.[19] A meta-analysis of studies performed in Brazil including 13,978 elderly has shown a 68% AH prevalence.[20]

Sex and ethnicity

The 2013 Brazilian National Health Survey (PNS) showed a self-reported AH prevalence statistically different between sexes, being higher among women (24.2%) and black

Table 2 – Blood pressure knowledge, treatment and control in 14 Brazilian population-based studies published from 1995 to 2009.[7]

Author/year per geopolitical region	Place	Number of individuals	Knowledge	Treatment	Control
Southern					
Fuchs et al. 1995	Porto Alegre (RS)	1,091	42.3	11.4	35.5
Gus et al. 2004	Rio Grande Sul	1,063	50.8	40.5	10.4
Oliveira e Nogueira, 2003	Cianorte (PR)	411	63.2	29.9	20.9
Trindade, 1998	Passo Fundo (RS)	206	82.2	53.3	20
Pereira et al. 2007	Tubarão (SC)	707	55.6	50.0	10.1
Southeastern					
Freitas et al. 2001	Catanduva (SP)	688	77	61.8	27.6
Souza et al. 2003	Campos dos Goytacazes (RJ)	1,029	29.9	77.5	35.2
Barreto et al. 2001	Bambuí (MG)	2,314	76.6	62.9	27
Castro et al. 2007	Formiga (MG)	285	85.3	67.3	14.7
Mill et al. 2004	Vitória (ES)	1,656	27.0		
West-Central					
Jardim et al. 2007	Goiânia (GO)	1,739	64.3	43.4	12.9
Cassanelli, 2005	Cuiabá (MT)	1,699	68.3	68.5	16.6
Rosário et al. 2009	Nobres (MT)	1,003	73.5	61.9	24.2
Souza et al. 2007	Campo Grande (MS)	892	69.1	57.3	-

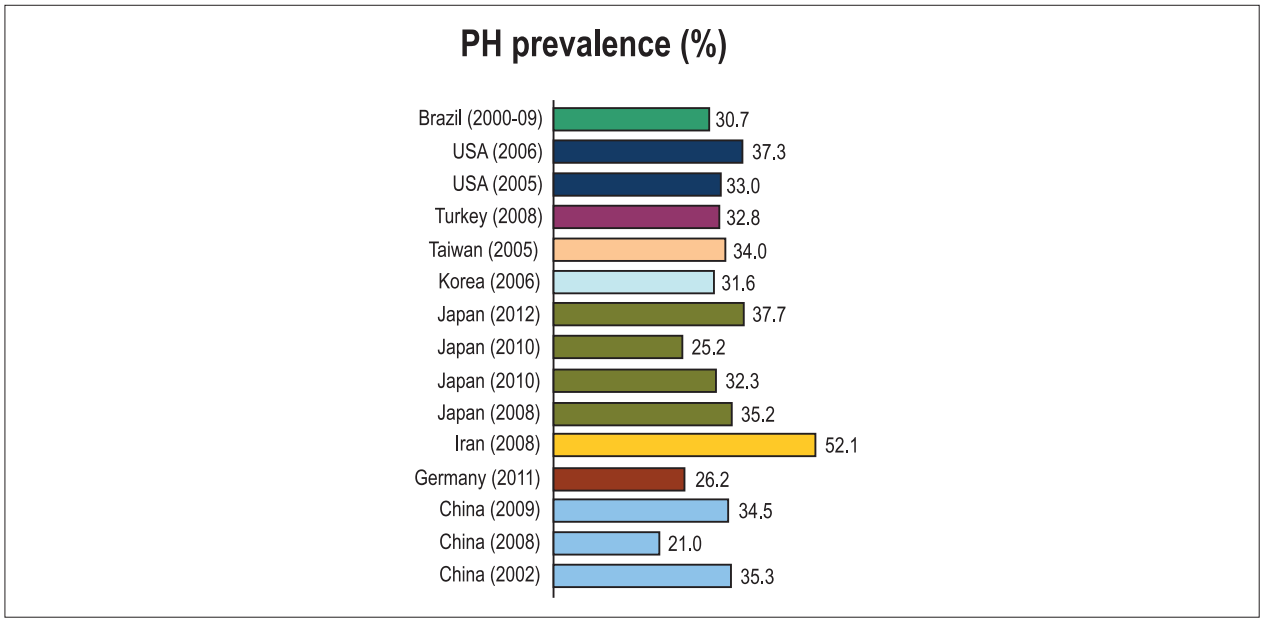

Figure 4 – *Prevalence of prehypertension (PH).*

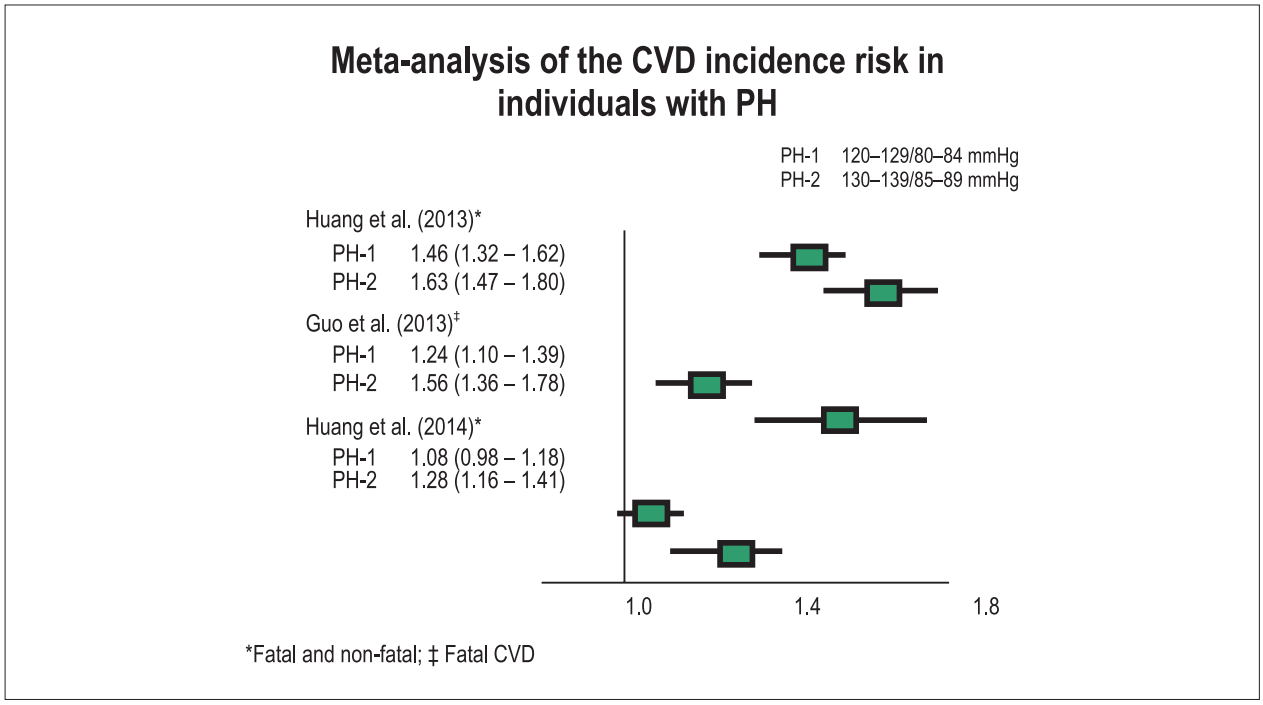

Figure 5 – *Meta-analysis of the risk of the incidence of cardiovascular disease (CVD) in individuals with prehypertension (PH).*

individuals (24.2%) as compared to mixed-heritage adults (20.0%), but not white individuals (22.1%). The *Corações do Brasil* Study has reported the following distribution: native population, 11.1%; yellow population, 10%; mixed heritage/mulatto, 26.3%; white, 29.4% and black, 34.8%.[21] The ELSA-Brazil Study has shown the following prevalences: white, 30.3%; mixed heritage, 38.2%; and black, 49.3%.[11]

Overweight and obesity

In Brazil, the 2014 VIGITEL data revealed, between 2006 and 2014, an increase in the prevalence of overweight (BMI ≥ 25 kg/m^2), 52.5% *vs* 43%. In that same period, obesity (BMI ≥ 30 kg/m^2) increased from 11.9% to 17.9%, predominating among 35-to-64-year-old individuals and women (18.2% *vs* 17.9%), but remained stable from 2012 to 2014.

Salt intake

The excessive consumption of sodium, one of the major RF for AH, associates with CV and renal events.[22,23]

In Brazil, data of the Survey on Family Income (POF), collect from 55,970 dwellings, have shown home availability of 4.7g of sodium/person/day (adjusted for the consumption of 2,000 kcal), exceeding more than twice the maximum recommended consumption (2 g/day), lower in the urban area of the Southeastern region, and higher in the rural area of the Northern region.[24]

The impact of the sodium-rich diet estimated in the 2014 VIGITEL data showed that only 15.5% of the individuals interviewed acknowledged high or extremely high salt content in their meals.[12]

Alcohol intake

A chronic and high consumption of alcoholic beverages increases BP consistently. A meta-analysis of 2012, including 16 studies with 33,904 men and 19,372 women compared the consumption intensity between non-drinkers and drinkers.[25] For women, there was a protective effect with doses lower than 10g of alcohol/day, and risk for AH with a consumption of 30-40g of alcohol/day. For men, the increased risk for AH became consistent from 31g of alcohol/day onwards.

The 2006-2013 VIGITEL data showed that abusive alcohol consumption – at least four doses for women, or at least five doses for men, of alcoholic beverages on the same occasion, within the past 30 days – is stable in the adult population, around 16.4% (24.2% for men and 9.7% for women). For both sexes, abusive alcohol consumption was more often among youngsters, and increased with schooling.[25]

Sedentary lifestyle

A population-based study in the city of Cuiabá, Mato Grosso State, (n = 1,298 adults ≥ 18 years) has revealed a 75.8% overall prevalence of sedentary lifestyle (33.6% during leisure time; 19.9% at work; 22.3% during both). A significant association of AH was observed with age, male sex, overweight, central adiposity, sedentary lifestyle during leisure time and work, less than 8 years of schooling, *per capita* income < 3 minimum wages.[26]

Brazilian National Health Survey (PNS) data indicate that insufficiently active individuals (adults not practicing at least 150 minutes per week of physical activity including leisure, work and displacement time) represent 46.0% of the adults, the percentage being significantly higher among women (51.5%). The frequencies of insufficiently active individuals differed between age groups, mainly among the elderly (62.7%) and the adults with no formal education and those with incomplete elementary education (50.6%).[27]

Socioeconomic factors

Adults with lower schooling (no formal education or incomplete elementary education) have a higher prevalence of self-reported AH (31.1%). The proportion decreases among those with complete elementary education (16.7%), being 18.2% among those with complete higher education.[26] However, the ELSA Brazil Study, performed with employees of six Brazilian universities and university-affiliated hospitals with higher schooling, has shown a 35.8% AH prevalence, higher among men.[11]

Genetics

Brazilian studies assessing the impact of genetic polymorphisms in the *quilombola* population could not identify a more prevalent pattern, showing the strong impact of miscegenation, and hindering the identification of a genetic pattern for the elevation of BP levels.[28,29]

Strategies for the implementation of preventive measures

The strategies for preventing the development of AH comprise public policies for health in combination with action from the medical societies and communication media. They should be aimed at stimulating early diagnosis, continuous treatment, control of BP and associated RF, by use of lifestyle changes and/or regular use of medications.

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Chapter 2 - Diagnosis and Classification

Introduction

The initial assessment of a patient with systemic arterial hypertension (SAH) comprises diagnostic confirmation, suspicion and identification of the secondary cause, and assessment of CV risks. In addition, target-organ damage (TOD) and associated diseases should be investigated. Such assessment comprises BP measurement in the office and/or outside the office, by use of proper technique and validated equipment, medical history (personal and family), physical examination and clinical and laboratory investigation.

General assessments directed to all, and, in some cases, complementary assessments only for specific groups are proposed.

Measurement of BP

In the office

Blood pressure should be measured in all assessments performed by physicians of any specialty and other health care professionals properly trained.

Blood pressure should be measured at least every two years for adults with BP levels ≤ 120/80 mm Hg, and annually for those with BP levels > 120/80 mm Hg and < 140/90 mm Hg.[1] Manual, semi-automated or automated sphygmomanometers can be used. They should be validated, and calibrated annually following the INMETRO recommendations (Chart 1). The BP should be taken in the arm, with a cuff size adequate to arm circumference (Chart 2). When AH secondary to coarctation of the aorta is suspected, BP should be measured in the lower limbs with proper cuffs.[2]

Orthostatic hypotension should be suspected in elderly, diabetic and dysautonomic patients, as well as in those on any antihypertensive medication. Thus, particularly in such conditions, BP should be read with the patient standing for 3 minutes, and orthostatic hypotension being defined as a reduction in SBP > 20 mm Hg or in DBP > 10 mm Hg.[3,4] Several measurements should be taken, with the patient sitting in a calm and comfortable environment to improve reproducibility and to obtain office BP levels closer to those provided by ambulatory BP monitoring (ABPM) during wakefulness.[5,6]

Procedures recommended for BP measurement:[7]

Patient's preparation:

1. Explain the procedure to the patient, who should be left to rest for 3-5 minutes in a calm environment and instructed not to talk during the measurement. Possible doubts should be clarified before or after the procedure.

2. Make sure the patient:

- does not have a full urinary bladder;

- did not practice physical exercise in the past 60 minutes;

- did not consume alcohol, coffee or any food;

- did not smoke in the past 30 minutes.

3. Position:

- The patient should be sitting relaxed in a chair, with back supported, legs uncrossed and feet on the floor;

- The patient's arm should be supported at heart level, not compressed by clothes, with hand palm turned upward.

4. After 3 minutes, BP should be read in the upstanding position in diabetic and elderly patients, or in any other situation at risk for orthostatic hypotension.

Steps of BP measurement

1. Determine arm circumference in the middle point between the acromion and olecranon;

2. Select proper cuff size (Chart 3);

3. Place the cuff snugly, 2-3 cm above the cubital fossa;

4. Centralize the compressive part of the cuff on the brachial artery;

5. Estimate BP level based on palpation of the radial pulse*;

6. Palpate the brachial artery on the cubital fossa and place the stethoscope's diaphragm without excessive compression*;

7. Inflate cuff rapidly until the estimated SBP level obtained on palpation is exceeded by 20-30 mm Hg*;

8. Proceed to deflation slowly (velocity of 2 mm Hg/second)*;

Chart 1 – INMETRO ordinances n. 24, of February 22, 1996, for mechanical aneroid sphygmomanometers, and n. 96, of March 20, 2008, for digital electronic sphygmomanometers for non-invasive measurement.

By means of these ordinances, the manufacturers or importers of sphygmomanometers should submit their products to metrological control, defined in Technical Regulation, comprising the following steps:

Technical appreciation of the model – every manufacturer or importer of sphygmomanometers should submit each model manufactured or imported to INMETRO approval, and no change in the sphygmomanometer model approved can be performed without INMETRO's authorization;

Initial verification – should be performed in all sphygmomanometers inside the manufacturer's facilities or any other place at INMETRO's discretion before their release to use;

Periodical verification – should be performed once a year, preferably inside the RBMLQ agency (IPEM) or any other place at INMETRO's discretion; and

Occasional verification – should be performed at the owner's request, after device repair and/or maintenance, or when INMETRO deems it necessary.

RBMLQ: Brazilian Legal Metrology and Quality Network; IPEM: State Department of Weights and Measures

Chart 2 – Correction factors of BP measurement with standard adult cuff (width, 13 cm, and length, 30 cm), according to patient's arm circumference

Circumference (cm)	Correction factor (mm Hg)	
	SBP	DBP
26	+5	+3
28	+3	+2
30	0	0
32	-2	-1
34	-4	-3
36	-6	-4
38	-8	-6
40	-10	-7
42	-12	-9
44	-14	-10
46	-16	-11
48	-18	-13

Chart 3 – Cuff dimensions (bladder width and length) according to arm circumference

Arm circumference (cm)	Cuff denomination	Bladder width (cm)	Bladder length (cm)
≤ 6	Newborn	3	6
6-15	Infant	5	15
16-21	Child	8	21
22-26	Small adult	10	24
27-34	Adult	13	30
35-44	Large adult	16	38
45-52	Thigh	20	42

9. Determine SBP by auscultation of the first sound (Korotkoff phase I), and then, slightly increase the deflation velocity*;

10. Determine DBP when the sounds disappear (Korotkoff phase V)*;

11. Auscultate until 20-30 mm Hg below the last sound to confirm its disappearance, and then proceed to rapid and complete deflation*;

12. If heart beats persist until level zero, determine DBP on the muffling of sounds (Korotkoff phase IV) and write down the values of SBP/DBP/zero*;

13. Take at least two measurements at 1-minute intervals. If the first two are very different, additional readings should be taken. When appropriate, consider the mean value;

14. Measure BP in both arms on the first medical visit and take the higher value as reference;

15. Inform the patient of the BP reading; and

16. Write down the exact BP values, with no rounding, and the arm used for the measurement.

* Items performed exclusively in the auscultatory technique.

The use of validated and periodically calibrated equipment is paramount.[8]

Outside-the-office BP measurement

Outside the office, BP can be measured by use of home BP monitoring (HBPM), following a specific protocol, or by use of 24-hour ABPM.[9,10]

Outside-the-office BP measurements should be stimulated, and can be performed by using a patient's semi-automated device or one belonging to a health care provider. The major advantages of outside-the-office BP measurements are as follows:

- Higher number of BP readings;
- Assessment of the individuals' usual activities;
- Abolition or significant reduction of the 'white-coat effect' (WCE);
- Patients' higher adhesion to diagnosis and follow-up.

The methods usually used to measure BP outside the office are ABPM and HBPM. Both provide similar BP information, but only ABPM assesses BP during sleep. However, both estimate CV risk, and should be considered to assess BP outside the office, provided their indications and limitations are respected.[9,10] Chart 4 lists the reference values for SAH definition by using office measurements, ABPM and HBPM.[9,10] Because they are different assessment methods, certain values will be considered for the definition of abnormality. Chart 5 lists the indications for outside-the-office BP measurement by using ABPM and HBPM.

Measurement of BP in children, elderly, obese and pregnant individuals

Children

Measuring BP in children is recommended at all clinical assessments after the age of 3 years, at least once a year, as part of primary pediatric care, and should abide by the standards established for adults.[11] The interpretation of the BP levels for children and adolescents should consider age, sex and height. The assessment of BP levels according to those variables should be based on specific tables (Chapter 10 of this guideline) or smartphone applications, BP Kids and Ped(z).

Elderly

Special aspects of BP measurement in the elderly are due to changes resulting from aging, such as higher frequency of auscultatory gap, which is the absence of sounds during cuff deflation, resulting in falsely low SBP or falsely high DBP readings. The wide BP variability in the elderly throughout 24 hours makes ABPM a useful tool. Pseudohypertension, associated with the atherosclerotic process, can be detected by use of Osler's maneuver,

Chart 4 – Reference values for the definition of AH based on office, ABPM and HBPM measurements

Category	SBP (mm Hg)		DBP (mm Hg)
Office	≥ 140	and/or	≥ 90
ABPM			
Wakefulness	≥ 135	and/or	≥ 85
Sleep	≥ 120	and/or	≥ 70
24 hours	≥ 130	and/or	≥ 80
HBPM	≥ 135	and/or	≥ 85

SBP: systolic blood pressure; DBP: diastolic blood pressure.

Chart 5 – Clinical indications for outside-the-office BP measurement aimed at diagnosis[9,10,18]

Clinical indications for ABPM or HBPM
Suspected WCH
- office stage 1 AH
- office high BP in asymptomatic individuals with no TOD and low total CV risk
Suspected MH
- office BP between 130/85 and 139/89 mm Hg
- office BP < 140/90 mm Hg in asymptomatic individuals with TOD or high total CV risk
Identification of WCE in hypertensive individuals
Wide variation of office BP in the same medical visit or in different visits
Postural, postprandial, siesta or drug-induced hypotension
High office BP or suspected preeclampsia in pregnant women
Confirmation of resistant hypertension
Specific indications for ABPM
Significant disagreement between office and outside-the-office BP
Assessment of BP descent during sleep
Suspected AH or usual lack of BP descent during sleep in individuals with sleep apnea, CKD or diabetes
Assessment of BP variability

AH: arterial hypertension; MH: masked hypertension; TOD: target-organ damage; WCE: white-coat effect; CKD: chronic kidney disease.

that is, the radial artery remains palpable after cuff inflation at least 30 mm Hg above the reading of radial pulse disappearance.[12] The higher occurrence of WCE and orthostatic and postprandial hypotension, and the presence of arrhythmias, such as atrial fibrillation, can hinder BP measurement.

Obese individuals

The BP measurement of obese patients requires longer and wider cuffs to prevent BP overestimation.[13] When the arm circumference exceeds 50 cm, and a proper cuff is not available, BP can be taken in the forearm, and the radial pulse should be auscultated.[13] However, restrictions apply to that practice. Cone-shaped, wide, short arms, where large cuffs do not fit, represent a special difficulty.

Pregnant women

The BP should be measured following the same methodology recommended for adults, emphasizing that it can also be taken on the left arm in the left lateral decubitus position at rest, and should not differ from that obtained in the sitting position. Consider Korotkoff's fifth sound as DBP.[14] White-coat hypertension (WCH) and masked hypertension (MH) are common during pregnancy, and, thus, ABPM and HBPM can be useful for clinical decision making. Chapter 9 provides further information on AH during pregnancy.

Recommendations for diagnosis and follow-up

To establish the diagnosis and to identify WCH and MH, HBPM and ABPM are recommended (Figure 1).[15] Another recommendation is suspected AH originating from auto-measurement, when ABPM or HBPM should be used to confirm or rule out the suspected diagnosis of WCH or MH.[16]

Home BP measurement

Home BP measurement is performed with a specific protocol, and consists in taking three BP readings in the morning, prior to breakfast and medication intake, and three in the evening, before dinner, for five days. Another option is to take two BP measurements in each of those sessions, for seven days.[9,17,18]

Blood pressure levels ≥ 135/85 mm Hg are considered abnormal.

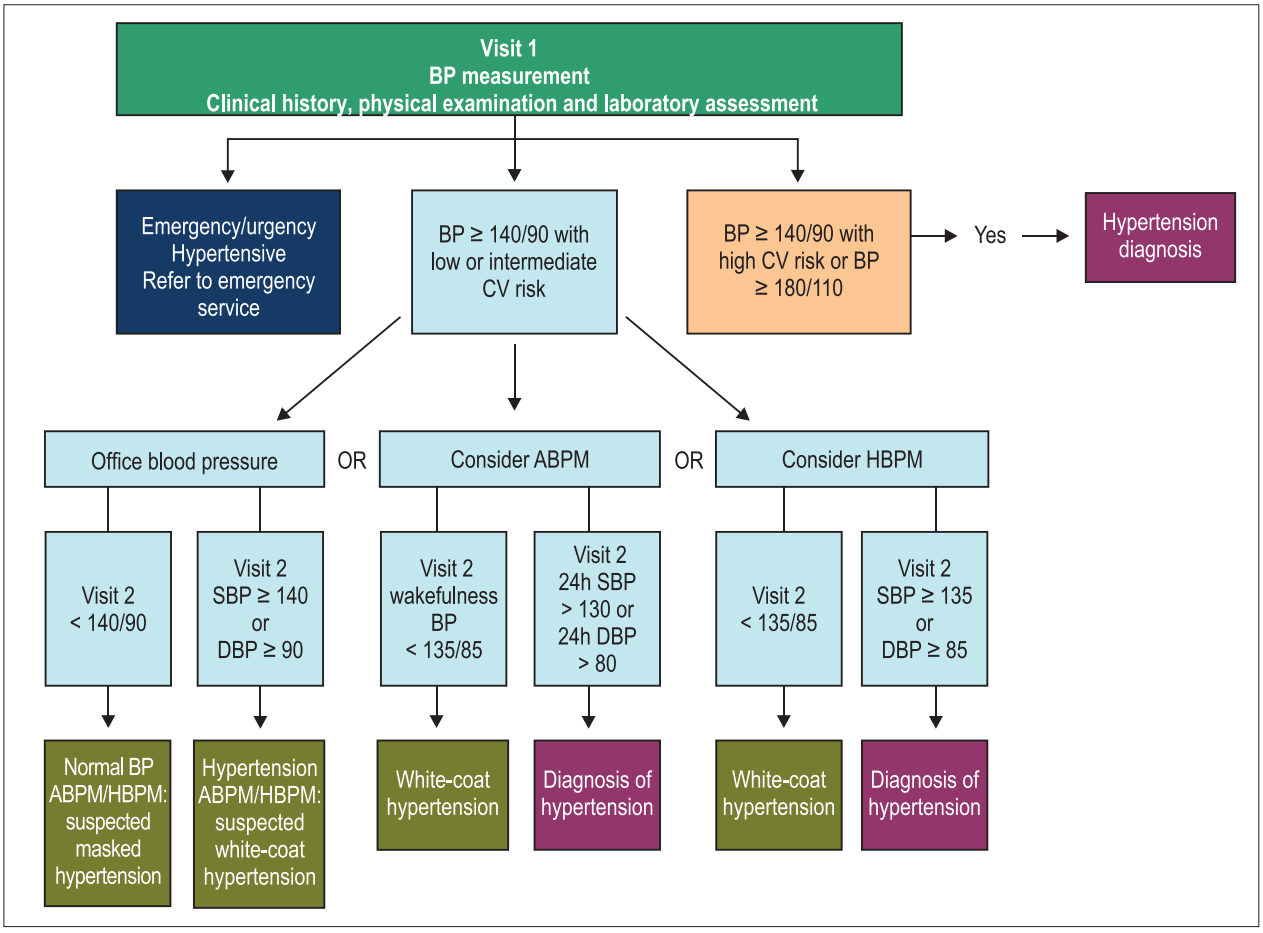

Figure 1 – *Flowchart for the diagnosis of arterial hypertension (modified from Canadian Hypertension Education Program). Laboratory assessment recommended in Chapter 3. ** Cardiovascular risk stratification recommended in Chapter 3.*

Ambulatory BP monitoring

Ambulatory BP monitoring allows indirect and intermittent BP recording during 24 hours or longer, while the patient performs their usual chores during wakefulness and sleep. One of its most specific characteristics is the likelihood to identify BP circadian changes, especially during sleep, which has considerable prognostic implications.[19]

Currently, the following BP means are considered abnormal: 24-hour ≥ 130/80 mm Hg, wakefulness ≥ 135/85 mm Hg, and sleep ≥ 120/70 mm Hg.[10,18]

Classification

The BP limits considered normal are arbitrary. However, the values to classify BP in adults by using casual or office measurements are shown in Chart 6.

Hypertension

Chart 4 shows the values that define SAH. The BP readings obtained by using different methods have different abnormality levels, therefore, the abnormality levels defined for each method should be considered when establishing the diagnosis of SAH. When using office measurements, the diagnosis should always be validated with repeated readings, under ideal conditions, on at least two occasions, and confirmed by use of outside-the-office measurements (ABPM or HBPM), except for patients with detected TOD.[2,20] Non-controlled SAH is defined as maintenance of elevated BP, both in and outside the office, by use of either ABPM or HBPM, even under anti-hypertensive treatment.

Normal blood pressure

Blood pressure is considered normal when office BP levels are ≤ 120/80 mm Hg, and outside-the-office measurements (ABPM or HBPM) confirm those normal readings (Figure 2).[2,21] Controlled AH is defined as maintenance of controlled BP levels, both in the office and outside it, under anti-hypertensive treatment.

Prehypertension

Prehypertension is characterized by SBP levels between 121 and 139 and/or DBP levels between 81 and 89 mm Hg. Prehypertensive individuals are more likely to become hypertensive and at higher risk for CV complications than those with normal BP levels, ≤ 120/80 mm Hg, requiring, thus, periodical assessment.[22]

White-coat effect

The WCE is the BP difference between measurements taken in the office and outside it, if that difference equals at least 20 mm Hg in SBP and/or 10 mm Hg in DBP. It does not change the diagnosis: if normotensive, the individual will remain normotensive; if hypertensive, the individual will remain hypertensive. However, the BP stage can change and/or there might be a false impression of need for change in the therapeutic regimen.

White-coat hypertension

It is the clinical situation characterized by abnormal office BP levels, but normal BP readings on ABPM or HBPM (Figure 2). Based on four population-based studies, the overall WCH prevalence is 13% (range, 9-16%), and WCH can affect 32% (range, 25-46%) of hypertensive individuals, being more common (55%) in stage 1 hypertensives and affecting 10% of stage 3 hypertensives.[23,24] However, in terms of prognosis, whether WCH is comparable to normal BP is still controversial, because some studies have shown that its long-term CV risk is intermediate between that of AH and of normotension.[25]

Masked hypertension

It is characterized by normal office BP, but elevated BP on ABPM or HBPM (Figure 2). The MH prevalence is 13% (range, 10-17%) in population-based studies.[23] Several factors can elevate outside-the-office BP as compared to office BP, such as young age, male sex, smoking habit, alcohol consumption, physical activity, exercise-induced hypertension, anxiety, stress, obesity, DM, CKD and family history of SAH. The MH prevalence is higher when office BP is borderline.[26] Meta-analyses of prospective studies report that the incidence of CV events is twice higher in MH than in normal BP, and comparable to that in SAH.[23,26,27] In diabetic individuals, MH is associated with an increased risk of nephropathy, especially when BP elevation occurs during sleep.[28,29]

Figure 2 shows the different possibilities of BP classification according to its diagnosis, based on the new definition forms.

Chart 6 – Classification of BP according to casual or office measurement from 18 years of age onwards

Classification	SBP (mm Hg)	DBP (mm Hg)
Normal	≤ 120	≤ 80
Prehypertension	121-139	81-89
Stage 1 hypertension	140 – 159	90 – 99
Stage 2 hypertension	160 – 179	100 - 109
Stage 3 hypertension	≥ 180	≥ 110
When SBP and DBP are in different categories, the highest should be used to classify BP.		

Isolated systolic hypertension: SBP ≥ 140 mm Hg and DBP < 90 mm Hg, and is should be classified into stages 1, 2 and 3.

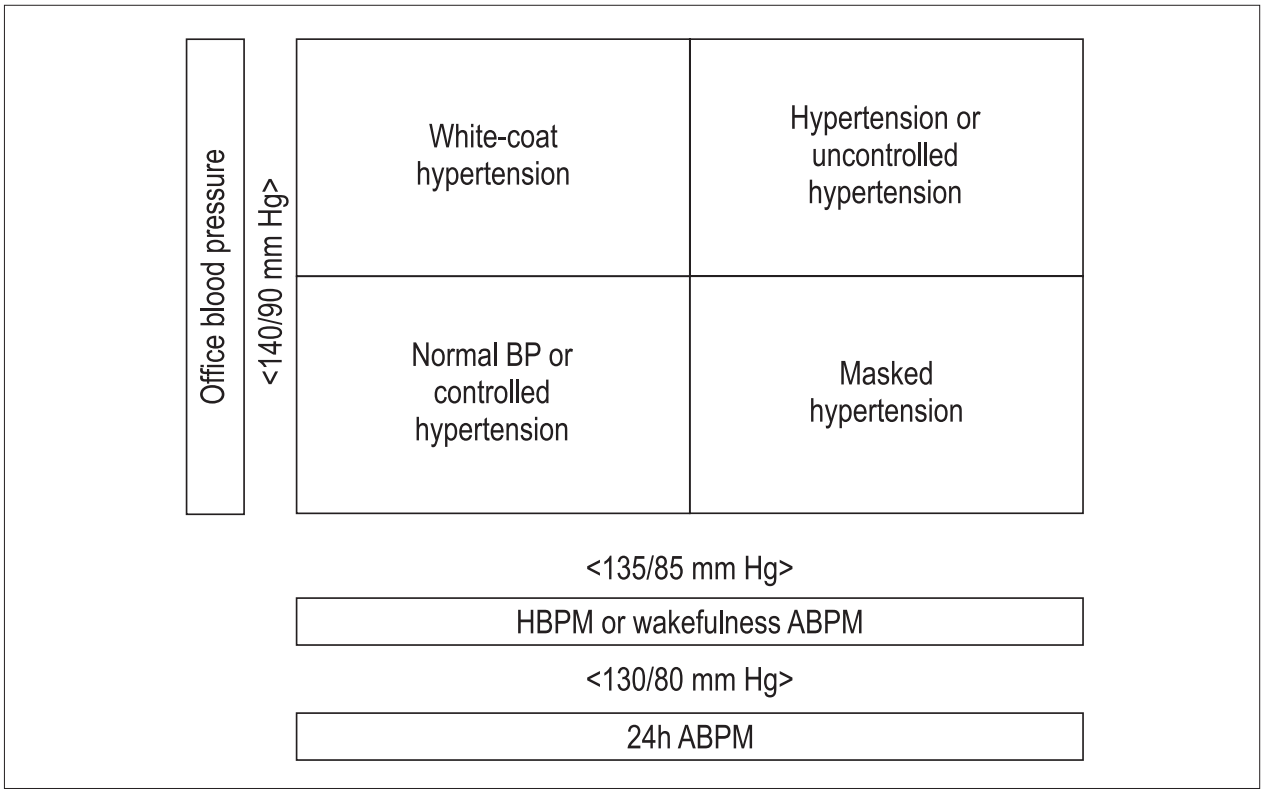

Figure 2 – *Diagnostic possibilities based on casual BP measurement, ABPM or HBPM. *Consider the diagnosis of prehypertension for casual SBP levels between 121 and 139 and/or DBP between 81 and 89 mm Hg.*

Isolated systolic hypertension

Isolated systolic hypertension (ISH) is defined as increased SBP with normal DBP, and, along with pulse pressure (PP), is an important cardiovascular risk factor (CVRF) in middle-aged and elderly patients.[30]

The recommendations are summarized in Chart 7.

Chart 7 – Summary of the recommendations

Recommendations	Grade of recommendation	Level of evidence
Screening and diagnosis of AH with office BP measurement.	I	B
Diagnosis of SAH based on at least two BP readings per visit, in at least two visits.	I	C
Measuring BP outside the office should be considered to confirm the diagnosis of SAH, identify the type of SAH, detect episodes of hypotension, and maximize the prediction of CV risk.	IIa	B
Outside-the-office BP, ABPM or HBPM can be considered, depending on indication, availability, easiness, cost of use, and, when applicable, patient's preference.	IIb	C

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Chapter 3 - Clinical and Complementary Assessment

Clinical history and objectives

The major objectives of clinical and laboratory assessment are shown in Chart 1. Meeting those goals allows the correct AH diagnosis and prognosis, enabling choosing the better therapy for the patient.

Clinical assessment

Clinical history

Complete clinical history with questions about time since AH diagnosis, course and previous treatment should be obtained. Information on the family history is essential to increase the chance of an accurate diagnosis of primary AH.[1] (GR: I; LE: B). The patient should be asked about specific RF for CVD, comorbidities, socioeconomic aspects and lifestyle,[2] in addition to previous and current use of medications or other substances that can interfere with BP measurement and/or AH treatment. Similarly, evidence of a secondary cause of AH should be investigated.

Physical examination

Blood pressure should be measured with proper technique (Chapter 2). Anthropometric data, such as weight, height [for body mass index (BMI) calculation], abdominal circumference (AC) and heart rate (HR), should be recorded. The normal values of AC and BMI are those recommended by the International Diabetes Federation (IDF) in 2006, and can vary according to ethnicity.[3,4] (GR: IIa; LE: C).

Assessment (Chart 2) should comprise palpation and auscultation of the heart, carotid arteries and pulses, ankle-brachial index (ABI) measurement and retinal exam.

To calculate ABI, measure SBP in the arm and ankle, in both sides. An arm SBP/ankle SBP ratio greater than 0.90 is defined as normal, while PAD is defined as mild, if that ratio is 0.71-0.90, moderate, if 0.41-0.70, and severe, if 0.00-0.40.

Basic laboratory investigation, assessment of subclinical and clinical target-organ damage

Complementary assessment is aimed at detecting subclinical or clinical TOD to better stratify CV risk. To stratify global CV risk, the classical RF (Chart 3), as well as the new ones identified, should be considered, although they have not been incorporated to the clinical scores of risk stratification.[4,5]

Of the new RF, the following stand out: fasting glycemia between 100 mg/dL and 125 mg/dL, abnormal glycated hemoglobin (HbA1c), abdominal obesity (metabolic syndrome - MS), PP (SBP-DBP) > 65 mm Hg in the elderly,[5] history of preeclampsia, and family history of AH (for borderline hypertensive patients).

The laboratory assessment shown in Chart 4 should be part of the initial routine of all hypertensive patients.[4]

The Cockroft-Gault formula is used to calculate creatinine clearance:[6] CrCl (mL/min) = [140 - age] x weight (kg) /serum creatinine (mg/dL) x 72 for men; for women, multiply the result by 0.85.

To estimate glomerular filtration rate (GFR) use the CKD-EPI equation.[7] The interpretation of the GFR values to classify CKD (stages) is performed according to the National Kidney Foundation (NKF).[7]

Chart 1 – Objectives of clinical and laboratory assessment

Confirmation of AH diagnosis by use of BP measurement
Identification of CVRF
Search for TOD, both subclinically and clinically manifested
Search for other associated diseases
Stratification of global CV risk
Assessment of evidence for suspected secondary AH

Chart 2 – Clinical assessment

Physical Examination
BP measurement in both arms
Weight, height, BMI and HR
Abdominal circumference
Signs of TOD
Brain: motor or sensorial deficits
Retina: lesions on retinal exam
Arteries: pulse absence, asymmetry or reduction, skin lesions and murmurs
Heart: apical beat displaced, presence of S3 or S4, murmurs, arrhythmias, peripheral edema, pulmonary rales
Suggestive signs of secondary causes*
Cushingoid characteristics
Abdominal palpation: enlarged kidneys (polycystic kidney)
Abdominal or thoracic murmurs (renovascular, coarctation of the aorta, disease of the aorta or its branches)
Decreased femoral pulses (coarctation of the aorta, disease of the aorta or its branches)
Difference of BP between arms (coarctation of the aorta and subclavian stenosis)

**For further information, see Chapter 12.*

Chart 3 – Additional cardiovascular risk factors

Age (men > 55 years, women > 65 years)
Smoking habit
Dyslipidemias: triglycerides > 150 mg/dL; LDL-C > 100 mg/dL; HDL-C < 40 mg/dL
DM
Family history of premature CVD: men < 55 years, women < 65 years

Chart 4 – Routine tests for hypertensive patients

Urinalysis (GR: I; LE: C)
Serum potassium (GR: I; LE: C)
Fasting glycemia (GR: I; LE: C) and HbA1c (GR: I; LE: C)
Estimated glomerular filtration rate (GR: I; LE: B)
Serum creatinine (GR: I; LE: B)
Total cholesterol, HDL-C and serum triglycerides (GR: I; LE: C)*
Serum uric acid (GR: I; LE: C)
Conventional electrocardiogram (GR: I; LE: B)

**LDL-C is calculated by use of the formula: LDL-C = total cholesterol - (HDL-C + triglycerides/5) (when triglycerides < 400 mg/dL).*

The CKD-EPI equation[8] used to estimate GFR is available at: www.nefrocalc.net

GFR (mL/min/1.73m^2):

Stage 1: ≥ 90 = normal or high;

Stage 2: 60-89 = mildly decreased;

Stage 3a: 45-59 = mildly to moderately decreased;

Stage 3b: 30-44 = moderately to severely decreased;

Stage 4: 15-29 = severely decreased;

Stage 5: < 15 = end-stage kidney disease (KDIGO).

Certain clinical situations, discussed in Chart 5, require more detailed complementary tests.

Chart 5 – Tests recommended for certain populations

Test/assessment	Recommended population and indication
Chest X ray	Follow-up of patients with clinical suspicion of cardiac (GR: IIa; LE: C) and/or pulmonary impairment. Assessment of hypertensive individuals with aorta impairment when echocardiogram is not available.[9]
Echocardiogram More sensitive than ECG to diagnose LVH. Important in the assessment of the geometrical forms of left atrial hypertrophy and size, analysis of systolic and diastolic function. Consider LVH when left ventricular mass corrected for body surface is equal to or greater than 116 g/m^2 for men and 96 g/m^2 for women.[10]	Evidence of LVH on ECG or patients with clinical suspicion of HF (GR: I; LE: C).
Albuminuria Predicts fatal and non-fatal CV events. Normal values < 30 mg/24h (GR: I; LE: C).[7,11]*	Diabetic hypertensive patients, with MS or at least two RF.
Carotid US The carotid IMT and/or identification of plaques predict the occurrence of stroke and MI independently of other CVRF. IMT values > 0.9 mm, as well as the presence of atherosclerotic plaques, have been considered abnormal (GR: IIa; LE: B).[12]	Carotid murmur, CbVD signs or atherosclerotic disease in other sites.
Renal US or with Doppler	Patients with abdominal masses or abdominal murmur (GR: IIa; LE: B).[13]
HbA1c	- When fasting glycemia > 99 mg/dL - Family history of type 2 DM or previous diagnosis of type 2 DM and obesity (GR: IIa; LE: B).[14]
Exercise test	- Suspicion of stable CAD, DM or family antecedent of CAD in patients with controlled BP (GR: IIa; LE: C).[15]
ABPM/HBPM	- According to the conventional indication of those methods (GR: IIa; LE: B).
PWV "Standard" for assessing arterial stiffness. Values greater than 12 m/s are abnormal (GR: IIa; LE: B).[16]	- Intermediate-to-high-risk hypertensive patients.
MRI of the brain: to detect silent infarctions and micro hemorrhages (GR: IIa; LE: C).[17]	- Patients with cognitive disorders and dementia.

LVH: left ventricular hypertrophy; CV: cardiovascular; RF: risk factor; US: ultrasonography; IMT: intima-media thickness; MS: metabolic syndrome; MI: myocardial infarction; CVRF: cardiovascular risk factor; CbVD: cerebrovascular disease; HbA1c: glycated hemoglobin; DM: diabetes mellitus; CAD: coronary arterial disease; ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring; PWV: pulse wave velocity; MRI: magnetic resonance imaging.
**Next figure shows the current classification and nomenclature for albuminuria and GFR according to KDIGO, 2012.[7]*

Prognosis of CKD according to the category of GFR and albuminuria: KDIGO 2012

Categories of GFR (mL/min/1.73m²) Description and intervals				Categories of persistent albuminuria Description and intervals		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				< 30 mg/g < 3 mg/mmol	30-300 mg/g 3-30 mg/mmol	> 300 mg/g > 30 mg/mmol
	E1	Normal or high	⩾ 90			
	E2	Mildly decreased	60-89			
	E3a	Mildly to moderately decreased	45-59			
	E3b	Moderately to severely decreased	30-44			
	E4	Severely decreased	15-29			
	E5	End-stage kidney disease	⩽15			

Figure 1 – *Prognosis of CKD according to the category of GFR and albuminuria. Green: low risk; yellow: moderately increased risk; orange: high risk; red: extremely high risk.*

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Chapter 4 - Cardiovascular Risk Stratification

Introduction

The global CV risk should be assessed in each hypertensive individual, because it aids the professionals in therapeutic decision-making and allows prognostic analysis. The identification of hypertensive individuals prone to CV complications, especially myocardial infarction (MI) and stroke, is fundamental to a more aggressive therapy. Several algorithms and risk scores based on population studies were created in past decades,[1] but, considering the lack of Brazilian data for a more accurate assessment of CV risk in the Brazilian population, the use of one single risk score should be avoided to support therapeutic decisions. Multifactorial models of risk stratification can be used for a more accurate individual risk classification.

Informing patients about their RF can improve the efficacy of pharmacological and non-pharmacological measures to reduce global risk. In addition, estimating indicators and using aging-related terms, such as "vascular age" or "cardiometabolic age", can aid in the strategy to change the RF.[2,3] See below some electronic addresses to estimate the vascular or cardiometabolic age recommended by American, Canadian and British societies.[4-6]

1. www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php

→ supported by the *National Heart, Lung, and Blood Institute and Boston University*

2. www.nhs.uk/Conditions/nhs-health-check/Pages/check-your-heart-age-tool.aspx

→ supported by the *British Heart Foundation*

3. cardiometabolicage.com

→ supported by the *Canadian Institute for Health Research (CIHR) and McGill University*

In clinical practice, CV risk stratification of hypertensive patients can be based on two different strategies. In the first, the assessment is aimed at determining the global risk directly related to hypertension, in which case the risk classification depends on BP levels, associated risk factors, TOD and presence of CVD or kidney disease. In the second strategy, the objective is to determine the risk of a certain individual to develop general CVD within 10 years. Although that form of assessment is not specific to hypertensive patients, since it can be applied to any individual aged 30-74 years, it is worth noting that AH is the major CVRF.

Additional cardiovascular risk stratification

Only a small minority of hypertensive patients has only one BP elevation. Aimed at making risk stratification easier, the classification system in Table 1, contemplating only low, moderate and high risk, should be used. It is worth noting that the identification of previous CVD, kidney disease or DM considerably increases the risk of future CV events, independently of BP levels.[7,8]

The large majority of the hypertensive population has additional RF. Therefore, the CV risk assessment depends on information obtained from clinical history, physical examination and complementary tests, always aiming at:

- Coexistence of other CVRF (Table 2);
- Presence of hypertension TOD (Table 3);
- Diagnosis of CVD or kidney disease already established (Table 4).

Thus, to facilitate and speed the classification process of additional CV risk in the medical visit setting, the health professional in charge should follow the flowchart described in Figure 1. It is worth noting that, in some cases, the initial classification can be modified according to the best or worst control of BP levels and RF.

Global cardiovascular risk stratification

The CV risk stratification based on three steps has been recently recommended in the V Brazilian Guideline for Dyslipidemia and Atherosclerosis Prevention[9] and the I Brazilian Guideline for Cardiovascular Prevention,[10] and it can be adopted for hypertensive patients. The steps should be performed as follows.

Identification of atherosclerotic disease or of its equivalents

The first step to estimate CV risk is the identification of clinically evident or subclinical atherosclerotic disease,

Table 1 – Risk stratification in hypertensive patients based on additional risk factors, presence of target-organ damage and cardiovascular or kidney disease

	SBP 130-139 or DBP 85-89	Stage 1 SAH SBP 140-159 or DBP 90-99	Stage 2 SAH SBP 160-179 or DBP 100-109	Stage 3 SAH SBP ≥ 180 or DBP ≥ 110
No risk factor	No additional risk	Low Risk	Intermediate risk	High Risk
1-2 risk factors	Low Risk	Intermediate risk	High Risk	High Risk
≥ 3 risk factors	Intermediate risk	High Risk	High Risk	High Risk
Presence of TOD, CVD, CKD or DM	High Risk	High Risk	High Risk	High Risk

SBP: systolic blood pressure; DBP: diastolic blood pressure; SAH: systemic arterial hypertension; CVD: cardiovascular disease; CKD: chronic kidney disease; DM: diabetes mellitus: TOD: target-organ damage.

Table 2 – Cardiovascular risk factors in the assessment of additional risk in hypertensives

- Male sex
- Age
  - Men ≥ 55 years or women ≥ 65 years
- History of premature CVD in first-degree relatives
  - Men < 55 years or women < 65 years
- Smoking habit
- Dyslipidemia
  - Total cholesterol > 190 mg/dL and/or
  - LDL-cholesterol > 115 mg/dL and/or
  - HDL-cholesterol < 40 mg/dL in men or < 46 mg/dL in women and/or
  - Triglycerides > 150 mg/dL
- Insulin resistance
  - Fasting serum glycemia: 100-125 mg/dL
  - Oral glucose tolerance test: 140-199 mg/dL in 2 hours
  - Glycated hemoglobin: 5.7 – 6.4%
- Obesity
  - BMI ≥ 30 kg/m^2
  - AC ≥ 102 cm in men or ≥ 88 cm in women

CVD: cardiovascular disease; LDL: low-density lipoprotein; HDL: high-density lipoprotein; BMI: body mass index; AC: abdominal circumference.

Table 3 – Target-organ damage in the additional risk assessment of hypertensives

- Left ventricular hypertrophy
  - ECGI: Sokolow-Lyon index (SV_1 + RV_5 or RV_6) ≥ 35 mm
  - ECGI: R aVL > 11 mm
  - ECGI: Cornell voltage > 2440 mm*ms
  - ECHOI: LVMI > 115 g/m^2 in men or > 95 g/m^2 in women
- Carotid IMT > 0.9 mm or carotid plaque
- Carotid-femoral PWV > 10 m/s
- ABI < 0.9
- Stage 3 chronic kidney disease (GFR 30-60 mL/min/1.73m^2)
- Albuminuria = 30 - 300 mg/24h or UACR = 30 - 300 mg/g

ECG: electrocardiogram; ECHO: echocardiogram; IMT: intima-media thickness; LVMI: left ventricular mass index; PWV: pulse wave velocity; ABI: ankle-brachial index; GFR: estimated glomerular filtration rate; UACR: urine albumin-creatinine ratio.

or of its equivalents, such as DM and CKD[11] (Table 5). If positive, the individual is immediately classified as at high risk, because the chance of having the first or a new CV event within 10 years is greater than 20%. (GR: I; LE: A).

Table 4 – Established cardiovascular and kidney disease in the additional risk assessment of hypertensives.

- Cerebrovascular disease
  - Ischemic stroke
  - Cerebral hemorrhage
  - Transient ischemic attack
- Coronary artery disease
  - Stable or unstable angina
  - Myocardial infarction
  - Myocardial revascularization: percutaneous (angioplasty) or surgical
  - Heart failure with reduced or preserved ejection fraction
  - Symptomatic peripheral arterial disease of lower limbs
  - Stage 4 chronic kidney disease (GFR < 30 mL/min/1.73m^2) or albuminuria > 300 mg/24h
  - Advanced retinopathy: hemorrhages, exudates, papilledema

GFR: estimated glomerular filtration rate.

Global risk score analysis

When the individual does not meet any of the step 1 conditions, the next step is to estimate the Global Risk Score (GRS).[6] The algorithm estimates the risk of having a CV event (CAD, stroke, PAD, HF) within 10 years. The distribution of points and percentage of risk is differentiated for women (Tables 6A and 6B) and men (Tables 7A and 7B). When the GRS is lower than 5%, the patient is classified as 'low risk' (GR: A; LE: I), except those with a family history of premature CV disease, who are reclassified as 'intermediate risk'. (GR: IIa; LE: B).

Men with GRS between 5% and 20%, and women with GRS between 5% and 10% are initially considered at 'intermediate risk'.[12] (GR: I; LE: A).

Men with GRS > 20% and women with GRS > 10% are considered at 'high risk' (GR: I; LE: A).

Risk reclassification based on the presence of aggravating factors

Patients at intermediate risk with the aggravating factors listed in Table 8 are reclassified as at high risk.[9,13-15] (GR: IIa; LE: B).

The criteria used in the diagnosis of MS are shown in Table 9.

In addition, to facilitate the global CV risk determination in hypertensive patients, the flowchart in Figure 2 shows all steps necessary for the final classification.

In conclusion, so far no CV risk assessment way has been validated in Brazil. In addition, some young women tend to a risk estimate lower than the actual one, and older men are usually identified as at high risk, even with no relevant RF. Thus, the use of more than one classification allows better understanding of CV risk in hypertensive patients.

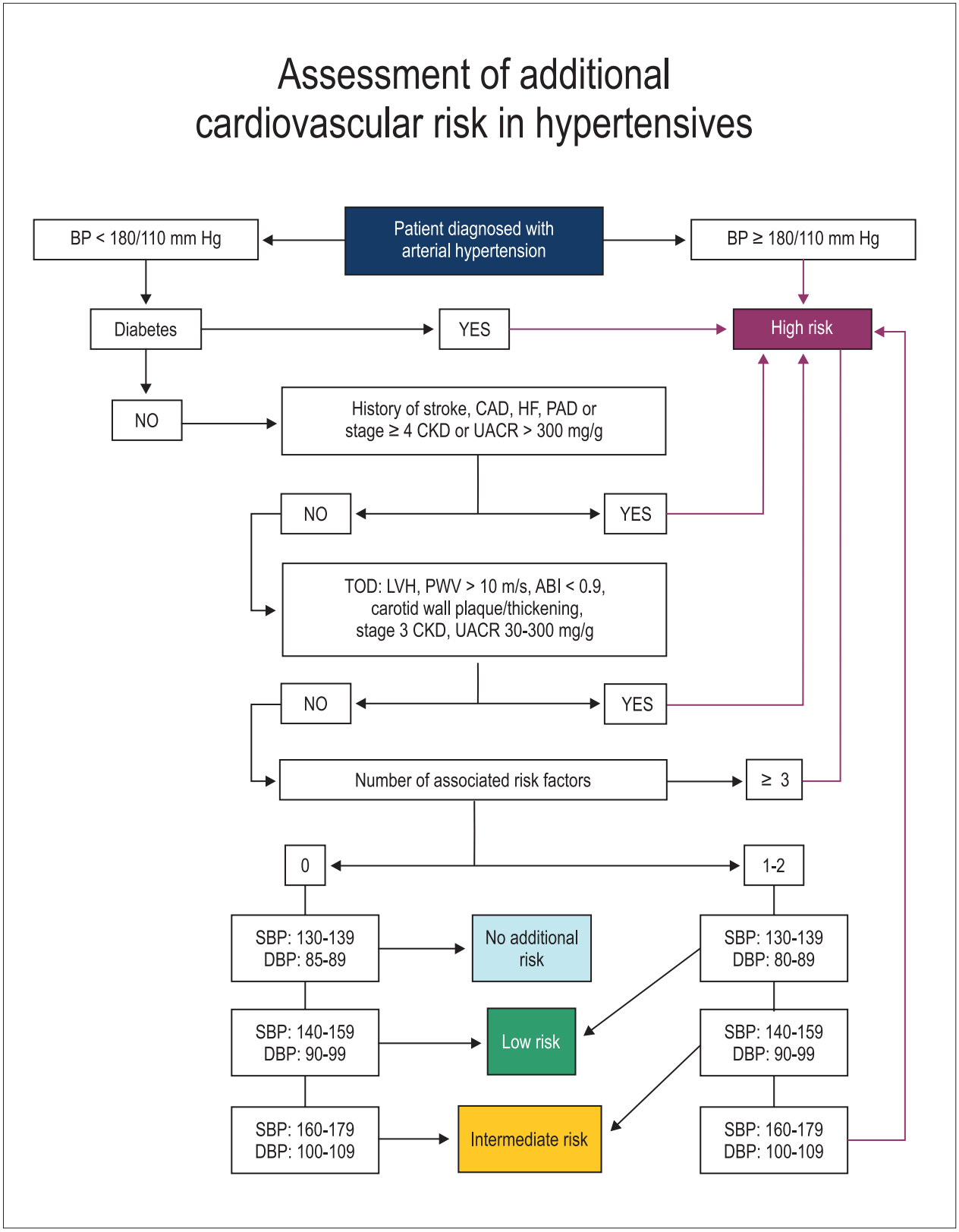

Figure 1 – *Flowchart of classification of additional CV risk for hypertensive patients. BP: blood pressure; CAD: coronary artery disease; HF: heart failure; PAD: peripheral arterial disease; CKD: chronic kidney disease; UACR: urine albumin/creatinine ratio; TOD: target-organ damage; LVH: left ventricular hypertrophy; PWV: pulse wave velocity; ABI: ankle-brachial index; SBP: systolic blood pressure; DBP: diastolic blood pressure. Risk factors: male sex, age > 55 years (men) or > 65 years (women), family history, smoking, dyslipidemia, obesity and insulin resistance.*

Table 5 – Definition of atherosclerotic disease and of its equivalents

1. Atherosclerotic disease (clinically evident): coronary, cerebrovascular or peripheral obstructive disease
2. Significant subclinical atherosclerosis documented by use of diagnostic methods
3. Arterial revascularization procedures
4. Types 1 and 2 diabetes mellitus
5. Chronic kidney disease
6. Family hypercholesterolemia

Table 6(A) – Points in the global risk score for women

Points	Age (years)	HDL-C	TC	SBP (non-treated)	SBP (treated)	Smoking	Diabetes
-3				< 120			
-2		60+					
-1		50-59			< 120		
0	30-34	45-49	< 160	120-129		No	No
1		35-44	160-199	130-139			
2	35-39	< 35		140-149	120-129		
3			200-239		130-139	Yes	
4	40-44		240-279	150-159			Yes
5	45-49		280+	160+	140-149		
6					150-159		
7	50-54				160+		
8	55-59						
9	60-64						
10	65-69						
11	70-74						
12	75+						

HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; SBP: systolic blood pressure.

Table 6(B) – Global CV risk for women according to the points obtained

Points	Risk (%)	Points	Risk (%)
≤ -2	< 1	10	6.3
-1	1.0	11	7.3
0	1.2	12	8.6
1	1.5	13	10.0
2	1.7	14	11.7
3	2.0	15	13.7
4	2.4	16	15.9
5	2.8	17	18.5
6	3.3	18	21.6
7	3.9	19	24.8
8	4.5	20	28.5
9	5.3	21+	>30

Table 7(A) – Points in the global risk score for men

Points	Age (years)	HDL-C	TC	SBP (non-treated)	SBP (treated)	Smoking	Diabetes
-2		60+		< 120			
-1		50-59					
0	30-34	45-49	< 160	120-129	< 120	Não	Não
1		35-44	160-199	130-139			
2	35-39	< 35	200-239	140-159	120-129		
3			240-279	160+	130-139		Sim
4			280+		140-159	Sim	
5	40-44				160+		
6	45-49						
7							
8	50-54						
9							
10	55-59						
11	60-64						
12	65-69						
13							
14	70-74						
15+	75+						

HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; SBP: systolic blood pressure.

Table 7(B) – Global CV risk for men according to the points obtained

Points	Risk (%)	Points	Risk (%)
≤ -3	< 1	8	6.7
-2	1.1	9	7.9
-1	1.4	10	9.4
0	1.6	11	11.2
1	1.9	12	13.2
2	2.3	13	15.6
3	2.8	14	18.4
4	3.3	15	21.6
5	3.9	16	25.3
6	4.7	17	29.4
7	5.6	18+	> 30

Table 8 – Aggravating factors of CV risk

Aggravating factor	Recommendations and evidence
1. Family history of premature CAD in first-degree relative, men < 55 years or women < 65 years	GR: IIa; LE: A
2. Diagnosis of MS according to the IDF criteria	GR: IIb; LE: A
3. Microalbuminuria (30-300 mg/g creatinine) or albuminuria (> 300 mg/g creatinine)	GR: IIa; LE: B
4. LVH	GR: IIa; LE: B
5. High-sensitive C-reactive protein > 2 mg/L	GR: IIa; LE: B
6. Carotid IMT > 1.0 mm	GR: IIb; LE: B
7. Coronary calcium score > 100 or > 75th percentile for age and sex	GR: IIa; LE: A
8. ABI < 0.9	GR: IIa; LE: A

CAD: coronary artery disease; MS: metabolic syndrome; IDF: International Diabetes Federation; LVH: left ventricular hypertrophy; IMT: intima-media thickness; ABI: ankle-brachial index.

Table 9 – Diagnostic criteria for metabolic (syndrome defined with 3 or more criteria)[15,16]

Criteria	Definition
1. Abdominal obesity	
Men	≥ 94 cm
Women	≥ 80 cm
2. HDL-cholesterol	
Men	< 40 mg/dl
Women	< 50 mg/dl
3. Triglycerides (or treatment for hypertriglyceridemia)	≥ 150 mg/dl
4. BP (or treatment for arterial hypertension)	
SBP and/or	≥ 130 mmHg
DBP	≥ 85 mmHg
5. Glycemia (or treatment for DM)	≥ 100 mg/dl

BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; DM: diabetes mellitus.

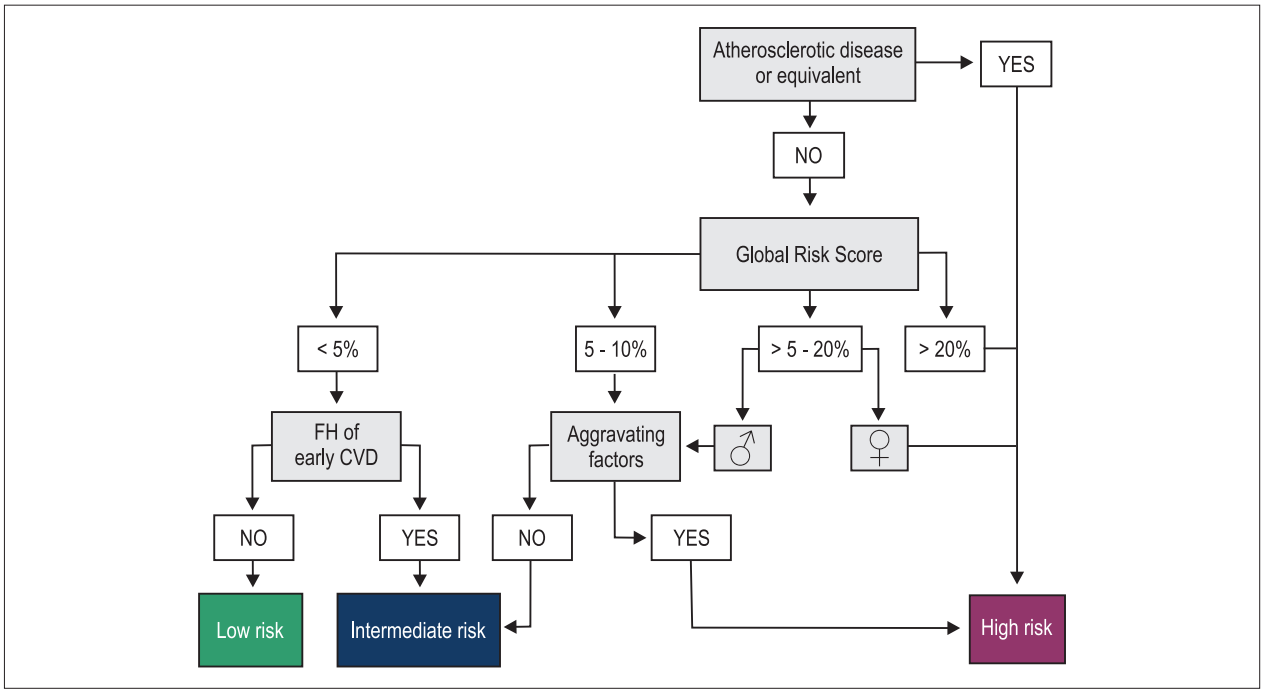

Figure 2 – *Flowchart to estimate global cardiovascular risk. FH: family history; CVD: cardiovascular disease.*

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Chapter 5 - Therapeutic Decision and Targets

Introduction

The therapeutic management of elevated BP includes non-pharmacological measures and the use of antihypertensive drugs to reduce BP, protect target organs and prevent CV and renal outcomes.[1-3] Non-pharmacological measures have proven efficient to reduce BP, although limited by medium- and long-term lack of adherence to treatment. A systematic review[4] of studies with a minimum duration of 12-24 months, combining dietary interventions and moderate-to-high-intensity physical activity in patients using or not medications, has revealed a reduction in SBP and DBP for < 12 months of -4.47 (-7.91 to -1.04) mm Hg and -1.10 (-2.39 to 0.19) mm Hg, respectively. For 12 to 24 months, the reductions were -2.29 (-3.81 to -0.76) mm Hg and -1.00 (-3.22 to 1.22) mm Hg in SBP and DBP, respectively. The direct impact of those measures on the risk of CV outcomes is uncertain, the studies are small and short, and the effects on other RF could contribute to CV protection.

On the other hand, results of randomized placebo-controlled clinical trials on the use of antihypertensive drugs for hypertensive individuals have clearly shown a significant reduction in CV mortality, stroke, MI and HF. It is worth noting that most of those studies have assessed individuals aged ≥ 55 years, at high CV risk and for a follow-up period of 3 to 6 years, hindering, thus, the extrapolation of those benefits for long-term treatment and patients with other characteristics.

The therapeutic decision should be based not only on BP levels, but consider the presence of RF, TOD and/or established CVD.

Treatment decision making

Approach to stages 2 and 3 and/or high-risk hypertensives

Individuals with BP ≥ 160/100 mm Hg and/or high CV risk, even if stage 1, should begin immediately drug treatment associated with non-pharmacological therapy.[5-9] Studies on antihypertensive drugs, most of which performed with patients with that profile, have shown efficacy in BP reduction and CV protection.[5-8] Non-pharmacological therapy alone cannot reduce BP sufficiently to meet the recommended BP target,[4] despite being an effective adjuvant treatment to control BP and other CVRF often present. Although the absolute benefit of therapy is higher in stages 2 and 3, it also increases the residual risk because of the frequent presence and influence of other RF and already installed TOD, neutralizing part of that benefit. This reinforces the importance of approaching CV risk globally.[7-9]

Approach to stage 1 hypertensives at low and intermediate risk

The last international guidelines[2,3] point to a gap in the evidence favoring the impact of antihypertensive therapy on the outcome reduction of stage 1 hypertensives at low-to-intermediate risk. A meta-analysis[10] of four randomized studies with a minimum duration of 1 year has included 8,912 individuals with SBP of 140-159 mm Hg and/or DBP of 90-99 mm Hg. As compared to placebo, the treatment for 5 years has not reduced total mortality, CAD, stroke or CV events, having even increased by five times the chance of adverse events. Another meta-analysis[6] by the *Blood Pressure Lowering Treatment Trialists' Collaboration*, selecting ten randomized studies on treatment vs placebo for stage 1 hypertensives, has shown a reduction in the risk for stroke, total mortality and CVD, but had included individuals on antihypertensive therapy and/or individuals with DM. When such patients were excluded, the results lost statistical power. Later, the analysis of six studies on stage 1 SAH, involving 16,036 individuals, excluding those with DM and those on baseline antihypertensive therapy, has shown significant reductions in the risk of stroke (36%), CAD (12%), CV death (22%) and total mortality (18%). An analysis restricted to stage 1 SAH and low to intermediate risk of events (up to 5% in 10 years) has shown a reduction in the risk of those same outcomes, apparently strengthening those findings. However, the absolute benefit increased as the global CV risk increased.[7-9]

Recently, the HOPE-3 Study has contributed to that subject.[11] In a significant population sample of 12,705 individuals at intermediate CV risk (38% hypertensive), the treatment combining candesartan and hydrochlorothiazide (16 mg/day and 12.5 mg/day, respectively) has shown a 27%-reduction in the risk of composite primary outcome (mortality, stroke and non-fatal AMI) in patients with initial SBP > 143.5 mm Hg (upper tertile). Those with lower SBP, in the first and second tertiles, however, showed no reduction in CV outcomes, and, on the contrary, the risk for the study's primary outcome tended to increase, although not significantly, in individuals of the first tertile of SBP.

The result of the HOPE-3 Study supports a recent meta-analysis on hypotensive therapy stratified by CV risk, in which a BP reduction of 4.6/3 mm Hg from baseline systolic levels around 155 mm Hg has determined an 18% reduction in the risk of outcomes.[12]

Thus, for stage 1 hypertensives at intermediate or low CV risk, non-pharmacological therapy should be attempted[13,14] for 3 and 6 months, respectively (GR: I; LE: B), after which, the lack of BP control determines the beginning of pharmacological therapy. It is mandatory, however, to follow those individuals up with periodical assessment of adherence to the non-pharmacological measures. Once the lack of adherence or worsening of BP levels is detected, pharmacological therapy should be started. It is worth noting that the intervention in stage 1 hypertensives at low risk can prevent progression of the CV risk. Currently, the wide availability of antihypertensive drugs favors a safe and well-tolerated treatment.

Approach to BP levels of 130-139/85-89 mm Hg

Several meta-analyses with individuals with PH have shown a greater risk of progression to SAH and of CV events in that group after adjusting for other RF.[15-20] Interventions in individuals with those BP levels are justified by the finding

that half of the burden attributed to BP occurs in those with SBP between 130 and 150 mm Hg.[21] It is worth noting, in that BP range, the expressive number of individuals with CVD, kidney disease, DM, metabolic syndrome and multiple CVRF.[21] Non-pharmacological measures are recommended for that BP range. Prospective, observational studies of lifestyle intervention have shown lower risk of developing AH in those adopting a healthy lifestyle.[13,22-24] (GR: I; LE: A).

Drug treatment can be considered for prehypertensive individuals with BP of 130-139/85-89 mm Hg and previous history of CVD[25] (GR: IIb; LE: B) or individuals at high CV risk with no CVD[26] (GR: IIb, LE: B), but there is no evidence of benefit for those at intermediate risk.[11] Studies of renin-angiotensin-aldosterone system (RAAS) blockers for individuals with BP of 130-139/85-89 mm Hg at high CV risk have shown a reduction in the incidence of AH.[27,28] There is no consistent evidence of the benefit of antihypertensive therapy to CV outcomes in that group. Thus, the decision to institute pharmacological therapy should be customized.

Approach to hypertensive elderly

The most common mechanism of AH in the elderly is wall stiffness of the large arteries, leading to a predominant increase in SBP, and maintenance or decrease in DBP. There is no study assessing the impact of antihypertensive therapy in this group with baseline SBP between 140 and 159 mm Hg. Because of the inclusion criteria of the major studies, the BP level at entrance in the study was ≥ 160 mm Hg, clearly showing the advantage of the intervention from that level onward. Lower thresholds have not been tested, leaving a gap of evidence. Presumably, the benefits demonstrated on TOD for the general population should not differ from those of the elderly population. Studies conducted with individuals aged ≥ 80 years have shown favorable results of the use of antihypertensive drugs for those with BP ≥ 160 mm Hg, especially to prevent stroke and HF.[29,30] Thus, antihypertensive pharmacological therapy in the elderly should begin from SBP levels ≥ 140 mm Hg onward, as long as well tolerated and considering the individual's general conditions.[31] (GR: IIb; LE: B).

In very old individuals (aged ≥ 80 years), the threshold to begin pharmacological therapy increases to SBP ≥ 160 mm Hg.[29,30] (GR: I; LE: A).

Approach to youngsters with isolated systolic hypertension

The ISH is frequent among healthy male youngsters aged < 30 years and can be associated with normal central BP. In such cases, the treatment yields no significant benefits,[32] and non-pharmacological measures should be adopted, with TOD monitoring. When managing ISH, pharmacological therapy should begin immediately if the CV risk is high. If DBP elevation occurs, the same criteria for the treatment of the general population should be adopted.

Tables 1 and 2 show the grades of recommendation and levels of evidence for beginning the treatment.

BP targets

Recent international guidelines[2,3] have recommended more conservative BP targets for the elderly and those at high CV risk, such as diabetic individuals, mainly because of the lack of evidence supporting recommendations for different types of patients. However, meta-analyses[7,9] and the SPRINT Study[31] have suggested reviewing those recommendations. A meta-analysis[7] of 32 controlled and randomized studies with 104,359 individuals with different initial BP levels (stages 1 to 3) has compared the impact of the BP levels obtained (SBP: < 150 mm Hg, < 140 mm Hg and < 130 mm Hg; and DBP: < 90 mm Hg and < 80 mm Hg) on total and CV mortality and CV outcomes (stroke, CAD and HF). The

Table 1 – Recommendations to begin antihypertensive therapy: lifestyle interventions and pharmacological therapy

Situation	Population (casual measure)	Recommendation	Class	Level of evidence
Beginning of lifestyle interventions	All hypertension stages and BP of 135-139/85-89 mm Hg	At the time of diagnosis	I	A
	Stage 2 and 3 hypertensives	At the time of diagnosis	I	A
	Stage 1 hypertensives and high CV risk	At the time of diagnosis	I	B
Beginning of pharmacological therapy	Elderly hypertensives aged < 80 years	SBP ≥140 mmHg	IIa	B
	Elderly hypertensives aged ≥ 80 years	SBP ≥160 mmHg	IIa	B
	Stage 1 hypertensives and intermediate or low CV risk	Wait 3-6 months for the effect of lifestyle interventions	IIa	B
	Individuals with BP of 130-139/85-89 mm Hg and preexisting CVD or high CV risk	At the time of diagnosis	IIb	B
	Individuals with BP of 130-139/85-89 mm Hg and no preexisting CVD and low or intermediate CV risk	Not recommended	III	-

BP: blood pressure; SBP: systolic blood pressure; CV: cardiovascular; CVD: cardiovascular disease.

Table 2 – Blood pressure targets to be met according to individual characteristics

Category	Target recommended	Class	Level of evidence
Stage 1 and 2 hypertensives with intermediate or low CV risk and stage 3 AH	< 140/90 mm Hg	I	A
Stage 1 and 2 hypertensives with high CV risk	< 130/80 mm Hg*	I	A**

*CV: cardiovascular; AH: arterial hypertension. *For patients with CAD, BP should not be < 120/70 mm Hg, particularly those with DBP < 60 mm Hg, because of the risk of coronary hypoperfusion, myocardial damage and CV events. **For diabetic patients, the class of recommendation is IIb, level of evidence B.*

BP reduction to 140-149 mm Hg (mean, 143.3 mm Hg) as compared to > 150 mm Hg has shown a significant decrease in the risk of total and CV mortality, stroke, CAD and HF. The comparison of the SBP levels obtained of 30-139 mm Hg (mean, 137.2 mm Hg) with values > 140 mm Hg has shown reductions in the risk of total and CV mortality, stroke, CAD, but not of HF. In addition, the comparison of the SBP levels achieved of 120-129 mm Hg (mean, 126.8 mm Hg) with those > 130 mm Hg has revealed a reduction in the risk of total mortality and stroke. The same analysis carried out for DBP revealed that DBP of 80-89 mm Hg (mean, 86.6 mm Hg) as compared to > 90 mm Hg reduced the risk of total and CV mortality, stroke, CAD and HF, while DBP of 70-79 mm Hg (mean, 78.5 mm Hg) as compared to > 80 mm Hg reduced the risk of only stroke. Thus, the BP target < 140/90 mm Hg has unequivocal benefits in reducing the risk of CV mortality and outcomes, and the BP target < 130/80 mm Hg is safe and provides more protection against stroke.

The randomized, controlled clinical trial SPRINT[31] has included 9,361 individuals > 50 years, with SBP of 130-180 mm Hg and high CV risk (risk ≥ 15% within 10 years by the Framingham score, CVD, kidney disease or ≥ 75 years), excluding those with DM, polycystic kidney disease or previous stroke. The study population was randomized for more intense (< 120 mm Hg) and less intense (< 140 mmHg) SBP reduction. The composite primary outcome was the occurrence of AMI or other acute coronary syndrome, stroke, HF and CV death. In the first year, the BP levels achieved were 121.4/68.7 mm Hg and 136.2/76.3 mm Hg, respectively. The early interruption of the study in 3.26 years was due to the benefit demonstrated in the more intense SBP treatment arm, with a 25% reduction in the risk of the study's primary outcome as compared to that of the less intense SBP treatment arm (1.65%/year vs 2.19%/year, HR = 0.75; 95% confidence interval: 0.64-0.89; p < 0.001). In addition, the more intense treatment group had a 27% reduction (HR = 0.73; 95% confidence interval: 0.60-0.90; p = 0.003) in the risk of total mortality. The benefit was demonstrated in pre-specified subgroups. The incidence of adverse events, mainly hypotension, syncope, electrolyte disorders and acute kidney injury, was higher in the group with more intense BP reduction. In individuals ≥ 75 years, the occurrence of adverse events was similar to that in the entire population studied. Despite the greater rate of severe adverse events, the CV benefits and the benefits on mortality overlapped the risks of adverse events.

There is a major controversy regarding diabetic patients. The ACCORD study,[33] including 4,733 diabetic patients, also randomized for SBP reduction < 120 mm Hg and < 140 mm Hg, could not reduce significantly the risk of the study's primary outcome (HR = 0.88; 95% confidence interval: 0.73-1.06; p = 0.20), and, thus, does not support the recommendations for stricter BP targets in that group of patients. In the ACCORD study,[33] the SBP means achieved in the first year of treatment were 119.3 mm Hg and 133.5 mm Hg for the arms of greater and smaller SBP reductions, respectively. In addition, it is worth noting that, even with a small number of events, the more intense treatment arm reduced the risk of stroke by 41% (HR = 0.59; 95% confidence interval: 0.39-0.89; p = 0.01) and had a low incidence of adverse events.

Several differences in the conception of the SPRINT[31] and ACCORD[33] studies indicate the need for caution when interpreting their apparently different conclusions: the number of patients recruited in the ACCORD study was almost half that of the SPRINT study and with a lower mean age. The SPRINT study included older individuals (28% ≥ 75 years) and with CKD. The 2X2 factorial design of the ACCORD study, simultaneously assessing the effect of glycemic control, might have contributed to reduce the statistical power of the population sample, because, in later analyses, the sample restriction to individuals with strict BP control regardless of their serum glucose levels has revealed a 26% risk reduction, in accordance with the SPRINT data.[31] Therefore, the findings suggest that the divergence in the results of the two studies could have been due to differences in study design, interactions between treatments, or to chance. However, specific changes in arteriolar function and blood flow in DM could have influenced the difference between the results of the two studies. Regarding DBP, the HOT study[34] has shown, in diabetic patients, a 51% reduction in the risk of major CV outcomes in the treatment arm aimed at reaching DBP < 80 mm Hg (actual mean achieved: 81 mm Hg) as compared to the treatment arm aimed at reaching DBP < 90 mm Hg.

Based on the results of clinical trials and systematic reviews cited, this guideline chose to recommend a BP target lower than 130/80 mm Hg for patients at high CV risk. Exceptions apply to two situations: 1) for diabetic patients – so far considered as at high risk - that PB target was not supported by the results of the ACCORD study, therefore, the recommendation was defined as GR: IIb; LE: B; 2) for patients with CAD, recent records and cohort studies have shown an increase in fatal and non-fatal CV events,[35] in addition to an increase in troponin[36] when BP levels were < 120/70 mm Hg, especially DBP < 60 mm Hg.[36] Thus, for those patients, BP target should be within a narrower safe range (< 130/80 mm Hg, but not < 120/70 mm Hg).

The BP target of stage 3 hypertensive individuals, despite their high CV risk, should be < 140/90 mm Hg,[7] because there is no scientific evidence supporting greater BP reductions. (GR: I; LE: A).

For elderly hypertensives ≥ 80 years, there is no evidence of benefits deriving from BP levels < 140 mm Hg, in addition to the increased likelihood of adverse effects. The HYVET Study supports the recommendation of BP target < 150/90 mm Hg with a reduction in the risk for stroke and HF.[30] The presence of ISH requires care regarding the excessive reduction in DBP, which should be maintained over 60 mm Hg or even over 65 mm Hg in the presence of CAD.[34] (GR: IIb; LE: B). In the SPRINT Study, the elderly aged ≥ 75 years allocated to the more intense BP treatment arm (mean SBP achieved, 123.4 mm Hg) as compared to the group of standard SBP reduction (mean BP achieved, 134.8 mm Hg) had a 24% reduction in the risk of the study's primary outcome, regardless of the degree of fragility, and no increase in the number of adverse events in relation to the rest of the study population.[37] Thus, the BP targets for the elderly should be defined in the same way they are for other adults; however, BP reduction should be performed carefully and considering the presence of comorbidities and the use of multiple medications.

Table 1 shows the major recommendations for BP targets.

Hypertensives without proper BP control should undergo monthly medical assessments, aimed at reaching the BP target recommended as soon as possible by using sequential therapeutic adjustments. Whenever possible, BP control should be confirmed with outside-the-office BP measurements, by use of either 24-hour ABPM or HBPM. In the elderly and those with significant BP elevations, BP levels should be reduced carefully and progressively, on a case-by-case basis, depending on the patient's general conditions, presence of comorbidities and of concomitant medication.

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Chapter 6 - Non-pharmacological treatment

Introduction

Non-pharmacological treatment (NPT) of AH involves body weight control, nutritional measures, practice of physical activities, smoking cessation and stress control. This chapter approaches the effects and recommendations of such measures.

Body weight

The increase in body weight is directly related to BP increase in adults[1] and children.[2] The relationship between overweight and BP changes can be observed from as early as 8 years of age.[2] In addition, the increase in visceral fat is considered a risk factor for AH.[2,3] Reductions in body weight and AC correlate with BP reductions and metabolic improvement (Table 1).[4] (GR: I; LE: A).

Nutritional aspects

Dietary pattern

The success of AH treatment with nutritional measures depends on the adoption of a healthy and sustainable dietary plan.[5] The use of radical diets results in treatment dropout.[6] The focus on one single nutrient or food has given space to the total dietary pattern analysis, which allows assessing the synergism between nutrients/foods.[7]

The DASH (*Dietary Approaches to Stop Hypertension*) diet emphasizes the consumption of fruits, vegetables and low-fat dairy products, includes the ingestion of whole cereals, chicken, fish and nuts, and recommends a reduction in the ingestion of red meat, candies and sugary beverages. That diet is rich in potassium, calcium, magnesium and fibers, and contains reduced amounts of cholesterol and of total and saturated fat. Adopting that dietary pattern reduces BP.[8,9] (GR: I; LE: A).

The Mediterranean diet is rich in fruits, vegetables and whole cereals, but has large amounts of olive oil (source of monounsaturated fats) and includes the consumption of fish and nuts, in addition to the moderate ingestion of wine.[7] Despite the limited number of studies, the adoption of the Mediterranean diet seems to low BP.[10] (GR: IIa; LE: B).

Vegetarian diets recommend the consumption of foods of plant origin, specially fruits, vegetables, grains and pulses. They exclude or rarely include meats, and some include dairy products, eggs and fish. They have been associated with lower BP levels.[11] (GR: IIa; LE: B).

Reduction in sodium intake

The increase in sodium intake is related to BP elevation.[12] However, the impact of sodium intake on CV health is controversial. Some studies have suggested that very low sodium intake increases the risk for CVD, while others argue that the decrease in sodium intake decreases the CV risk,[13] and that benefit is even higher with marked restriction of sodium intake.[14]

Limiting daily sodium intake to 2.0 g is associated with BP reduction.[15] The Brazilian mean sodium intake is 11.4 g/day.[16] (GR: IIa; LE: B).

Unsaturated fatty acids

Omega-3 fatty acids originating from fish oils (eicosapentaenoic and docosahexaenoic acids, EPA and DHA, respectively) are associated with a mild reduction in BP. Recent studies have indicated that the EPA+DHA ingestion ≥ 2 g/day reduces BP, and lower doses (1-2 g/day) reduce only SBP.[17] (GR: IIa; LE: B).

In addition, the consumption of monounsaturated fatty acids has been associated with BP reduction.[18] (GR: IIb; LE: B).

Fibers

Soluble fibers are present in oat bran, pectin (fruits) and starch (oat, barley and pulses: beans, chickpeas, lentils and green peas), while insoluble fibers are present in cellulose (wheat), hemicellulose (whole grains) and lignin (vegetables). The ingestion of fibers, mainly beta-glucan originating from oat and barley, causes a mild decrease in BP.[19] (GR: IIb; LE: B).

Nuts

The consumption of nuts helps control several CVRF, but few studies have related that consumption to BP reduction.[20] A meta-analysis has concluded that the ingestion of different types of nuts could reduce BP.[21] (GR: IIb; LE: B).

Dairy products and vitamin D

There is evidence that the ingestion of dairy products, especially low-fat ones, reduces BP.[22] Milk contains several components, such as calcium, potassium and bioactive peptides, that can decrease BP.[23] (GR: IIb; LE: B).

Some studies have shown that low serum levels of vitamin D are associated with a greater incidence of AH.[24] However, studies on vitamin D supplementation have failed to show BP reduction.[25] (GR: III; LE: B).

Garlic

Garlic has innumerous bioactive components, such as allicin (found in raw garlic) and s-allyl cysteine (found in processed garlic). Mild BP decrease has been reported with supplementation with several forms of garlic.[26,27] (GR: IIb; LE: B).

Coffee and green tea

Coffee, although rich in caffeine, substance with an acute pressor effect, has polyphenols that can favor BP reduction.[28] Recent studies have suggested that coffee intake at usual doses is associated with neither higher AH incidence nor BP elevation.[29] Coffee intake should not exceed low to moderate amounts. (GR: IIa; LE: B).

In addition to being rich in polyphenols, especially catechins, green tea has caffeine. There is no consensus, but

some studies have suggested that green tea might reduce BP when consumed at low doses, because greater doses have a higher caffeine content and can increase BP.[30] Green tea consumption is recommended at low doses. (GR: IIb; LE: B).

Bitter chocolate

Chocolate at least 70% cacao can cause mild BP reduction, because of its high polyphenol content.[31] (GR: IIb; LE: B).

Alcohol

Usual alcohol consumption increases BP linearly, and its excessive consumption associates with an increase in the AH incidence.[32,33] A 10-g/day increment in alcohol ingestion is estimated to increase BP by 1 mm Hg,[32] and a decrease in that consumption reduces BP.[3] Moderation in alcohol intake is recommended. (GR: I; LE: B).

Physical activity/physical exercise

Physical activity refers to any body movement that increases energy expenditure, such as street walking, stair climbing, domestic chores, and recreational activities. The term 'physical exercise' refers to planned, structured, repetitive and purposeful physical activity. In addition, sedentary lifestyle, measured by the time spent sitting, has CV health implications (Tables 2 and 3).

Physical inactivity/activity

Physical inactivity is "a major public health problem",[37] because it is the most prevalent RF and the second cause of death worldwide.[38] Survival is shorter among individuals who spend most of their time sitting than among those who do not.[39] There is a direct relationship between the time spent sitting or watching TV and BP.[40] To reduce the sitting time and to stand up for at least 5 minutes for every 30 minutes sited are recommended. (GR: IIb; LE: B).

Regular physical activity can benefit both AH prevention and treatment, and reduces CV morbidity and mortality. Active individuals have a 30% lower risk of developing AH as compared to those with a sedentary lifestyle.[41] The increase in daily physical activity reduces BP.[42] Physical activity practice should be encouraged for the entire population, and no previous test is required. The individual should be instructed to seek a doctor if any discomfort occurs during the physical activity practice. (GR: I; LE: A).

Physical exercise

The AH treatment can derive additional benefits from structured physical exercise practice, characterizing a customized training.

Aerobic exercise

Aerobic training reduces casual BP of prehypertensive and hypertensive individuals.[43] In addition, it reduces BP during wakefulness for hypertensives[44] and lowers BP in situations of physical, mental and psychological stress.[45] Aerobic training is recommended as the preferential exercise type for AH prevention and treatment. (GR: I; LE: A).

Dynamic and static resistance exercise

Dynamic or isotonic resistance training (contraction of localized body segments with joint movement) reduces BP of prehypertensive individuals, but has no effect in hypertensives. However, there are only four randomized, controlled studies on that exercise type for AH.[43] Static or isometric resistance training (contraction of localized body segments without joint movement) reduces BP of hypertensives, but the studies have used small muscle masses, thus, further information is required prior to its recommendation.[46] Dynamic resistance training is recommended to complement aerobic training for AH. (GR: IIa; LE: B).

Caution

Hypertensives with higher BP levels or with more than three RF, DM, TOD or heart disease should undergo exercise testing before engaging in moderate-intensity physical exercises. In addition, every hypertensive engaging in competitive sports or high-performance exercise should undergo complete CV assessment.[45] (GR: IIa; LE: C).

Table 1 – Changes in body weight and in dietary ingestion and their effects on BP

Measure	Approximate SBP/DBP reduction	Recommendation
Body weight control	20%-30% BP decrease for every 5% of weight loss[1]	Maintain BMI < 25 kg/m^2 up to 65 years of age. Maintain BMI < 27 kg/m^2 after the age of 65 years. Maintain AC < 80 cm in women and < 94 cm in men
Dietary pattern	Reduction of 6.7/3.5 mm Hg[35]	Adopt DASH diet
Sodium intake restriction	Reduction of 2-7 mm Hg in SBP and 1-3 mm Hg in DBP with progressive reduction of 2.4-1.5 g of sodium/day, respectively[12]	Limit daily sodium intake to 2.0 g (5 g of sodium chloride)
Moderation in alcohol intake	Reduction of 3.31/2.04 mm Hg with the reduction from 3-6 to 1-2 doses/day[34]	Limit daily alcohol intake to 1 dose for women and low-weight individuals, and 2 doses for men

BMI: body mass index; AC: abdominal circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure.
**One dose contains 14g of ethanol, and is equivalent to 350 mL of beer, 150 mL of wine, and 45 mL of distilled beverage.[36]*

Smoking cessation

Smoking increases the risk for more than 25 diseases, including CVD.[47,48] The smoking habit hinders AH control,[49] knowledge about SAH[50] and adherence to antihypertensive medications.[51] However, there is no evidence that smoking cessation reduces BP. (GR: III, LE: B).

Slow breathing

Slow or guided breathing requires respiratory rate reduction to 6-10 breaths/minute for 15-20 minutes/day to promote casual BP reduction (SBP: -3.67; 95% confidence interval: -5.99 to -1.39; and DBP: -2.51; 95% confidence interval: -4.15 to 0.87) after 8 weeks of treatment.[52] (GR: IIa; LE: B).

Stress control

Studies on stress management techniques emphasize the importance of behavioral psychotherapies and meditation,[53-55] biofeedback and relaxation[56] practices in AH treatment. Despite methodological contradictions, clinical indications have revealed a strong trend towards BP reduction when those techniques are performed separately or combined.[56] (GR: IIa; LE: B).

Multiprofessional team

The multiprofessional approach is mainly aimed at AH control, which is not satisfactory in our setting. Epidemiological studies have shown a 10% to 57.6% variation[57] in that control. The multiprofessional team promotes better AH control,[58] which is directly related to adherence to pharmacological and non-pharmacological treatment. The multiprofessional team can consist of all professionals managing hypertensive patients: doctors, nurses, technicians and nurse aides, nutritionists, psychologists, social workers, physical therapists, physical education coaches, music therapists, chemists, educators, media professionals, administrative workers and community health agents.

Table 2 – Evidence of physical activity and physical exercise for BP reduction

Measure	Approximate SBP/DBP reduction
Daily physical activity	3.6/5.4 mm Hg[42]
Aerobic exercise	2.1/1.7 in prehypertensives 8.3/5.2 mm Hg in hypertensives[43]
Dynamic resistance exercise	4.0/3.8 mm Hg in prehypertensives No reduction in hypertensives[43]

Table 3 – Recommendations regarding physical activity and physical exercise

For all hypertensives - Population recommendation – Physical activity practice
Moderate, continuous (1 x 30 min) or cumulative (2 x 15 min or 3 x 10 min) physical activity: at least 30 min/day, 5 - 7 days/week.
For greater benefits - Individual recommendation - Physical exercise
Aerobic training complemented with resistance training
Aerobic training
Several modalities: walking, running, dancing, swimming.
At least 3 times/week. Ideally: 5 times/week.
Minimum of 30 min. Ideally: 40 - 50 min.
Moderate intensity defined as:
1) Higher intensity, but still being able to talk (without being breathless)
2) Feeling mildly to moderately tired
3) Maintain training HR calculated as follows: Training HR = (maximum HR – resting HR) x % + resting HR where: maximum HR: obtained either on a maximum exercise test, using the regular medications, or by calculating maximum HR estimated according to age (220 - age). The formula cannot be applied to hypertensives with heart disease or on beta-blockers or nondihydropyridine calcium channel blockers. Resting HR: measured after 5-minute resting lying down. %: use 50% as lower threshold, and 70% as upper threshold.
Resistance training
2 - 3 times/week.
8 - 10 exercises for the large muscle groups, prioritizing unilateral execution, when possible.
1 - 3 sets
10 - 15 repetitions up to moderate fatigue (reduction in the velocity of movement and tendency towards apnea)
Long passive pauses - 90 - 120 s

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Chapter 7 – Pharmacological Treatment

Objectives

The treatment of AH is ultimately aimed at reducing CV morbidity and mortality.[1-11] Clinical studies of outcome have provided scientific evidence of the benefits of the use of diuretics (DIUs) (GR: I; LE: A),[5,10-15] beta-blockers (BBs) (GR: I; LE: A),[10-13,16] calcium-channel blockers (CCBs) (GR: I; LE: A),[10,11,15,17-23] angiotensin-converting-enzyme inhibitors (ACEIs) (GR: I; LE: A)[10,11,15,17,18,24-26] and angiotensin-receptor blockers (ARBs) (GR: I; LE: A).[10,11,27-33] It is worth noting that most of those studies have used an association of drugs. Based on the information available, the protection observed does not depend on the type of drug used, but mainly on BP reduction.[7,9-11,34] Recent meta-analyses have reported that the benefits obtained from BB are smaller[10,11,35-37] as compared to those provided by the other drug groups, and, thus, BBs should be reserved for specific situations. Regarding alpha-blockers and direct vasodilators, there is no effective information on the outcomes of morbidity and mortality. Regarding direct renin inhibitors, only one study of outcome in diabetic patients has been early interrupted due to lack of benefits and possible harm.[38] The higher the CV risk, the greater the benefits, which occur even for small BP elevations.[3-6,8,9,39]

General principles of the pharmacological treatment

When pharmacological treatment is indicated, the patient should be instructed about the importance of its continuity, the occasional need for dose adjustment and change or association of drugs, and the occasional appearance of adverse effects.

For one medicine to be indicated, it should preferably:

- have shown the ability to reduce CV morbidity and mortality;
- be effective orally;
- be well tolerated;
- be taken the fewest possible times per day;
- be started at the smallest effective doses;
- be able to be used in association;
- be used for at least four weeks, before any change, except for special situations;
- have quality control in its production.

Choice of the medication

All antihypertensive drugs available can be used if specific indications and contraindications are observed (Table 1). The initial preference is always for those with confirmed action in decreasing CV events, being the others reserved for special cases that require the association of multiple drugs to achieve BP targets.

Table 1 – Antihypertensive drugs available

- DIUs (GR: I; LE: A)
- adrenergic inhibitors
- Central action – central alpha-2 agonists (GR: IIb; LE: C)
- BBs – beta adrenergic blockers (GR: I; LE: A)
- Alpha-blockers – alpha-1 adrenergic blockers (GR: IIb; LE: C)
- Direct vasodilators (GR: IIb; LE: C)
- CCBs (GR: I; LE: A)
- ACEIs (GR: I; LE: A)
- ARBs (GR: I; LE: A)
- Direct renin inhibitors (GR: IIb; LE: C)

General characteristics of antihypertensive drugs

Diuretics

The mechanisms of antihypertensive action of DIUs are initially related to their natriuretic effects, with a decrease in the extracellular volume. After 4-6 weeks, the circulating volume normalizes and a reduction in peripheral vascular resistance (PVR) occurs. Diuretics reduce BP and CV morbidity and mortality.[12,14,15] Their antihypertensive effect is not directly related to their doses, but the side effects are.

Thiazide or similar DIUs (chlorthalidone, hydrochlorothiazide and indapamide) at low doses should be preferred, because they are milder and have a longer time of action. Loop DIUs (furosemide and bumetanide) should be reserved for cases of renal failure (creatinine > 2.0 mg/dL or estimated GFR < 30 mL/min/1.73m^2) and edema (HF or renal failure). Potassium-sparing DIUs (spironolactone and amiloride) are usually associated with a thiazide or loop DIU.

Adverse effects

Their major adverse effects are weakness, cramps, hypovolemia and erectile dysfunction. From the metabolic viewpoint, hypopotassemia is the most common, occasionally accompanied by hypomagnesemia, which can induce ventricular arrhythmias, mainly extrasystole. Diuretics can cause glucose intolerance by reducing insulin release, increasing the risk for type 2 DM. Uric acid increase is an almost universal effect of DIUs, of undocumented clinical consequences, except for triggering gout crises in predisposed individuals. The use of low doses decreases the risk for adverse effects, without hindering the antihypertensive efficacy, especially when associated with other drug classes. Spironolactone can cause hyperpotassemia, particularly in patients with impaired renal function.

Central action agents

Alpha-agonists of central action stimulate alpha-2 receptors involved in sympatho-inhibitory mechanisms.[40] Not all alpha-agonists of central action are selective. Their well-defined effects are as follows: a decrease in sympathetic activity and reflex of baroreceptors, contributing to relative bradycardia and postural hypotension; mild decrease in PVR and cardiac output; a reduction in serum levels of renin; and fluid retention.

Some representatives of that group are: methyldopa, clonidine, guanabenz and inhibitors of imidazoline receptors (moxonidine and rilmenidine).[41]

Clonidine can be useful in hypertensive situations associated with: restless legs syndrome,[42] withdrawal of opioids,[43] menopausal hot flushes,[44] diarrhea associated with diabetic neuropathy,[45] and sympathetic hyperactivity of patients with alcoholic cirrosis.[46] These drugs have no unwanted metabolic effect, because they interfere with neither peripheral resistance to insulin nor lipid profile.

Adverse effects

Methyldopa can cause autoimmune reactions, such as fever, hemolytic anemia, galactorrhea and liver dysfunction, which, in most cases, disappear with use cessation. If an adverse reaction occurs, it can be replaced by another central alpha-agonist.[41] Clonidine has a higher risk for the rebound effect with discontinuation, especially when associated with a BB, and can be dangerous in the preoperative period.[40] The drugs in this class have adverse reactions due to their central action, such as drowsiness, sedation, dry mouth, fatigue, postural hypotension, and erectile dysfunction.[40,41]

Beta-blockers

Beta-blockers promote initial decrease in cardiac output and renin secretion, with readaptation of baroreceptors and decrease in catecholamines in nervous synapses.[47,48] In addition to such actions, third-generation drugs (carvedilol, nebivolol) have a vasodilating effect via different mechanisms: carvedilol, via concomitant blockade of alpha-1 adrenergic receptor;[47-50] and nebivolol, by increasing nitric oxide synthesis and release on the vascular endothelium.[47,48,50] Propranolol is useful to patients with essential tremor, hyperkinetic syndromes, vascular headache and portal hypertension.[47,48]

Adverse effects

They consist of bronchospasm, bradycardia, atrioventricular conduction disorders, peripheral vasoconstriction, insomnia, nightmares, psychic depression, asthenia and sexual dysfunction. First- and second-generation BBs are formally contraindicated to patients with bronchial asthma, chronic obstructive pulmonary disease (COPD) and second- and third-degree atrioventricular blocks. They can cause glucose intolerance, induce new cases of DM, and lead to hypertriglyceridemia with LDL-cholesterol elevation and HDL-cholesterol reduction. The impact on glucose metabolism is potentiated when combined with DIUs. Third-generation BBs (carvedilol and nebivolol) have neutral impact or can even improve the glucose and lipid metabolism, possibly because of the vasodilating effect with decrease in insulin resistance and improvement of glucose uptake by peripheral tissues.[47,50] Studies on nebivolol have shown less sexual dysfunction, possibly because of the effect on endothelial nitric oxide synthesis.[47,50]

Alpha-blockers

Alpha-blockers act as competitive antagonists of postsynaptic alpha-1 receptors, leading to a reduction in PVR without major changes in cardiac output.[41] Some representatives of this drug class are doxazosin, prazosin and terazosin. The hypotensive effect is mild in monotherapy, the combined use being preferred. They have a favorable and discrete action on the lipid and glucose metabolisms, especially improving the symptoms related to benign prostate hypertrophy.[41]

Adverse effects

Alpha-blockers can cause symptomatic hypotension on the first dose. The phenomenon of tolerance is frequent, requiring increasing doses. Women can have urine incontinence. There is evidence that patients treated with doxazosin are at higher risk for CHF.[41]

Direct acting vasodilators

Representatives of this drug class are hydralazine and minoxidil. They act directly, relaxing arterial smooth muscle, leading to a PVR reduction.[40]

Adverse effects

The side effects of hydralazine are headache, flushing, reflex tachycardia and lupus-like reaction (dose-dependent).[41] Hydralazine should be used carefully in patients with CAD, and avoided in those with dissecting aortic aneurysm and a recent cerebral hemorrhage episode. In addition, it can cause anorexia, nausea, vomiting and diarrhea. A common side effect of minoxidil is hirsutism, in approximately 80% of the patients. A less common side effect is the general expansion of the circulating volume and reflex tachycardia.

Calcium-channel blockers

Calcium channel blockers cause a reduction in PVR, because of the decreased calcium amount inside arteriolar smooth muscle cells, due to calcium channel blockade in their membranes.[51] They are classified as dihydropyridine and nondihydropyridine CCBs.

Dihydropyridine CCBs (amlodipine, nifedipine, felodipine, nitrendipine, manidipine, lercanidipine, levamlodipine, lacidipine, isradipine, nisoldipine, nimodipine) have mainly a vasodilating effect, with minimum interference in HR and systolic function, being, thus, more often used as antihypertensive agents. Nondihydropyridine CCBs, such as phenylalkylamines (verapamil) and benzothiazepines (diltiazem), have a lower vasodilating effect, can cause bradycardia and have an antiarrhythmic effect, which limit their use to specific cases. Nondihydropyridine CCBs can depress the systolic function, mainly in patients with systolic dysfunction prior to their use, and, thus, should be avoided in that condition. Long-acting CCBs should be preferred to prevent unwanted oscillations in HR and BP. They are effective antihypertensive drugs that reduce CV morbidity and mortality.[52-55] A study of outcome has reassured the efficacy, tolerability and safety of this drug class for the AH treatment of patients with CAD,[56] being an alternative when BBs cannot be used, or even in association, in cases of refractory angina.

Adverse effects

Ankle swelling is usually the most common side effect, resulting from the vasodilating action (more arterial than venous), which causes capillary transudation. Throbbing headache and dizziness are not uncommon. Facial blushing is more common with fast-acting dihydropyridine CCBs. Hyperchromia of the distal third of the legs (ochre dermatitis) and gingival hypertrophy might occur. Such effects can be dose-dependent. Verapamil and diltiazem can worsen HF, bradycardia and atrioventricular block. Constipation is observed with verapamil.[55]

Angiotensin-converting-enzyme inhibitors

Angiotensin-converting-enzyme inhibitors are effective antihypertensive drugs whose major action is inhibition of angiotensin-converting-enzyme, hindering transformation of angiotensin I into angiotensin II, a vasoconstrictor. They are effective to treat AH, reducing CV morbidity and mortality.[57] They are useful in many other CV conditions, such as HF with reduced ejection fraction, post-infarction anti-remodeling, and might have antiatherosclerotic properties. They delay renal function decline in patients with diabetic nephropathy or nephropathy of other etiologies.[58]

Adverse effects

Usually well-tolerated by most hypertensive patients, dry cough is their major side effect, affecting 5-20% of patients. Angioneurotic edema[59] and skin rash are rare. Serum urea and creatinine elevation, usually small and reversible, is a transient phenomenon observed in the initial use of ACEIs in patients with renal failure.[60] In the long run, ACEIs are effective to halt the progression of CKD. They can cause hyperpotassemia in patients with renal failure, mainly those with DM. They can reduce GFR and increase the levels of urea, creatinine and potassium in patients with bilateral stenosis of the renal arteries or renal artery stenosis in a single functioning kidney. They are contraindicated during pegnancy,[61] because of the risk of fetal complicactions.[62] Thus, they should be carefully used and often monitored in adolescents and childbearing-age women.

Angiotensin II AT1 receptor blockers

The ARBs antagonize the action of angiotensin II via the specific blockade of AT1 receptors, responsible for angiotensin II own actions of vasoconstriction, proliferation and stimulation of aldosterone release. In the AH treatment, especially of populations at high CV risk or with comorbidities, ARBs reduce CV and renal (diabetic nephropathy) morbidity and mortality.[27-29,63-66]

Adverse effects

Adverse effects related to ARBs are not common, exanthema being rarely observed. Similarly to ACEIs, ARBs are contraindicated during pregnancy, and the same care should be taken for childbearing-age women.

Direct renin inhibitors

Aliskiren, the only representative of this drug class available for clinical use, causes direct renin inhibition with consequent decrease in angiotensin II production.[67] Other actions might contribute to BP lowering and tissue protection, such as the reduction in renin plasma activity,[67] the blockade of a renin/prorenin receptor,[68] and the decrease in intracellular angiotensin II production.[69] Studies of antihypertensive efficacy have confirmed its ability in monotherapy to lower BP in an intensity similar to that of other antihypertensive drugs.[70] There is, however, no evidence of its benefits on morbidity and mortality.

Adverse effects

They are well tolerated. Skin rash, diarrhea [especially at high doses (> 300 mg/day)], CPK increase, and cough are the most frequent events, whose incidence is usually < 1%. Their use is contraindicated during pregnancy.

The beginning of pharmacological treatment

Pharmacological treatment is indicated for individuals with stage 1 AH and at low and intermediate CV risk, when nonpharmacological measures proved ineffective after an initial period of at least 90 days. In especial situations, in which access and/or return to medical care is difficult, the initial use of antihypertensive drugs, even for that group of patients, might be considered. For individuals with stage 1 AH and at high CV risk or with established CVD, the use of antihypertensive agents should be started immediately. Likewise, for patients with stage 2 and 3 AH, regardless of the CV risk, pharmacological treatment should be started immediately. For prehypertensive individuals, pharmacological treatment might be an option, considering the CV risk and/or presence of CVD. For 60- to 79-year-old patients with SBP ≥ 140 mm Hg and those ≥ 80 years with SBP ≥ 160 mm Hg, pharmacological therapy should begin earlier.

Therapeutic schemes

The pharmacological treatment can be performed with one or more drug classes, as required, to meet the BP targets and according to specific situations (Figure 1).

Monotherapy

Monotherapy can be the initial antihypertensive strategy for stage 1 AH patients at low and intermediate CV risk. However, depending on the BP target to be achieved, most patients will require drug combination. The treatment should be individualized, and the initial choice of drug to be used as monotherapy should be based on the following aspects: ability to lower CV morbidity and mortality; predominant pathophysiological mechanism in the patient to be treated; individual characteristics; associated diseases; and socioeconomic conditions.

Based on those criteria, the classes of antihypertensive drugs currently preferred for BP control in the initial monotherapy are as follows (Figures 1 and 2):

- Thiazide DIUs (preference for chlorthalidone);[5,10-15,39,71,72]
- ACEIs;[7-11,15,17,18,24-26]
- CCBs;[7-11,15,17-23]
- ARBs.[10,11,27-33,73-78]

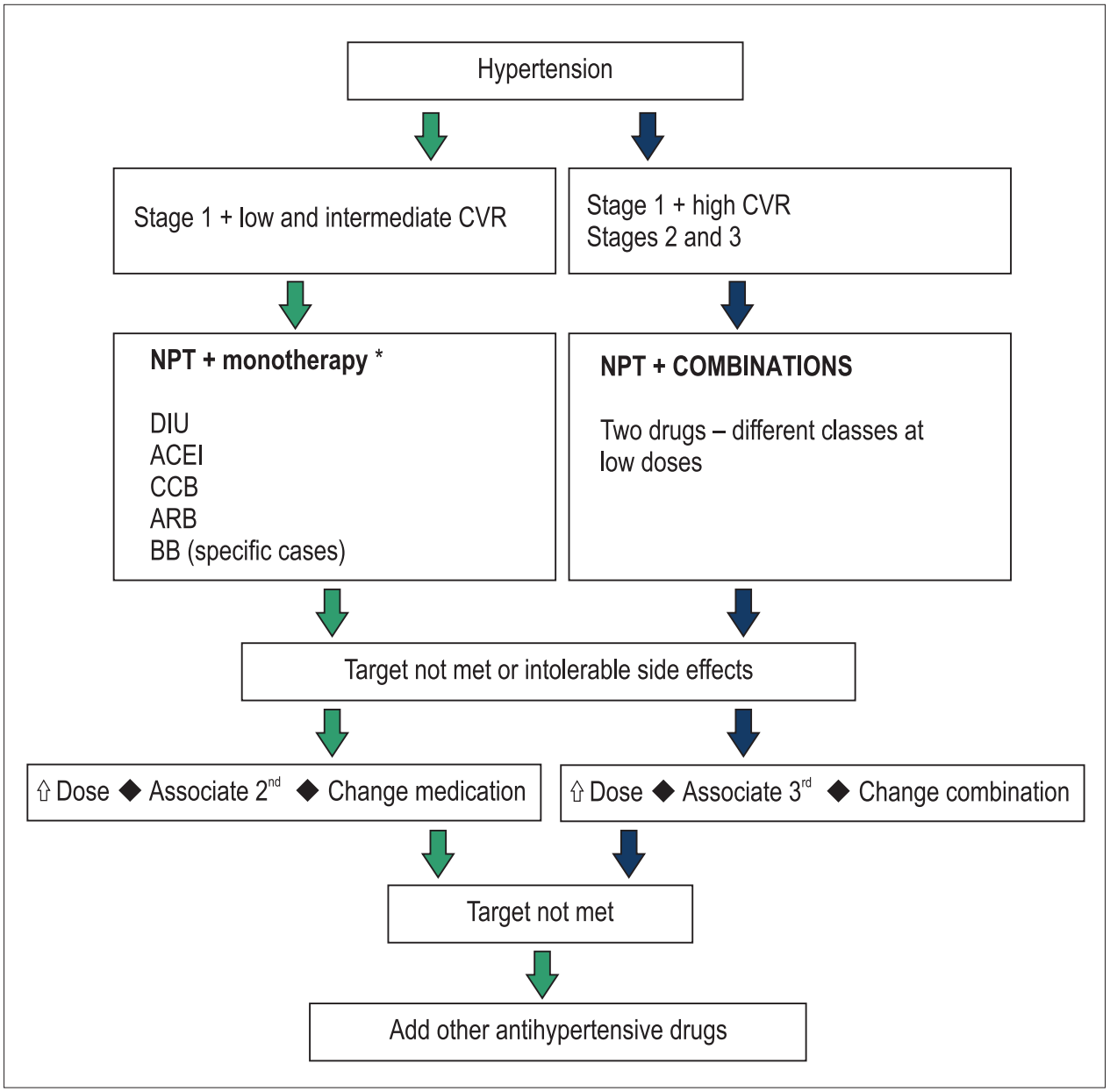

Figure 1 – *Flowchart for the treatment of hypertension. CVR: cardiovascular risk; NPT: non-pharmacological treatment; DIU: diuretics; ACEI: angiotensin-converting-enzyme inhibitors; CCB: calcium-channel blockers; ARB: angiotensin-receptor blockers; BB: beta-blockers.*

It is worth noting that DIUs have the greatest evidence of effectiveness regarding CV outcomes, with clear benefits for all types of events. In some situations, the indication of a certain group is reinforced, depending on the existing comorbidity. A BB can be considered the initial drug in certain situations, such as the presence of supraventricular arrhythmias, migraine, HF and CAD, and, in the last two conditions, the BB should be associated with other drugs.[47,48]

The dosage should be adjusted to provide BP lowering to levels considered adequate for each case (therapeutic targets).[1,2,8,79] If the therapeutic objective is not achieved with the initial monotherapy, there are three possible options:

- If the result is partial, but with no adverse effect, the dose of the drug used should be increased, and association with an antihypertensive drug of another group should be considered;
- When the therapeutic effect expected at the maximum dose recommended is not obtained or in the presence of adverse events, the following is recommended: replace the antihypertensive agent initially used, reduce its dosage, and add another antihypertensive agent of a different class or use another association of drugs;

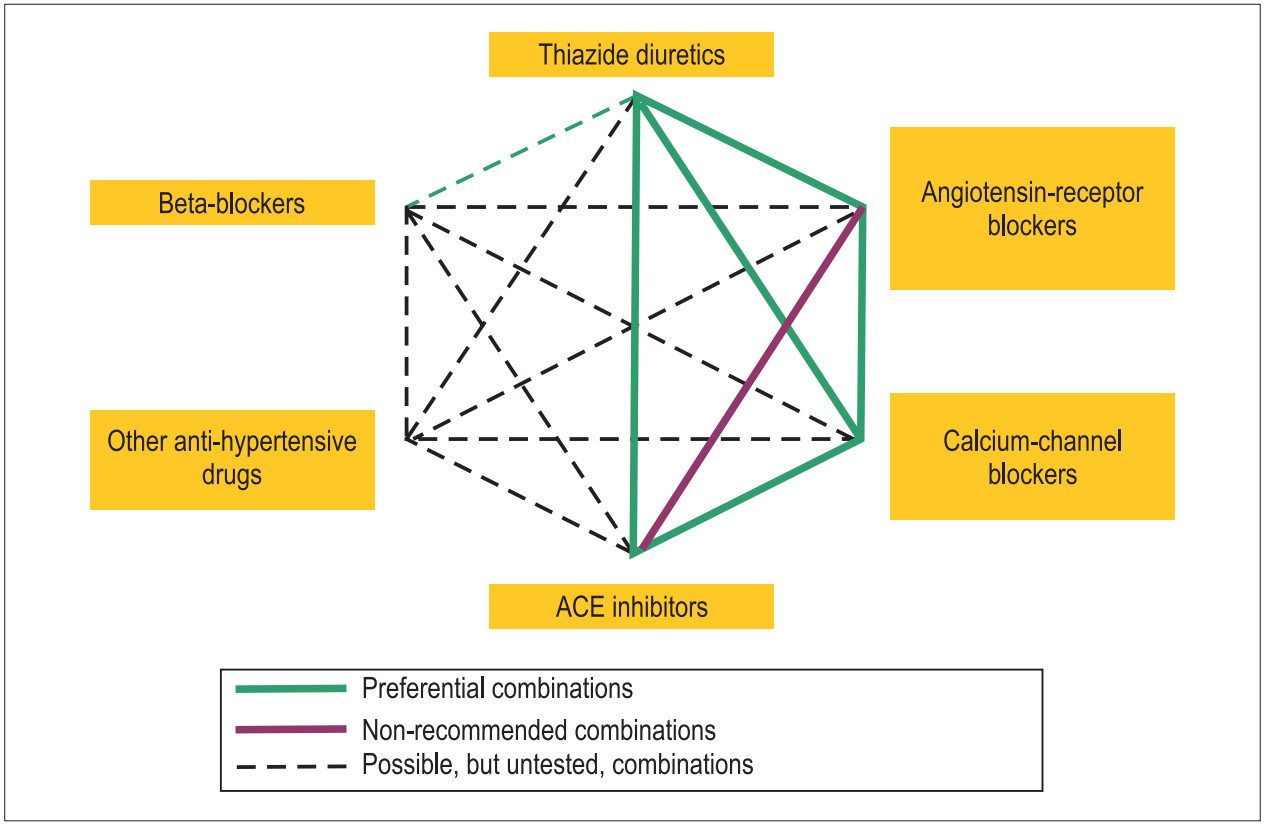

Figure 2 – *Preferential associations of drugs according to mechanisms of action and synergy. Adapted from Journal of Hypertension 2007, 25:1751-1762.*

• If the response is inappropriate, three or more drugs should be associated (Figure 1).

Combination of drugs

Most patients will need more than one drug to achieve BP targets. Therefore, patients with stage 1 AH and at high or very high CV risk or with CVD associated and those with stage 2 or 3 AH with or without other CVRF associated should be considered for drug combination (Figure 1). In addition, the association of two drugs at low doses for stage 1 hypertensive patients, even at low or intermediate CV risk, although not preferential, can be considered.

When choosing the drugs to be combined, antihypertensive agents sharing the same mechanism of action should be avoided, except for the association of thiazide DIUs and potassium-sparing DIUs. Loop DIUs should be reserved for individuals with GFR < 30 mL/min or severe edema. Associations with synergistic action provide better results (Figure 2).[80]

Particularities of the associations

Less tested associations should be reserved for cases requiring a larger number of drugs;

The association of BB and DIU should be performed carefully for patients with glucose metabolism changes, because both drugs contribute to worsen them;

The association of ACEI and ARB is not recommended, because, in addition to showing no benefit in CV outcomes, it increases the risk for adverse effects;[33]

Studies comparing directly the associations are scarce. A study has shown that the combination of ACEI and CCB, as compared to the association of ACEI and DIU, was more effective in lowering CV morbidity and mortality and the progression of kidney disease, for a similar reduction in BP, mainly in non-obese individuals.[81,82]

Combinations can be performed freely with separate drugs or in a fixed association (same galenic formulation). If, on the one hand, free combinations allow us to choose the dose of each component, on the other hand, the use of fixed associations favors adherence to treatment, because of the smaller number of tablets.[83]

If BP control is not attained with two drugs, some decisions can be made:

• in case of partial result and no side effect, the dose of the initial combination can be increased, or one more antihypertensive agent of another drug class can be added;

• when the target is not achieved at the maximum dose recommended, or if adverse events occur, the combination should be replaced;

• if, at maximum doses, BP control is not attained, other antihypertensive drugs should be associated (Figure 1).

If a DIU was not the first choice and is not being used in the association of two drugs, it should be the third drug to be added. Its use potentiates the antihypertensive action of any initial drug.

In cases of resistant AH (lack of BP control with at least three drugs at their maximum doses tolerated, one being a DIU), association of spironolactone is indicated.[84-86] Sympatholytic drugs of central action (clonidine) or BBs can be an alternative to the fourth drug to be added, direct vasodilators being reserved for special cases and in association with a DIU and a BB.

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Chapter 8 - Hypertension and Associated Clinical Conditions

Diabetes mellitus

The association of AH and DM doubles the CV risk and has increased the AH prevalence, which is related to the elevation in overweight and obesity rates, as well as the increase in the elderly population.[1] The incidence of AH in type 1 diabetic patients increases from 5%, at the age of 10 years, to 33%, at the age of 20 years, and to 70%, at the age of 40 years.[2] There is a strict relationship between the development of AH and the presence of albuminuria in that population.[3] That increase in the AH incidence can reach 75-80% in patients with diabetic kidney disease.[4] Approximately 40% of patients with a recent diagnosis of DM have AH.[5] In approximately 50% of type 2 diabetic patients, AH occurs before the development of albuminuria. All diabetic hypertensives are at high CV risk. In addition to all complementary tests recommended for hypertensives, diabetic patients require the search for urine albumin excretion, fundoscopic eye exam and assessment of probable postural hypotension, which can characterize the presence of autonomic nervous system dysfunction.[6]

The BP targets to be achieved are still controversial. However, there is recent consensus on a BP target < 130/80 mm Hg. (GR: IIb; LE: B). For the NPT of AH in diabetic individuals, all recommendations expressed in Chapter 6 apply. The therapeutic choice should be based on drug efficacy and tolerability. Considering that all diabetic patients are at high CV risk, the initial treatment includes the association of at least two drugs of different classes.[7] In diabetic hypertensives without nephropathy, all antihypertensive drugs can be used. In the presence of diabetic nephropathy, however, RAAS inhibitors are preferred.[8] (GR: I; LE: A). Simultaneous use of ACEI and ARB should be avoided because of the risk of complications.[9,10] Although worsening insulin resistance, BB are useful for BP control in diabetic patients, especially when used in combinations to treat hypertensives with CAD or HF.[11]

Metabolic syndrome

Metabolic syndrome (MS) is characterized by the coexistence of CVRFs (low HDL-C, high triglycerides, AH and dysglycemia) either associated or not with central obesity (identified by the AC measure). The definitions of MS differ according to different entities. In 2009, those entities convened a task force to conciliate the different definitions of MS.[12] The criteria are described in Chapter 4 about CV risk stratification. The presence of AH in MS increases global CV risk. The initial treatment is based on lifestyle changes in association or not with the use of drugs. Because nonpharmacological measures isolated do not control BP, pharmacological treatment is required whenever BP ≥ 140/90 mm Hg.[13] There is no evidence of benefit in the use of antihypertensive agents for MS with normal BP levels. When dysglycemia is present, the preferred drugs to begin AH treatment in MS are RAAS blockers and CCB.[13-19]

Coronary artery disease

The treatment of AH associated with CAD, which includes patients after myocardial infarction, with chest angina and myocardial revascularization, should preferably comprise BBs, ACEIs and ARBs, in addition to statins and acetylsalicylic acid. Beta-blockers have proven highly beneficial after AMI, especially within 2 years from the acute event.[20] Similarly, ACEIs tested on that condition have also proven beneficial.[21,22] In patients with chronic CAD and multiple RFs, such as AH, ACEIs have shown a favorable effect to reduce relevant clinical outcomes.[23] (GR: I; LE: A). Regarding BP target, it is worth considering the likelihood of the J curve effect, demonstrated in different studies,[24-27] in which the excessive BP reduction, mainly in DBP, can precipitate CV events in patients with obstructive CAD. Additional drugs to meet target BP (BP < 130/80 mm Hg) are CCBs and thiazide DIUs.[28] (GR: IIa; LE: B).

Stroke

Stroke is the most common manifestation of the vascular damage caused by AH. In transient ischemic attack (TIA), the neurologic deficit is solved in 24 hours, with no clinically detectable sequelae.

Pharmacological treatment of AH in the patient with previous stroke

Chronically, the effective antihypertensive therapy, maintaining BP < 130/80 mm Hg, has played a decisive role in the secondary prevention of all types of stroke and TIA.[29-35] (GR: IIa; LE: B). As long as BP is reduced, any antihypertensive drug can be used.[20,36,37] There is no clinical evidence allowing a definitive conclusion about the preferential use of ARBs as compared to other antihypertensive drugs for the secondary prevention of stroke.[34,35] There is currently no evidence showing the effectiveness of beginning antihypertensive therapy for SBP < 140 mm Hg for patients with a previous stroke. (GR: III; LE: B).

Chronic kidney disease

For patients with that disease, BP reduction is the most effective measure to reduce CV risk and to slow kidney damage progression, regardless of the antihypertensive drug used.[38,39] (GR: I; LE: A). Special attention should be paid to patients with high albuminuria, which determines the unfavorable course of kidney disease[40] and increases CV risk.[41] (GR: IIa; LE: A). Elderly patients with renovascular disease, CAD and risk for postural hypotension often require customization of the antihypertensive treatment.[40] (GR: IIa; LE: C). Usually, BP levels < 130/80 mm Hg are recommended, especially for those with albuminuria > 30 mg/g of creatinine and diabetic patients.[42,43] In such patients, maintaining BP < 130/80 mm Hg reduces albuminuria and the risk for stroke, but there is no evidence that it decreases CV events and mortality.[44,45] (GR: IIa; LE: A). However, it is controversial whether BP reduction to those levels is associated with better CKD course and with a reduction in mortality.[7,46,47] (GE: IIb; LE: B). The present guideline suggests the adoption of BP targets shown in Chart 1.

Chart 1 – Blood pressure targets for patients on conservative treatment, according to kidney disease etiology and albuminuria

	ALBUMINURIA < 30 mg/24 hours	ALBUMINURIA > 30 mg/24 hours
Non-diabetic CKD	< 140/90 mm Hg	< 130/80 mm Hg
Preferential drug	Any	ACEI or ARB
Diabetic CKD	<130/80 mm Hg	<130/80 mm Hg
Preferential drug	Any	ACEI or ARB

CKD: chronic kidney disease; ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-receptor blocker.

Choice of antihypertensive drug: stage 1 to 5 chronic kidney disease on conservative treatment

Thiazide DIUs are recommended, because they are effective in stages 1, 2 and 3 CKD, while loop DIUs are recommended for stages 4 and 5 CKD. That drug class reduces CV morbidity and mortality,[48,49] being considered the choice for association in CKD.[38,49,50] (GR: I; NE: A). The ACEIs and ARBs are widely used for CKD, being effective for AH control and albuminuria reduction.[51-55] (GR: I; LE: A). Regarding direct renin inhibitors and mineralocorticoid receptor antagonists, both with an antiproteinuric action, there is no evidence for their use in clinical practice.[56-58] The risk of hyperpotassemia should be considered, especially with the latter. The double RAAS block is controversial. The combination of ACEI with ARB[59,60] or of a renin inhibitor with ACEI or ARB[10] has resulted in more acute kidney damage and hyperpotassemia, leading to a ban on that strategy from nephrological practice. (GR: I; LE: A). However, in a recent study on adult polycystic kidney disease[61] and a meta-analysis on diabetic patients with CKD,[62] the association of IECA and ARB has delayed the course of nephropathy without causing severe hyperpotassemia and acute kidney damage. (GR: IIb; LE: B). However, the double RAAS block remains contraindicated. (GR: I; LE: A). The CCBs are effective, especially for combined use with ACEI or ARB, being associated with a reduction in CV events.[63,64] Other options include BBs, adrenergic inhibitors of central action, and, occasionally, direct acting vasodilators, such as minoxidil and hydralazine.

Approach to stage 5 chronic kidney disease on kidney replacement therapy

Most studies on AH in patients with CKD undergoing dialysis is based on measuring pre-dialysis BP levels. However, BP obtained in that way is known to have large variability, in addition to being usually overestimated, as it is underestimated when obtained after dialysis.[65,66] In those patients, BP should be preferably measured outside the dialysis centers, in the interdialytic intervals.[67] (GR: IIa; LE: B). Home BP measures are more reproducible than those obtained before and after dialysis, have a fair association with both 44-hour ABPM and CV prognosis in patients undergoing dialysis.[68-70] (GR: IIa; LE: B). In addition, a randomized study has shown that therapeutic decisions based on HBPM associate with better interdialytic BP control assessed with 24-hour ABPM as compared to pre-dialysis BP measurement.[71] Regarding ABPM, it is worth noting that, although the 44-hour long exam is considered gold-standard for assessment of hemodialysis patients, its technical difficulties favor the use of 24-hour ABPM and home BP measurements.

The association between BP and mortality in patients with CKD undergoing dialysis has a "U" distribution for SBP and DBP, thus, both elevated and reduced levels relate to bad prognosis.[70] (GR: IIa; LE: B). There are not enough studies to support with satisfactory level of evidence the diagnosis of AH in patients undergoing dialysis; however, the most accepted pre- and post-hemodialysis BP levels for that purpose are ≥ 140/90 mm Hg and ≥ 130/80 mm Hg, respectively.[70,71] (GR: IIa; LE: C). A study with 326 hemodialysis patients has associated better prognosis with mean SBP levels between 120 and 130 mm Hg, in HBPM, and between 110 and 120 mm Hg, in ABPM.[68] (GR: IIb; LE: B).

Because, in that population, hypervolemia plays a major role in AH etiology, the therapeutic management should consider that variable, focusing the treatment on gradual control of "dry weight", via salt and water restriction, in addition to promoting adequate ultrafiltration during hemodialysis sessions.[71-75] (GR: IIa, LE: B). The choice of antihypertensive drugs should be individualized and based on characteristics, such as comorbidities, and drug's cardioprotective effect, intra- and interdialytic pharmacokinetic characteristics, and side effects.[71,72] (GR: IIa; LE: C).

In kidney-transplanted patients, CCBs are a good option for AH treatment, because they are effective antihypertensive agents that antagonize arteriolar vasoconstriction caused by cyclosporine.[76] The RAAS blockers can improve the transplant outcome in patients with increased urine albumin excretion. Diuretics, BBs, central action sympatholytic drugs and vasodilators can be used based on clinical judgement.[77,78]

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Chapter 9 - Arterial Hypertension in pregnancy

Epidemiology

The hypertensive syndromes of pregnancy cause expressive maternal and fetal morbidity and mortality. There is no accurate information on the incidence of preeclampsia (PE), but it is estimated to affect 4% of gestations. In Brazil, the incidence of PE is 1.5 %, while the incidence of eclampsia is 0.6%.[1] More developed areas have an incidence of eclampsia of 0.2%, with a maternal death rate of 0.8%, while for less favored regions those indices are 8.1% and 22%, respectively.[2] A population-based study shows AH in 7.5% of the gestations in Brazil, with 2.3% of PE and 0.5% of superimposed PE.[3] Arterial hypertension during pregnancy accounts for 20% to 25% of all causes of maternal death, and data from SUS show a trend towards stagnation.[4]

Classification

This guideline recommends the American College of Obstetricians and Gynecologists's (ACOG) classification of hypertension in pregnancy[5] (Chart 1). (GR: IIb; LE: C).

Concept and diagnosis criteria

Arterial hypertension in pregnancy is defined as the presence of SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg, considering the fifth Korotkoff sound, confirmed by another measurement after 4 hours. For BP measurement, the patient should be ideally sitting, or, alternatively, in the lateral decubitus position. Proteinuria is considered: a) protein ≥ 300 mg in 24-hour urine; b) urine albumin/creatinine ratio (UACR) ≥ 0.3 mg/mg in an isolated sample; c) positive reagent strip test in at least two samples (quantification is suggested).

Preeclampsia is defined as the presence of AH after the 20th gestational week, associated with significant proteinuria. In the absence of significant proteinuria, the diagnosis can be based on the presence of: headache, blurred vision, abdominal pain, low blood platelet count (< 100,000/mm^3), elevation of liver enzymes (twice the baseline level), kidney impairment (creatinine > 1.1 mg/dL or twice the baseline level), pulmonary edema, visual or cerebral disorders, scotomas, and seizure. Eclampsia is defined as the presence of grand mal seizure in a pregnant woman with PE.

Chronic AH is defined by the detection of AH prior to pregnancy or before the 20th week of gestation. Preeclampsia might overlap. Gestational hypertension is characterized by AH after the 20th week of gestation without proteinuria.

Chart 1 – Classification of hypertension in pregnancy.

Preeclampsia – Eclampsia
Chronic AH (any etiology)
Chronic AH with overlapping PE
Gestational hypertension

Some clinical conditions increase the risk of PE dramatically. Severe PE should be considered in the presence of: SBP ≥ 160 or DBP ≥ 110 mm Hg; low blood platelet count; TGP twice the baseline level; persistent epigastric or right hypochondrial pain; acute kidney injury (AKI - creatinine > 1.1 mg/dL or twice the baseline level); pulmonary edema; visual or cerebral symptoms.[5]

Preeclampsia prevention

Regarding PE prevention, there is no unequivocally effective strategy for all pregnant women. Calcium supplementation (> 1 g/day) is not recommended for pregnant women with normal intake of that ion[6] (GR: III; LE: A), but to those with low calcium intake and at intermediate and increased risk for PE.[6] (GR: I; LE: A). Low doses of acetylsalicylic acid (75-150 mg/day) at the end of the first gestational trimester can be useful for primary prevention of PE in pregnant women at intermediate and increased risk for PE.[7,8] (GR: IIa; LE: B). That use, however, is not recommended in the absence of risk.[8] (GR: III; LE: A). Calcium supplementation (> 1 g/day) is associated with a reduction in the risk for PE, prematurity and a lower risk of gestational-hypertension-related death, particularly in women with a low-calcium diet (< 600 g).[6] For women at risk for PE, clinical trials have suggested a significant protective effect of the daily acetylsalicylic acid use.[7] Low acetylsalicylic acid doses reduce the risk of PE by 17%, with a decrease in the fetal death risk of 14% and in the prematurity risk of 8%. Daily doses of 75-150 mg seem safe.[8] Acetylsalicylic acid at low doses should be considered for primary prevention of women at high risk and should be initiated at the end of the first trimester.[9]

Nonpharmacological treatment

For persistent AH > 150 mm Hg for more than 15 minutes, NPT alone should not be used to prevent irreversible neurological damage.[10] (GR: III; LE: B). Systolic BP > 155 mm Hg, especially > 160 mm Hg, is detected immediately before stroke.[11] Severe diastolic AH (DAH: > 105 or 110 mm Hg) does not develop before most strokes of pregnant women with severe PE.[11] To avoid maternal deaths, SBP > 150-160 mm Hg should indicate urgent treatment.[12]

Relative rest at hospital or day-hospital with monitoring is suggested for PE. (GR: IIa; LE: B). Hospitalization should be indicated to pregnant patients with severe AH. (GR: I; LE: B). A systematic review has shown no difference in outcomes between strict rest and relative rest for pregnant women with AH and proteinuria. Relative rest at hospital, as compared with routine house activity, reduces the risk for severe AH; however, data do not support a clear recommendation. Rest is not routinely indicated for gestational hypertension.[13] Prenatal care units and hospitals have similar clinical outcomes for mothers and newborns, but women might prefer day-hospitals.[14]

Although there is no indication for specific care during hospitalization, maternal and fetal monitoring is required. Blood pressure should be periodically measured, with daily weight and diuresis assessment, and patients should be instructed about premonitory signs. Laboratory tests, such

as hemogram with platelet count, liver enzymes, uric acid, creatinine and proteinuria, should be performed once to twice a week. Fetal follow-up comprises assessment of growth, movements, well-being and biophysical profile, as well as US.

Expectant management

Expectant management is not recommended after the 36th gestational week for women with gestational hypertension.[15] (GR: III; LE: B). Expectant management is suggested between the 34th and 36th gestational weeks for stable women, without clinical worsening or severe hypertension.[16] (GR: IIa; LE: B). Premature delivery for patients with PE can be associated with decreased mortality. The ideal delivery time, before the 32nd-34th weeks, is a dilemma because of the uncertainty in the balance between maternal safety (end of pregnancy) and fetal maturity (expectant).[17] After the 34th week, survival is high and the baby and placenta delivery is effective in developed countries.[17]

The HYPITAT study has compared delivery induction versus expectant monitoring for severe AH or mild PE after the 36th week.[15] Women in the intervention group had a 29% lower risk of worse maternal outcome, without affecting neonatal outcome, suggesting that expectant treatment after 36 weeks is not indicated.[15] In the HYPTAT-II study, with non-severe AH between the 34th and 37th weeks, expectant management increased maternal risk as compared to immediate delivery, but decreased the occurrence of neonatal respiratory distress syndrome. In that situation, immediate delivery is not justified, and expectant monitoring until the clinical situation worsens should be considered.[16]

Pharmacological treatment

Urgent pharmacological treatment is indicated in severe AH (SBP > 155-160 mm Hg)[10,11] and presence of premonitory signs. (GR: I; LE: B). The treatment of severe AH in emergency situations can be performed with intravenous (IV) hydralazine (5 mg, repeat 5-10 mg IV every 30 minutes until the maximum of 20 mg). In exceptional situations, such as acute pulmonary edema (APE) and refractory severe SAH, the use of sodium nitroprusside (SNP) should be the preferential option for urgent BP control.[18] Oral administration of rapid-acting nifedipine (5 mg every 30 minutes) is an alternative, but associated complications have been reported.[19] Although sublingual nifedipine is not indicated in other forms of hypertensive crisis (HC), it is an alternative in gestational hypertension. Its use for hypertensive emergency (HE), however, has been considered bad practice, harmful to the patient in a report by the São Paulo Regional Medical Board.

Pharmacological treatment should be initiated whenever BP is > 150/100 mm Hg,[12] aiming at maintaining it 130-150/80-100 mm Hg. (GR: IIa; LE: B). For stable patients with PE, not requiring immediate delivery, oral antihypertensive treatment is indicated. Treatment with antihypertensive agents reduces the risk for severe AH, but not the risk for PE, restricted intrauterine growth, placental abruption and neonatal outcomes.[20] Treatment to meet the DBP target of 85 mm Hg as compared to 100 mm Hg showed neither maternal nor obstetric benefit, except for the less frequent occurrence of severe AH in the group with stricter control.[21]

The choice of the antihypertensive drug depends on the attending physician's experience and familiarity with the drug chosen and its possible side effects.[22] (GR: IIb; LE: B). The use of ACEIs, ARBs and direct renin inhibitors is contraindicated in pregnancy (GR: I; LE: B), and atenolol and prazosin should be avoided.[22,23] (GR: IIa; LE: B). In Brazil, the available oral drugs usually used are methyldopa, BBs (except atenolol), hydralazine and CCBs (nifedipine, amlodipine and verapamil). Atenolol is associated with a reduction in fetal growth, and prazosin can cause natimortality.[24-26] For PE, the prescription of a DIU is usually avoided; thiazide DIUs, however, can be continued in pregnant women with chronic AH (CAH),[27] as long as they do not cause volume depletion.

Magnesium sulfate is recommended for eclampsia prevention and treatment. (GR: I; LE: B). In case of HE or of hypertensive urgency (HU) requiring hospitalization, intensive monitoring, preterm delivery and parenteral administration of antihypertensive drugs, the IV administration of magnesium sulfate, considered the drug of choice to prevent and treat eclampsia, is recommended.[5,28-30] Magnesium sulfate is administered at an attack dose of 4-6 g IV for 10-20 minutes, followed by infusion of 1-3 g/h, usually for 24 hours. If the seizure reoccurs, 2-4 g can be administered IV. Deep intramuscular administration of 10 g (5 g in each gluteus), followed by intramuscular 5 g every 4 hours for 24 hours is an alternative. Magnesium sulfate is indicated during labor for patients with severe PE. Magnesium sulfate administration should continue for up to 24 hours after seizure, imminent eclampsia signs and delivery. Its administration should be generous to patients with PE, preferably before the administration of rapid-acting antihypertensive drugs to patients, in whom the possibility of eclampsia cannot be ruled out.

Other important aspects

Severe AH, per se, is not an indication for C section. In the presence of stable maternal clinical findings, good fetal vitality and lack of other C section indications, pregnancy termination can occur by delivery induction, always considering maternal clinical condition and fetal vitality during the procedure.[5,29] Labor analgesia is recommended with local-regional techniques (peridural or combined analgesia). Severe thrombocytopenia contraindicates anesthesia with lumbar puncture, and, if C section is required, it should be performed under general anesthesia. Invasive central monitoring is reserved to cases with hemodynamic instability (respiratory failure, disseminated intravascular coagulation related to placental abruption, or HELLP syndrome).[5]

Antihypertensive treatment in lactating women

Chart 2 shows the antihypertensive drugs available in Brazil considered safe, moderately safe and not recommended.[31,32] (GR: IIb, LE: C).

Chart 2 – Safety of the infant breastfed by a lactating woman on antihypertensive drugs.

Drugs	Recommendation
DIUs: hydrochlorothiazide and spironolactone. Adrenergic inhibitors: alpha-methyldopa and propranolol. Vasodilators: hydralazine and minoxidil. CCBs: verapamil, nifedipine, nimodipine and nitrendipine. ACEIs: benazepril, captopril and enalapril.	Safe
DIUs: indapamide, furosemide and triamterene. Adrenergic inhibitors: atenolol, bisoprolol, carvedilol, metoprolol, sotalol. CCBs: amlodipine, isradipine, nisoldipine. ACEIs: lisinopril, ramipril. ARBs: candesartan and olmesartan. Telmisartan after the perinatal period.	Moderately safe
Adrenergic inhibitors: reserpine, prazosin and terazosin. ARBs: telmisartan, in the perinatal period; valsartan.	Potentially harmful

DIUs: diuretics; CCBs: calcium-channel blockers; ACEIs: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin-receptor blockers.

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Chapter 10 - Hypertension in Children and Adolescents

Epidemiological context and importance of hypertension in pediatrics

Arterial hypertension was identified as the major source of combined mortality and morbidity, representing 7% of global disability-adjusted life years.[1] The adoption of the BP definitions and normalization of the "National High Blood Pressure Education Program" (NHBPEP) 2004[2] has standardized the BP classification in the pediatric population. The percentage of children and adolescents diagnosed with AH is estimated to have doubled in the past two decades. The current prevalence of AH in the pediatric population is around 3% to 5%,[3-5] while that of PH reaches 10% to 15%,[3,4,6,7] and such values are mainly attributed to the large increase in childhood obesity.[8] The etiology of pediatric AH can be either secondary, most often associated with nephropathies, or primary, attributed to genetic causes with environmental influence, predominating in adolescents.

Pediatric AH is usually asymptomatic, but as many as 40% of hypertensive children have LVH at the initial diagnosis of AH. Although oligosymptomatic in childhood, LVH is a precursor of arrhythmias and HF in adults.[9] In addition, pediatric AH is associated with the development of other changes in target organs, such as increased carotid IMT, arterial compliance reduction, and retinal arteriolar narrowing. Early diagnosis and treatment of childhood AH are associated with a lower risk for AH and for increased carotid atheromatosis in adult life.[10] Therefore, periodical BP measurements in children and adolescents are recommended, even contradicting the U.S. Preventive Services Task Force's suggestion, which considers the evidence of benefits of primary AH screening in asymptomatic children and adolescents insufficient to prevent CVD in childhood or adulthood.[11]

Definitions and diagnosis

Definition and etiology

Children and adolescents are considered hypertensive when SBP and/or DBP are greater than or equal to the 95th percentile for age, sex and height percentile, on at least three different occasions.[2] Prehypertension in children is defined as SBP/DBP ≥ the 90th percentile < the 95th percentile, and in adolescents as BP levels ≥ 120/80 mm Hg and < the 95th percentile. Stage 1 AH is considered for readings between the 95th percentile and the 99th percentile plus 5 mm Hg, while stage 2 AH, for readings > stage 1. The height percentiles can be obtained by using Centers for Disease Control and Prevention's (CDC) growth charts.[12] In addition, normal and high BP levels for children and adolescents are available in mobile apps, such as PA Kids and Ped(z).

In the pediatric population, WCH and MH can be diagnosed based on established normality criteria for ABPM.[13]

After a detailed clinical history and physical examination, children and adolescents considered hypertensive should undergo investigation. The younger the child, the greater the chance of secondary AH. Parenchymal, renovascular and obstructive nephropathies account for approximately 60-90% of the cases, and can affect all age groups (infants, children and adolescents), being more prevalent in younger children with higher BP elevations. Endocrine disorders, such as excessive mineralocorticoid, corticoid or catecholamine secretion, thyroid diseases and hypercalcemia associated with hyperparathyroidism, account for approximately 5% of secondary AH cases. Coarctation of the aorta is diagnosed in 2% of the cases, and 5% of secondary AH cases are attributed to other etiologies, such as adverse effects of vasoactive and immunosuppressive drugs, steroid abuse, central nervous system changes, and increased intracranial pressure.

Primary AH is more prevalent in overweight or obese children and adolescents with family history of AH. Currently, primary AH seems to be the most common form of AH in adolescence, being, however, a diagnosis of exclusion, and, in that population, secondary causes should be investigated whenever possible.

Diagnosis

Method for BP measurement

Measuring BP in children is recommended at every clinical assessment after the age of 3 years, abiding by the standards for BP measurement.[2] Children under the age of 3 years should have their BP assessed on specific situations.[2,14] For BP measurement, children should be calm and sitting for at least 5 minutes, with back supported and feet on the floor, having refrained from consuming stimulant foods and beverages. The BP should be taken at heart level on the right arm, because of the possibility of coarctation of the aorta. Table 1 shows the specific recommendations for auscultatory BP measurement in children and adolescents. Whenever BP is high on the upper limbs, SBP should be assessed on the lower limbs. Such assessment can be performed with the patient lying down, with the cuff placed on the calf, covering at least two-thirds of the knee-ankle distance. The SBP reading on the leg can be higher than that on the arm because of the distal pulse amplification phenomenon. A lower SBP reading on the leg as compared to that on the arm suggests coarctation of the aorta.

Tables 2 and 3 show the BP percentiles by sex, age and height percentile. Figures 1 and 2 show BP values for boys and girls, respectively, from birth to the age of 1 year based on data from the Report of the Second Task Force on Blood Pressure Control in Children - 1987.[15]

Note: Adolescents with BP ≥ 120/80 mm Hg should be considered prehypertensive, even if the 90th percentile value is greater than that. This can occur for SBP in patients older than 12 years, and for DBP in patients older than 16 years.

For children/adolescents, ABPM is indicated to investigate WCH and MH, and to follow prehypertensive

Table 1 – Specific recommendations for BP measurement in children and adolescents

- Auscultatory method.
- Use 1st Korotkoff sound for SBP, and 5th Korotkoff sound for DBP.
- When using the oscillometric device, it requires validation.
- Detection of AH by use of the oscillometric device requires confirmation with auscultation.
- Use appropriate cuff size; air bag width: 40% of arm circumference in the middle point between the acromion and olecranon, and air bag length: 80-100% of arm circumference.
- Conditions under which children < 3 years old should have BP measured: neonatal intensive care; congenital heart diseases, kidney diseases, treatment with drugs known to raise BP, and evidence of increased intracranial pressure.

or hypertensive patients up.[13] The prevalence of WCH has been reported as between 22% and 32%. The use of ABPM should be restricted to patients with borderline or mild AH, because patients with high office BP readings are more likely to be hypertensive.[16]

Anamnesis

A careful recollection of data on birth, growth and development, personal antecedents, and renal, urological, endocrine, cardiac and neurological diseases should be performed. The following patterns should be characterized: physical activity; dietary intake; smoking habit and alcohol consumption; use of steroids, amphetamines, sympathomimetic drugs, tricyclic antidepressants, contraceptives and illicit substances; and sleep history, because sleep disorders are associated with AH, overweight and obesity. In addition, family antecedents for AH, kidney diseases and other CVRF should be carefully assessed.

Physical examination

On physical examination, BMI should be calculated.[17] Growth delay might suggest chronic disease, and persistent tachycardia might suggest hyperthyroidism or pheochromocytoma. Pulse decrease on the lower limbs leads to the suspicion of coarctation of the aorta. Adenoid hypertrophy is associated with sleep disorders. *Acantosis nigricans* suggests insulin resistance and DM. Abdominal fremitus and murmurs can indicate renovascular disease.[18]

Complementary tests

Laboratory and imaging tests are aimed at defining the etiology of AH (primary or secondary) and detecting TOD and CVRF associated with AH (Tables 4 and 5).[2,14]

Target-organ assessment should be performed in all children and adolescents with stage 1 and 2 AH. Sleep study by use of polysomnography or home respiratory polygraphy is indicated for children and adolescents with sleep disorders detected on anamnesis.[2] To investigate secondary AH, see Chapter 12.

Table 5 shows some tests for children and adolescents suspected of having secondary AH.

Therapeutic aspects

In children and adolescents with confirmed AH, therapeutic management is guided by the AH etiology definition, CV risk assessment, and TOD characterization.

Nonpharmacological management

Nonpharmacological management should be introduced to all pediatric patients with BP levels above the 90th percentile.[2] (GR: IIa; LE: C). It includes body weight loss, a physical exercise program, and dietary intervention.[2] Body weight reduction yields good results in the treatment of obese hypertensive children,[19] similarly to physical exercise, which has better effect on SBP levels.[19] Regular aerobic activity is recommended as follows: moderate-intensity physical exercise, 30-60 minutes/day, if possible, every day. Children with AH can practice resistance or localized training, except for weight lifting. Competitive sports are not recommended for patients with uncontrolled stage 2 AH.[20] Dietary intervention can comprise sodium restriction,[21] and potassium and calcium supplementation; the efficacy in that population, however, is yet to be proven.[22]

Pharmacological management

Pharmacological therapy should be initiated for children with symptomatic AH, secondary AH, presence of TOD, types 1 and 2 DM, CKD and persistent AH nonresponsive to nonpharmacological therapy.[2] (GR: IIa; LE: B). The treatment is aimed at BP reduction below the 95th percentile in non-complicated AH, and BP reduction below the 90th percentile in both complicated AH, characterized by TOD and comorbidities (DM, CKD), and secondary AH.[2] (GR: IIa; LE: C). The treatment should begin with a first-line antihypertensive agent, whose dose should be optimized, and, if target BP level is not attained, other pharmacological groups should be added in sequence. A recent systematic review[23] has identified neither a randomized study assessing the efficacy of antihypertensive drugs on TOD, nor any consistent dose-response relationship with any drug class assessed.

The adverse events associated with the use of antihypertensive agents for children and adolescents have been usually of mild intensity, such as headache, dizziness, and upper respiratory tract infections. All classes of antihypertensive drugs seem safe, at least in the short run.[23] The only randomized, double-blind, controlled study, by Schaefer et al., comparing the efficacy and safety of drugs of parallel groups and assessing hypertensive children on enalapril or valsartan, has shown comparable results regarding the efficacy and safety of both drugs.[24]

In secondary AH, the antihypertensive drug choice should be in consonance with the pathophysiological

Table 2 – Blood pressure levels for boys by age and height percentile[2]

	BP	SBP (mm Hg)							DBP (mm Hg)						
Age	percentile	← Percentile of Height →							← Percentile of Height →						
(Year)		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	-103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

BP		SBP (mm Hg)							DBP (mm Hg)						
Age	percentile	← Percentile of Height →							← Percentile of Height →						
(Year)		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	J17	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

principle involved, considering the comorbidities present. For example, non-cardioselective BBs should be avoided in individuals with upper airway reactivity, because of the risk for bronchospasm.[25] In pregnancy, ACEIs and ARBs are contraindicated, because of their potential for fetal malformation.[26] The use of those drugs for childbearing-age girls should be always accompanied by contraceptive guidance.[26,27]

For renovascular AH, of ACEIs or ARBs are indicated in association with vasodilators and DIUs. In cases of coarctation of the aorta, in the preoperative period, the initial drug is usually a BB. If the AH persists postoperatively, the BB can be maintained, replaced or associated with an ACEI or ARB. For AH associated with DM and CKD, an ACEI or ARB is initially used. The use of ACEI and ARB relaxes the efferent arteriole, reducing the glomerular capillary hydrostatic pressure, and posing a risk for AKI in situations of hypovolemia. Similarly, those drugs are contraindicated for patients with bilateral renal artery stenosis.[26-29] For obese adults, ACEIs, ARBs, CCBs, BBs and DIUs are effective in reducing BP.[30] In adults, ACEIs and ARBs seem to reduce the risk of developing DM and to increase insulin sensitivity.[31-33]

Table 6 shows the updated pediatric doses of the most frequently prescribed hypotensive agents to treat CAH.[2,27,28]

Hypertensive crisis

Hypertensive emergency is characterized by acute BP elevation associated with TOD, which can comprise neurological, renal, ocular and hepatic impairment or myocardial failure, and manifests as encephalopathy,

Table 3 – Blood pressure levels for girls by age and height percentile[2]

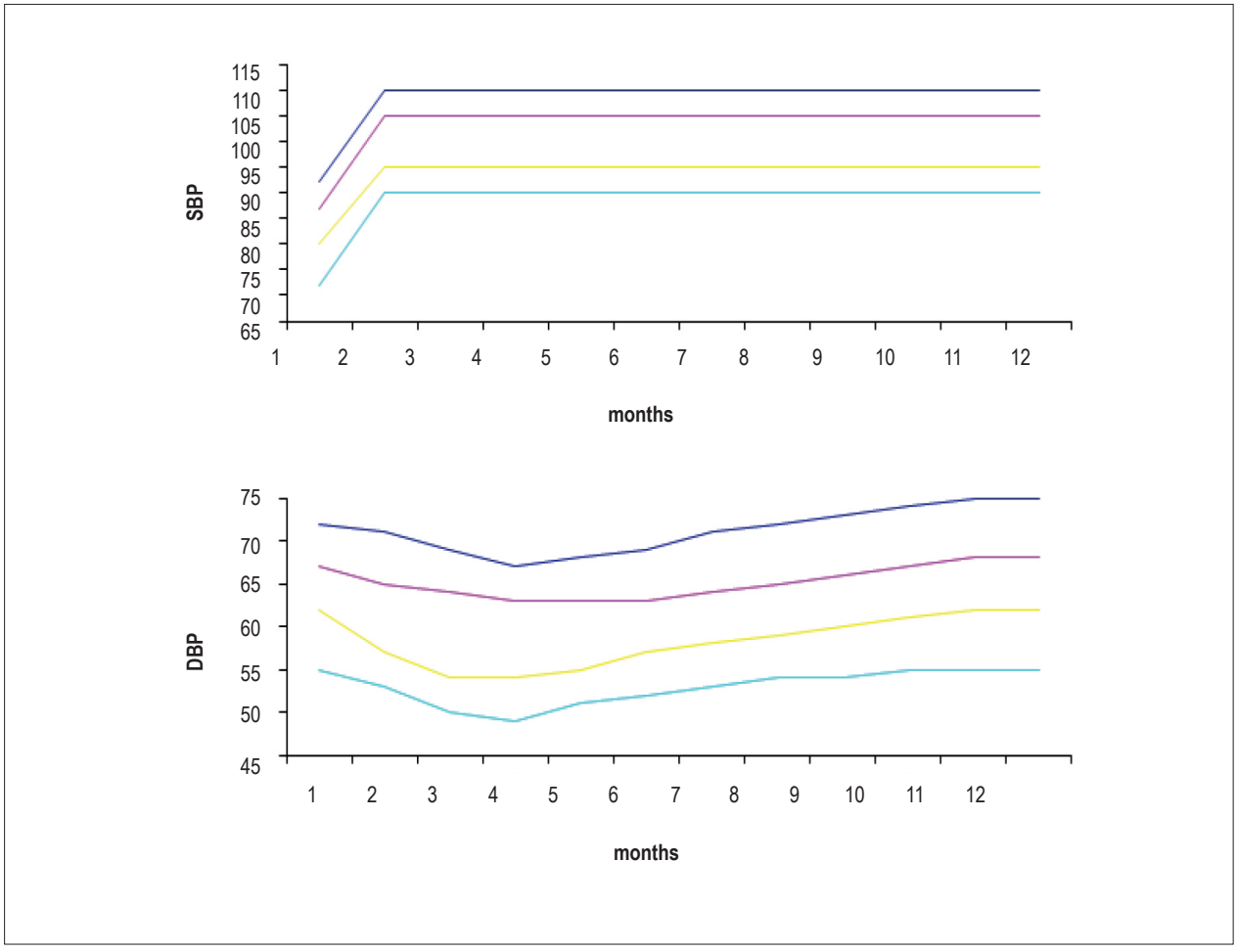
	BP	SBP (mm Hg)							DBP (mm Hg)						
Age	Percentile	← Percentile of Height →							← Percentile of Height →						
(Year)		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

BP		SBP (mm Hg)							DBP (mm Hg)						
Age	Percentile	← Percentile of Height →							← Percentile of Height →						
(Year)		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119 -121		122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

convulsions, visual changes, abnormal electrocardiographic or echocardiographic findings, and renal or hepatic failure.[34] Hypertensive urgency is described as BP elevation above the 99th percentile plus 5 mm Hg (stage 2), associated with less severe symptoms, in a patient at risk for progressive TOD, with no evidence of recent impairment. Oral drugs are suggested, under monitoring, with BP reduction in 24-48 hours.[2] In HE, the BP reduction should occur slowly and progressively: 30% reduction in the programed amount in 6-12 hours, 30% in 24 hours, and final adjustment in 2-4 days.[35] Very rapid BP reduction is contraindicated, because it leads to hypotension, failure of self-regulating mechanisms, and likelihood of cerebral and visceral ischemia.[36] The HE should be treated exclusively with parenteral drugs. In Brazil, the most frequently used drug for that purpose is SNP, which is metabolized into cyanide, which can cause metabolic acidosis, mental confusion, and clinical deterioration. Thus, SNP administration for more than 24 hours requires monitoring of serum cyanide levels, especially in patients with renal failure.[35,36] After patient's stabilization with SNP, an oral antihypertensive agent should be initiated, so that the SNP dose can be reduced. The use of SNP should be avoided in pregnant adolescents and patients with central nervous system hypoperfusion.

Special clinical conditions can be managed with more specific hypotensive agents for the underlying disease. Patients with catecholamine-producing tumors can be initially alpha-blocked with phenoxybenzamine, or prazosin if the former is not available, followed by the careful addition of a BB. After BP control and in the absence of kidney or heart dysfunction, a sodium-rich diet

Figure 1 – Blood pressure levels for boys, from birth to the age of 1 year[97]



90th percentile

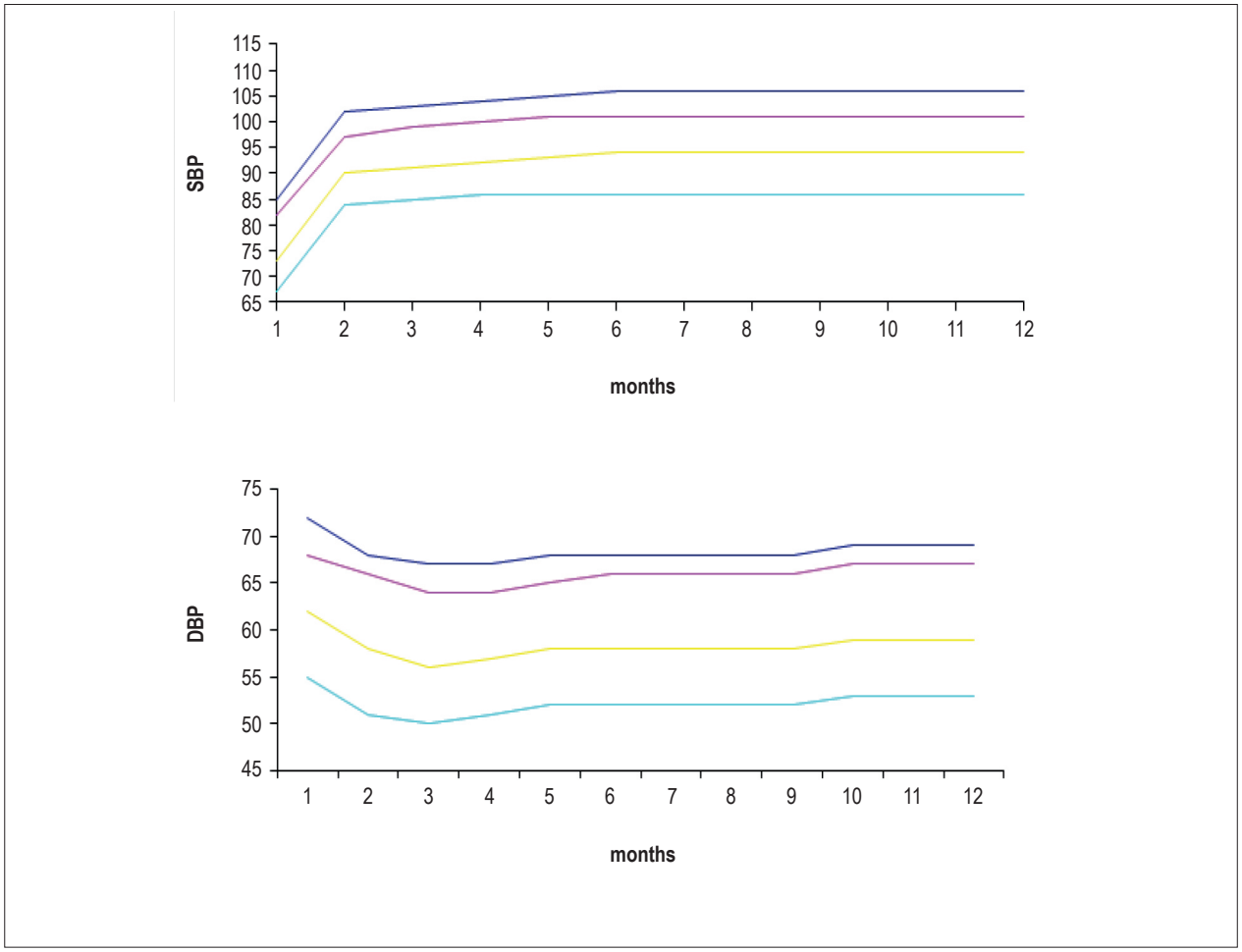
SBP	87	101	106	106	106	106	106	106	106	106	106	106	106
DBP	68	66	63	63	63	66	66	67	68	68	69	69	69
Height (cm)	51	59	63	66	68	70	72	73	74	76	77	78	80
Weight (kg)	4	4	5	5	6	7	8	9	9	10	10	11	11

Source: *Report of the Second Task Force on Blood Pressure Control in Children - 1987. Task Force on Blood Pressure Control in Children. National Heart, Lung and Blood Institute, Bethesda, Maryland. Pediatrics 1987;79(1):1-25.*

is suggested to expand blood volume, usually reduced by the excess of catecholamines, favoring postoperative BP management and reducing the chance of hypotension. An IV short-acting antihypertensive drug should be used for intraoperative BP control. Furosemide is the first-choice drug for HC caused by fluid overload, for example, in patients with kidney disease, such as acute glomerulonephritis. In case of oliguria/anuria, other antihypertensive drugs can be used concomitantly, and dialysis might be necessary for blood volume control. Arterial hypertension associated with the use of cocaine or amphetamines can be treated with lorazepam or other benzodiazepine, which is usually effective to control restlessness and AH. In the presence of a HE, phentolamine, if available, is the drug of choice, and should be used in combination with lorazepam.[37]

Table 7 shows the most frequently used drugs in pediatric HE.[38,39]

Figure 2 – Blood pressure levels for girls, from birth to the age of 1 year[97]



90th percentile

SBP	76	96	101	104	105	106	106	106	106	106	106	106	106
DBP	68	66	64	64	65	66	66	66	66	67	67	67	67
Height (cm)	54	56	56	56	61	63	66	68	70	72	74	75	77
Weight (kg)	4	4	4	5	5	6	7	8	9	9	10	10	11

Source: *Report of the Second Task Force on Blood Pressure Control in Children - 1987. Task Force on Blood Pressure Control in Children. National Heart, Lung and Blood Institute, Bethesda, Maryland. Pediatrics 1987;79(1):1-25.*

Table 4 – Initial investigation of children and adolescents with AH

Complete blood count
Renal function and electrolytes (including calcium, phosphorus and magnesium)
Fasting lipid panel
Plasma uric acid levels
Fasting glucose
Urinalysis and urine culture
Retinal exam
Chest X ray
ECG / Doppler echocardiography
Renal US with Doppler of renal arteries

Table 5 – Complementary tests to confirm the etiology of secondary AH in children and adolescents

Measurement of urine electrolytes, proteinuria and urine creatinine
Plasma levels of renin (or plasma renin activity) and aldosterone, salivary cortisol test, PTH, TSH, free T4 and T3
Hemoglobin electrophoresis
Specific auto-antibodies: FAN, anti DNA, ANCA p, ANCA c
Urine catecholamines and metanephrines (or plasma metanephrine) and MIBG scintigraphy

MIBG: metaiodobenzylguanidine

Table 6 – Most frequently used oral drugs for management of pediatric chronic arterial hypertension2

Drug	Initial dose (mg/kg/dose)	Maximum dose (mg/kg/day)	Interval
Amlodipine (6-17 years)	0.1	0.5	24h
Nifedipine XL	0.25-0.5	3 (max:120 mg/day)	12-24h
Captopril			
Children	0.3-0.5	6	8h
Neonate	0.03-0.15	2	8-24h
Enalapril	0.08	0.6	12-24h
Losartan	0.7 (max: 50 mg/day)	1.4 (max: 100 mg/day)	24h
Propranolol	1-2	4 (max: 640 mg/day)	8-12h
Atenolol	0.5-1	2 (max: 100 mg/day)	12-24h
Furosemide	0.5-2	6	4-12h
Hydrochlorothiazide	1	3 (max: 50 mg/day)	12h
Spironolactone	1	3.3 (max: 100 mg/day)	6-12h
Clonidine (≥12 years)	0.2 mg/day	2.4 mg/day	12h
Prazosin	0.05-0.1	0.5	8h
Hydralazine	0.75	7.5 (max: 200 mg/day)	6h
Minoxidil < 12 years ≥ 12 years	 0.2 5 mg/day	 50 mg/day 100 mg/day	6-8h

max: maximum; h: hour.

Table 7 – Major pediatric drugs and doses used to control hypertensive emergency[2,95,96]

Drug	Route	Dose	Action beginning	Duration
Sodium nitroprusside	IV	0.5-10 µg/kg/min	Seconds	Only during infusion
Labetalol	IV	0.25-3 mg/kg/h or Bolus: 0.2-1 mg/kg followed by infusion: 0.25-3 mg/kg/h	2-5 min	2-4 h
Nicardipine	IV	1-3 µg/kg/min	2-5 min	30 min-4 h, the greater, the longer the use
Hydralazine	IV IM	Bolus: 0.2-0.6 mg/kg IV, IM, max = 20 mg	10-30 min	4-12 h
Esmolol	IV	Attack: 100-500 µg/kg followed by infusion: 50-300 µg/kg/min	Seconds	10-30 min
Phentolamine	IV	Bolus: 0.05-0.1 mg/kg, max = 5 mg/dose	Seconds	15-30 min

IV: intravenous; IM: intramuscular; min: minute; h: hour.

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Chapter 11 - Arterial Hypertension in the elderly

Arterial hypertension is the most common chronic noncommunicable disease among the elderly.[1] Its prevalence increases progressively with aging, AH being considered the major modifiable CVRF in the geriatric population.[2] From the chronological viewpoint, elderly are individuals aged 65 years and older, living in developed countries, or individuals aged 60 years and older, living in developing countries.[3] Within that age group, the very elderly are those in their eighth decade of life.[4]

There is a direct and linear relationship between BP and age, the prevalence of AH being greater than 60% in the age group older than 65 years.[5] The Framingham Study has reported that 90% of the individuals with normal BP levels up to the age of 55 years will develop AH throughout life.[6] In addition, that study has shown that both SBP and DBP, in both sexes, increase up to the age of 60 years, when DBP begins to decrease. Systolic BP, however, continues to increase linearly.[7] The high prevalence of other concomitant RFs in the elderly and the consequent increase in the rate of CV events, in addition to the presence of comorbidities, compound the relevance of AH with aging.[8]

Vascular aging is the major aspect related to BP elevation in the elderly, characterized by changes in the microarchitecture of vascular walls, with consequent arterial stiffening. Large vessels, such as the aorta, lose their distensibility, and, although the precise mechanisms are not clear, they primarily involve structural changes in the media layer of the vessels, such as fracture due to elastin fatigue, collagen deposition and calcification, resulting in increased vascular diameter and IMT. Clinically, arterial wall stiffness is expressed as ISH, highly prevalent in the geriatric population, and considered an independent RF for the increase in CV morbidity and mortality.[6,9-11] Other consequences are increased PWV and elevated PP.[12]

Changes inherent in aging determine different aspects in that population's BP, such as the higher frequency of auscultatory gap, which consists in the disappearance of the Korotkoff sounds during cuff deflation, usually between the end of phase I and beginning of phase II, resulting in falsely low SBP levels or falsely high DBP levels.

The wide BP variability in the elderly throughout 24 hours makes ABPM useful. Pseudohypertension, which is associated with the atherosclerotic process, can be detected by use of Osler's maneuver, that is, the radial artery remains palpable after cuff inflation at least 30 mm Hg above the reading of radial pulse disappearance. The higher occurrence of WCE and orthostatic and postprandial hypotension, and the presence of arrhythmias, such as atrial fibrillation, can hinder BP measurement.[5]

In the elderly, BP should be carefully measured from the technical viewpoint. The recommendations in Chapter 2 should be observed. In addition, it is necessary to assess the presence of postural hypotension, defined as a SBP reduction equal to or greater than 20 mm Hg, or any SBP decrease accompanied by clinical symptoms, and/or a 10-mmHg reduction in DBP when comparing, after 3 minutes, the BP levels obtained in the standing position with those obtained in the decubitus or sitting position.[13]

Previous diagnosis of AH is estimated to occur in 69% of the elderly with previous AMI, in 77% of those with history of stroke, and in 74% of those with history of HF. Although individuals in that age group are more aware of their condition and more frequently undergo treatment than middle-aged hypertensive individuals, the BP control rates among the elderly are lower, especially after the age of 80 years.[6]

In that age group, the treatment of AH has unequivocal benefits in reducing major CV events (AMI, stroke and HF). In addition, there is evidence that it might prevent dementia syndrome, an additional benefit that should be considered in the therapeutic decision.[14-16]

The NPT should be encouraged for all AH stages, based on the adoption of a healthy lifestyle. Although it might be simple and apparently easy to adopt, there is resistance, because it implies changes in old habits.

The main guidance on lifestyle changes that reduces BP and minimizes the CV risk are: physical activity; smoking cessation; loss of excessive body weight; and balanced diet (low-sodium, rich in fruits and vegetables).[15,16] (GR: I; LE: A). This type of therapy is recommended for the elderly, whose diet is benefited from moderate salt reduction. This lifestyle change is one of the best studied interventions for BP control; the BP reduction is usually more significant when the oldest individuals are considered. The TONE study[17] provides strong evidence about the effects of dietary sodium reduction for the elderly, with a 4.3-mmHg decrease in SBP and 2-mmHg decrease in DBP of individuals aged 60-80 years with BP < 145/85 mm Hg and daily sodium intake of 5 grams. The benefits of the regular physical activity for the elderly largely extrapolate BP reduction, because it provides better control of other comorbidities, reducing global CV risk. In addition, regular physical activity can reduce the risk of falls and depression, promoting the sensation of general well-being, improving self-esteem and quality of life.[18]

The patients should preferably be accompanied by a multidisciplinary team, and their families should be involved in the entire process, which increases adherence to treatment and its chances of success.[5]

The HYVET study[19] has shown that active treatment significantly reduces the rates of HF and global mortality in that group. That study has compared active treatment (DIU: indapamide plus, if necessary, ACEI: perindopril) with placebo for octogenarians with initial SBP greater than 160 mm Hg. Target SBP was lower than 150 mm Hg, with a mean BP of 144 mm Hg. A limitation of that important study was that it included elderly usually healthier than the general population.

A large number of randomized studies on the antihypertensive treatment of elderly, including patients aged 80 years and older,[19] has shown a reduction in CV events due to BP reduction; however, the mean SBP levels attained were never below 140 mm Hg.[20] Two Japanese studies, comparing strict treatment with mild treatment, have not been able to show any benefit by reducing mean SBP levels to 136 and 137 as compared to 145 and 142, respectively.[21,22] An analysis of the elderly subgroup in the FEVER study[23] has shown a reduction in CV events with SBP lowering to below 140 mm Hg, as compared to 145 mm Hg.

There is strong evidence of the benefit of BP reduction with antihypertensive treatment in elderly aged 80 years and older. That advantage is limited to individuals with SBP ≥ 160 mm Hg, whose SBP was reduced to < 150 mm Hg (GR: I; LE: A).

For elderly under the age of 80 years, the antihypertensive treatment should be considered for those with SBP > 140 mm Hg, with target SBP < 140 mm Hg, if they have a good clinical condition and tolerate the treatment well.[19-23] (GR: IIb; LE: C).

The randomized controlled studies showing the successful effects of antihypertensive treatment on the elderly have used different drug classes. There is evidence favoring DIUs,[12,19,24-27] CCBs,[28-30] ACEIs[30] and ARBs.[31] The three studies on ISH have used DIUs[12] or CCBs.[28,29]

A prospective meta-analysis has compared the benefits of different therapeutic regimens for patients divided into two groups by age: under 65 years and 65 years and older. It has confirmed the lack of evidence that different drug classes have different effectiveness in younger or older patients.[32]

It is worth noting the likelihood of secondary AH in the elderly, whose most frequent causes are stenosis of the renal artery, obstructive sleep apnea-hypopnea syndrome (OSAHS), thyroid function changes, and use of drugs that can raise BP.[24,33-35]

Investigating secondary AH in the elderly might be necessary as part of the diagnosis.

Some features of the elderly are worth noting and require a differentiated approach. Elderly with multiple non-CV morbidities, frailty syndrome and/or dementia have an increased risk for functional dependence and death.[36,37] Despite the trend towards slow BP reduction with the progression of those conditions and organic reserve decrease, some still have significantly high BP levels. Those elderly have not been included in randomized clinical trials, and, thus, should be assessed in an even more global way, carefully weighing the individual priorities and the risk/benefit of antihypertensive treatment, either pharmacological or not. The treatment target should be less strict, with special attention paid to the higher risk of postural and postprandial hypotension. In addition, frail elderly are at higher CV risk, and their treatment should be individualized.

In the presence of established CVD or TOD, they become a priority and should guide both the intensity of treatment, and the choice of drugs.[38-40] (GR: IIa; LE: C).

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Chapter 12 - Secondary Arterial Hypertension

Introduction

Secondary AH has a prevalence of 3-5%. The treatment of the cause can cure AH or improve BP control. Chart 1 shows the situations in which secondary causes of AH should be investigated.

Chronic kidney disease

Chronic kidney disease is defined by a GFR < 60 mL/min or abnormal findings in urinalysis and/or kidney morphology for 3 months.[1] As CKD advances, AH increases progressively, affecting 90% of stage 5 patients.[2]

All patients with AH should have plasma creatinine measured, their GFR calculated and urinalysis performed to screen for CKD.[3] (GR: I; LE: A). Additional investigation includes renal US for all.[3] Other exams (albuminuria, CT, MRI) can be necessary. Kidney biopsy is indisputably indicated in the presence of rapid decline in glomerular filtration or proteinuria > 3.5 g/g of urine creatinine.[4] Arterial hypertension accelerates the progression of CKD[5] and BP reduction attenuates CKD course.[6] The treatment goals and most indicated medications for BP control in patients with CKD are described in Chapter 8. For CKD patients on dialysis, BP reduction decreases mortality,[7] and loop DIUs are indicated in the presence of residual renal function, as well as ultrafiltration, in selected cases.[8]

Renovascular hypertension

Renovascular hypertension (RVAH) is secondary to partial or total, uni- or bilateral stenosis of the renal artery or of one of its branches, triggered and maintained by renal tissue ischemia. The RVAH prevalence is 5% of hypertensive patients.[9] Its major cause is atherosclerosis (90%), followed by renal artery fibromuscular dysplasia,[10] Takayasu's arteritis being the less frequent.[9] Regardless of its cause, it is an important determinant of CV morbidity and mortality.[10]

The diagnosis and assessment of the extent of involvement with TOD are essential for the choice of treatment. A cost-effective investigation requires proper selection of candidates, and anatomical and functional assessment of the stenosis, in addition to methods to correct the anatomical and functional defect.[11] Charts 2 and 3[12-14] list the main steps.

Chart 1 – Major causes of secondary AH, signs and diagnostic screening

Clinical findings	Diagnostic suspicion	Additional studies
Snoring, daytime sleepiness, MS	OSAHS	Berlin questionnaire, polysomnography or home respiratory polygraphy with at least 5 episodes of apnea and/or hypopnea per sleep hour
RAH and/or hypopotassemia (not necessary) and/or adrenal nodule	Primary hyperaldosteronism (adrenal hyperplasia or adenoma)	Measurements of Aldo (>15 ng/dL) and plasma renin activity/concentration; Aldo/renin > 30. Confirmatory tests (furosemide and captopril). Imaging tests: thin-sliced CT or MRI
Edema, anorexia, fatigue, high creatinine and urea, urine sediment changes	Parenchymal kidney disease	Urinalysis, GFR calculation, renal US, search for albuminuria/proteinuria
Abdominal murmur, sudden APE, renal function changes due to drugs that block the RAAS	Renovascular disease	Renal Doppler US and/or renogram, angiography via MRI or CT, renal arteriography
Absent or decreased femoral pulses, decreased BP in the lower limbs, chest X ray changes	Coarctation of the aorta	Echocardiogram and/or chest angiography via CT
Weight gain, decreased libido, fatigue, hirsutism, amenorrhea, moon face, "buffalo hump", purple striae, central obesity, hypopotassemia	Cushing's syndrome (hyperplasia, adenoma and excessive production of ACTH)	Salivary cortisol, 24-h urine free cortisol and suppression test: morning cortisol (8h) and 8 hours after administration of dexamethasone (1 mg) at 24h. MRI
Paroxysmal AH with headache, sweating and palpitations	Pheochromocytoma	Free plasma metanephrines, plasma catecholamines and urine metanephrines. CT and MRI
Fatigue, weight gain, hair loss, DAH, muscle weakness	Hypothyroidism	TSH and free T4
Increased sensitivity to heat, weight loss, palpitations, exophthalmos, hyperthermia, hyperreflexia, tremors, tachycardia	Hyperthyroidism	TSH and free T4
Renal lithiasis, osteoporosis, depression, lethargy, muscle weakness or spasms, thirst, polyuria	Hyperparathyroidism (hyperplasia or adenoma)	Plasma calcium and PTH
Headache, fatigue, visual disorders, enlarged hands, feet and tongue	Acromegaly	Baseline IGF-1 and GH and during oral glucose tolerance test

OSAHS: obstructive sleep apnea-hypopnea syndrome; Aldo: aldosterone; RAH: resistant arterial hypertension; GFR: glomerular filtration ratio; APE: acute pulmonary edema; RAAS: renin-angiotensin-aldosterone system; CT: computed tomography; ACTH: adrenocorticotropin; TSH: thyroid stimulating hormone; PTH: parathormone; IGF-1: insulin-like growth factor type 1; GH: growth hormone.

Chart 2 – ACC/AHA recommendations for renal artery stenosis search during coronary angiography

Clinical characteristics	Level of evidence
Beginning of hypertension < 30 years	B
Beginning of severe hypertension > 55 years	B
Accelerated/malignant hypertension	C
Resistant hypertension	C
Uremia or renal function worsening after use of ACEI or ARB (> 30% drop in glomerular filtration)	B
Atrophic kidney of unknown cause or size discrepancy between the two kidneys > 1.5 cm	B
Unexpected sudden pulmonary edema (mainly in uremic patients)	B

Chart 3 – Clinical indicators of probable renovascular hypertension

Probability	Clinical characteristics
Low (0.2%)	Uncomplicated borderline or mild/moderate AH
Intermediate (5-15%)	Severe or resistant AH Recent AH < 30 years or > 50 years Presence of abdominal murmur Asymmetry of radial or carotid pulses Moderate AH associated with smoking or atherosclerosis in another site (coronary or carotid) Undefined renal functional deficit Exaggerated BP response to ACEIs
High (25%)	Severe or resistant AH with progressive renal failure Accelerated or malignant AH Sudden APE ACEI-induced creatinine increase Asymmetry of renal size or function

The indication for the therapeutic option should consider the etiology and clinical conditions associated with renal artery stenosis, such as AH, ischemic nephropathy and accelerated CVD. Evidence of benefit of the percutaneous or surgical mechanical treatment is restricted to situations, such as progressive renal function loss, APE and difficulty to control BP, that cause irreversible TOD.[15] Regarding patients with RVAH due to fibromuscular dysplasia, 82-100% of them have BP control, and 10%, restenosis.[11] (GR: IIa; LE: B). Regarding atherosclerotic RVAH without complications, three randomized studies have shown no benefit of stent implantation as compared to optimized clinical treatment in BP control, kidney disease progression, and occurrence of clinical events and mortality.[16-18] For patients with atherosclerotic renal artery stenosis and controlled BP with clinical treatment, without heart complications and stable kidney function for 6-12 months, the mechanical intervention is not recommended, clinical treatment being the first option. (GR: II; LE: B).

Figure 1 shows a flowchart for the assessment of patients suspected of having renal artery stenosis.

Obstructive sleep apnea-hypopnea syndrome

Obstructive sleep apnea-hypopnea syndrome is characterized by recurring upper airway obstructions during sleep, causing reductions in intrathoracic pressure, intermittent hypoxia and sleep fragmentation.[19] There is evidence that OSAHS is related to the development of AH regardless of obesity.[20,21] The prevalence of OSAHS in patients with AH is 30-56%,[22,23] reaching 64-83% in those with resistant AH (RAH).[24,25] OSAHS contributes to TOD[26] and acceleration of atherosclerosis in hypertensives.[27]

The risk factors for OSAHS are age, male sex, obesity and MS. The Berlin questionnaire[28] can be used to screen for OSAHS,[23] but does not seem useful in patients with RAH.[29] Changes in the physiological BP decrease during nocturnal sleep can indicate the presence of OSAHS.[30] Polysomnography or home respiratory polygraphy confirms the diagnosis with the finding of at least five episodes of apnea and/or hypopnea per hour of sleep (apnea-hypopnea index - AHI), and an AHI ≥15 events/hour seems to have a higher impact on AH.[31]

The treatment of choice for moderate or severe OSAHS is the use of continuous positive airway pressure (CPAP) during sleep.[31] Meta-analyses have shown a small effect of CPAP in reducing BP, but they have limitations because they included studies on individuals with normal BP and controlled hypertensives.[32-34] Most randomized studies[35-38] on patients with OSAHS and RAH have shown more significant reductions in BP than those of patients with non-resistant AH. Body weight loss in combination with CPAP has resulted in greater BP reduction than each isolated intervention in obese individuals with OSAHS.[39] Mandibular advancement with mobile orthodontic devices for mild to moderate OSAHS can

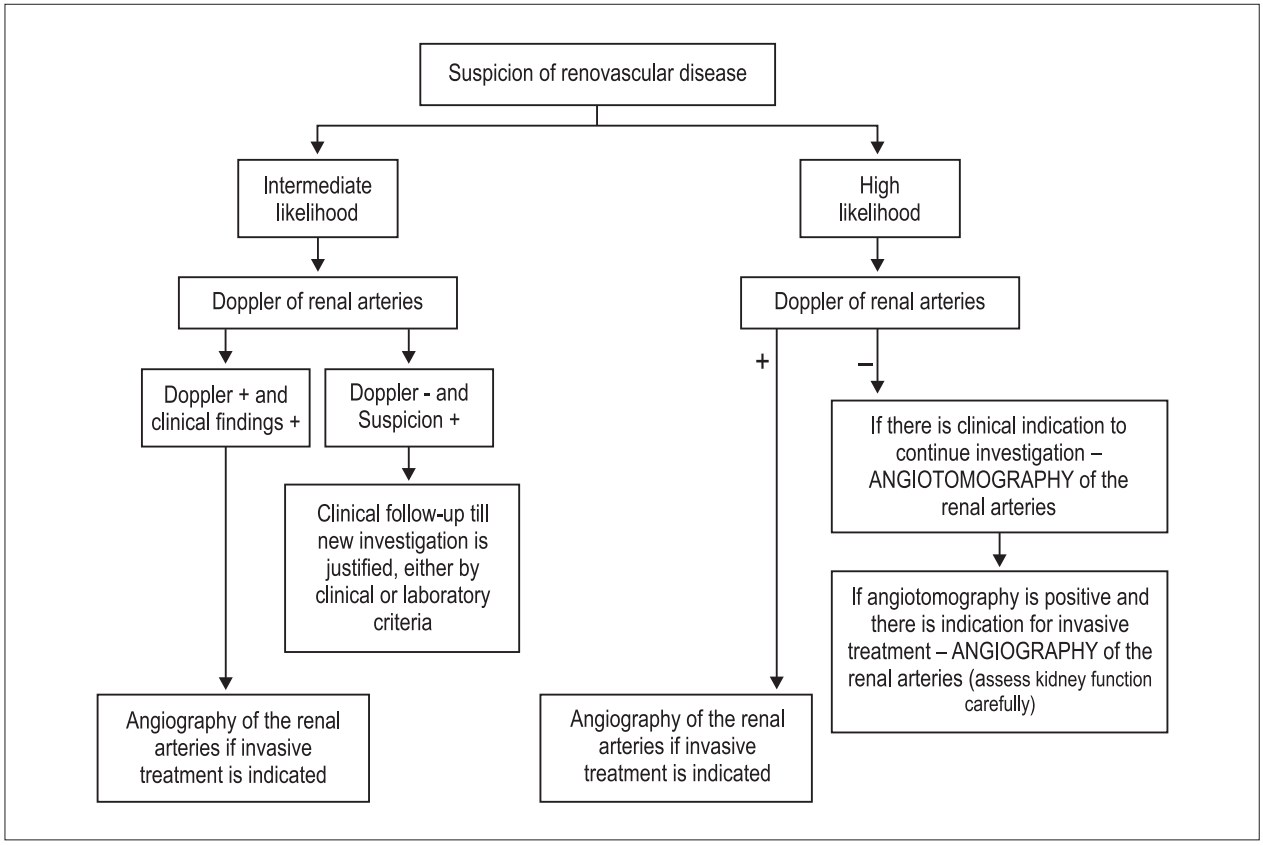

Figure 1 – *Flowchart for the investigation of patients suspected of having renal artery stenosis.*

also reduce BP,[34] but further studies are necessary.[34] Although several antihypertensive classes have been tested,[40] there is no definitive conclusion about the best drug for hypertensives with OSAHS.[40,41]

Primary hyperaldosteronism

Primary hyperaldosteronism (PHA) is a clinical condition characterized by excessive, inappropriate and autonomous production of aldosterone[42] (Aldo), caused by bilateral adrenal hyperplasia or unilateral Aldo producing adenoma (APA), and, more rarely, unilateral adrenal hyperplasia, adrenal carcinoma or genetic origin (monogenic or chimeric gene). The prevalence of PHA in hypertensives is 3-22%, being higher in stage 3 and/or resistant hypertensives.[43]

Primary hyperaldosteronism is suspected when AH is associated with: spontaneous or DIU-induced hypokalemia; adrenal incidentaloma; RAH; family history of AH or CbVD before the age of 40 years; and MS. The prevalence of hypokalemia in PHA is 9-37%.[43]

Figure 2 shows the flowchart for screening, diagnostic confirmation and treatment of PHA.

Laboratory tests do not require suspension of antihypertensive agents, except for spironolactone for 4-6 weeks.[43] Suppressed plasma renin activity (PRA) and Aldo > 15 ng/dL, with an Aldo/PRA ratio > 30, indicate the diagnosis of PHA. Confirmatory testing is recommended when Aldo > 15 ng/dL and < 25 ng/dL, with an Aldo/PRA ratio > 30 and < 100. The furosemide and captopril tests have higher diagnostic accuracy than the saline infusion test.[44] In the furosemide upright test, the patient should remain lying down for at least 30 minutes, then receive 40 mg of furosemide (IV), and renin should be measured after 2 hours of walking. The test is positive if PRA < 2 ng/mL/h. In the captopril challenge test, 50 mg of captopril are administered orally after the patient remained seated or in the upright position for at least 1 hour. Renin and Aldo should be measured at the times 0, 60 and 120 minutes. The test is positive if there is no drop > 30% in plasma Aldo or if it remains > 12 ng/dL. In the saline infusion test, 2 liters of 0.9% saline are administered (IV) in 4 hours. The Aldo measurement will be ≥ 5 ng/dL.

For APA or hyperplasia to be detected, thin-sliced CT or MRI of the adrenal glands is indicated.[43] Catheterization of the adrenal veins is indicated when, on CT, the adrenal glands are normal, have bilateral abnormalities (thickening or micronodules) or a unilateral lesion in patients > 40 years.[44] The dexamethasone suppression test is indicated to investigate PHA suppressible with glucocorticoid in patients with PHA and AH beginning before the age of 40 years.[44]

Laparoscopic surgery is indicated in APA,[43] preferably with previous treatment with spironolactone up to 3-4 weeks.[45]

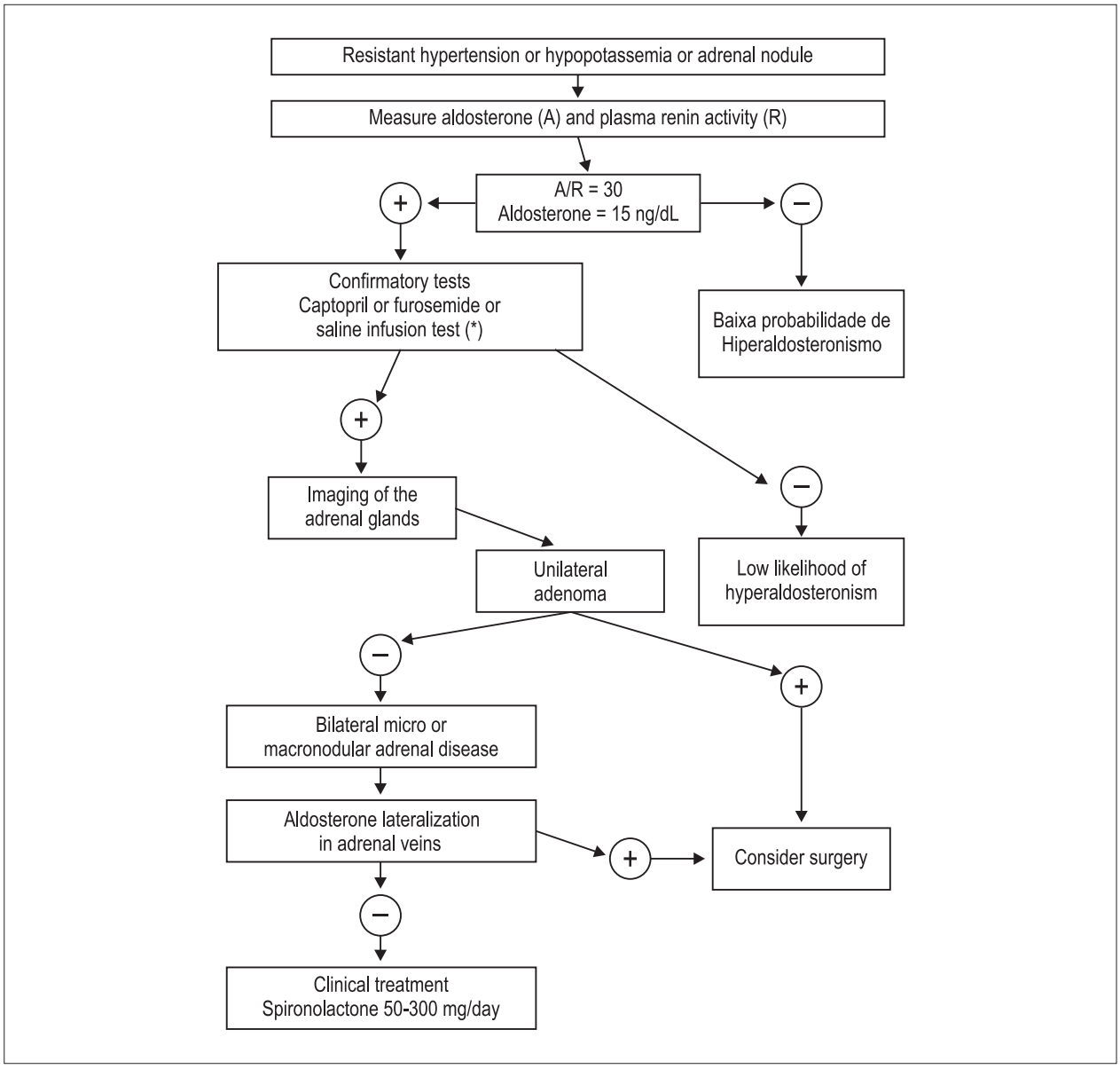

Figure 2 – *Flowchart for primary hyperaldosteronism screening, diagnostic confirmation and treatment. *The furosemide and captopril tests have higher diagnostic accuracy than the saline infusion test.*

Clinical treatment of hyperplasia requires spironolactone, 50-300 mg/day, if well tolerated.[45] Cure of AH with surgery is observed in 35-60% of the patients.[42,45]

Pheochromocytomas

Pheochromocytomas (PHEO) are tumors of chromaffin cells of the sympathetic adrenomedullary axis that produce catecholamines.[46] Of PHEOs, 10% to 15% are extraadrenal (paragangliomas), 10% are bilateral, and 10% are malignant.[47] Familial forms have the dominant autosomal trait or are part of syndromes with known gene mutations.[47]

Presence of persistent or paroxysmal AH (50%), paroxysmal headache, excessive sweating and palpitations (classic triad)[46] is indicative of the disease, and concomitance of the classic triad with HC has sensitivity of 89% and specificity of 67% for the PHEO diagnosis.[46]

Laboratory diagnosis is based on the measurement of catecholamines and their metabolites in blood and urine. Free plasma metanephrine has the highest sensitivity and specificity,[48] but because of its higher cost, urine metanephrine isolated or associated with plasma catecholamines is indicated in cases of high likelihood.[48] The measurement of urine vanillylmandelic acid has good specificity, but the lowest sensitivity of all methods, being indicated only when the other tests are not available.[48] If the diagnosis is not certain, clonidine suppression test is indicated in hypertensives, and glucagon stimulation test, in individuals with normal BP levels.[47]

The imaging tests to locate adrenal tumors are CT and MRI, with sensitivity of 89% and 98%, respectively.[49] The MRI is superior to identify paragangliomas. MIBG whole body scan is useful in extraadrenal, bilateral PHEOs, and metastases and relapses.[50] Octreoscan, bone scan and positron-emission CT can be indicated when the localizing exams cited are negative or when investigating malignancy.[51]

The preferential treatment is surgery, whose preoperative preparation should include alpha1-blockers (doxazosin or prazosin) and appropriate hydration for at least 2 weeks before surgery.[52] The chronic pharmacological treatment includes alpha1-blockers, BBs (only after beginning alpha1-blockers, in the presence of symptomatic tachycardia), CCBs, ACEIs and central action agonists.[52] The paroxysmal HC of PHEO is a HE, and should be treated with SNP or injectable phentolamine and volume replacement, if necessary.[46]

Total and early removal of the neoplasm usually determines total remission of symptoms and cure of AH.[47,49] For malignant PHEOs with unresectable metastases, the following are indicated: chemotherapy, embolization, radiotherapy, and, if possible, ablation with MIBG-131.[47] Clinical, biochemical and radiological follow-up of the patients is essential to detect recurrences or metastases, in the malignant form, and other tumor in familial syndromes.

Other endocrine causes

Hypothyroidism

In hypothyroidism, AH occurs in 20% of hypothyroid patients.[53] The diagnosis is established by finding high TSH levels and gradual decrease in free T4. The most common clinical findings are weight gain, hair loss and muscle weakness. The treatment is initiated with thyroid hormone replacement,[53] and, if AH persists, antihypertensive drugs are indicated. (GR: II; LE: C).

Hyperthyroidism

In hyperthyroidism, AH is a frequent finding in hyperthyroidism, and the clinical presentation mimics hyperadrenergic findings. The main symptoms are palpitation, tremor, fatigue, increased sensitivity to heat, hyperactivity, weight loss and emotional lability.[54] The most important signs are exophthalmos, hyperthermia, hyperreflexia and humid skin.[54] The diagnosis is confirmed by low TSH levels and high free T4 levels. The treatment usually normalizes BP. Beta-blockers are the first choice to control the adrenergic symptoms. (GR: IIb; LE: C).

Hyperparathyroidism

In hyperparathyroidism, there is excessive secretion of parathormone (PTH) by the parathyroid glands, with consequent hypercalcemia and hypophosphatemia.[55] It can be caused by an adenoma or hyperplasia of the parathyroid glands. Secondary hyperparathyroidism results from a situation that induces hypocalcemia, CKD being the major cause. The most common symptoms are depression, thirst, polyuria, renal lithiasis, osteoporosis, lethargy, muscle weakness, muscle spasms, and renal function reduction. Arterial hypertension is present in up to 75% of the patients, and can be resistant.[43] The diagnosis is established with plasma calcium and PTH measurement. Surgical correction of hyperparathyroidism can cure or reduce BP in hypertensives.[56]

Cushing's syndrome

Cushing's syndrome (CS) is a disorder caused by excessive cortisol levels associated with a deficiency in the control mechanism of the hypothalamus-hypophysis-adrenal axis and of the cortisol secretion circadian rhythm.[57] It can result from adrenal tumors with autonomous cortisol production (benign or malignant adenoma), adrenal hyperplasia, excessive adrenocorticotropin (ACTH) production, or ectopic tumor.[57] The prevalence of AH in CS is 80% in adults and 47% in children.[57] The major signs and symptoms are decreased libido, central obesity, moon face, striae, muscle weakness, and hirsutism.[58] The confirmatory tests are: 24-hour urine free cortisol; nocturnal salivary cortisol; dexamethasone suppression test; dexamethasone combined with corticotropin-releasing hormone test; and ACTH measurement.[58] Pituitary MRI shows an adenoma in 35% to 60% of patients.[58] Surgical removal of the tumor can cure AH, but 30% of the patients maintain SAH, and 25%, DAH.[59] The AH duration before surgery correlates with postoperative AH persistence.[59] Thiazides and furosemide should be avoided, because they can worsen hypokalemia, ACEIs and ARBs being recommended.[59]

Acromegaly

Acromegaly is usually caused by a pituitary adenoma that secrets growth hormone (GH) and insulin-like growth factor type 1 (IGF-1). It manifests as progressive excessive growth of the hands, feet and facial bones, increased interdental spacing, mandibular prognathism, macroglossia, excessive sweating, and respiratory, CV, metabolic-endocrine and skeletal-muscle changes.[60] In acromegaly, AH has a 35% prevalence, and contributes to increase the disease's morbidity and mortality. Acromegalic cardiomyopathy contributes to raise BP, and can be aggravated by the coexistence of AH. The treatment of acromegaly reduces BP in parallel with GH reduction.[60]

Coarctation of the aorta

Coarctation of the aorta is the aortic constriction close to the ductus arteriosus or ligament, found mainly in children and young adults. Clinical suspicion is based on symptoms (epistaxis, headache and weakness of the legs on exertion or manifestations of HF, angina, aorta dissection or intracerebral hemorrhage) and physical exam (upper limb AH, with SBP at least 10 mm Hg greater in the brachial artery than in the popliteal artery; pulse absence or decrease in lower limbs; interscapular and thoracic systolic murmur).[61-63]

The imaging exams include: chest X ray (thoracic aorta with pre- and post-stenosis dilations, costal corrosion);

echocardiogram (posterior protrusion, expanded isthmus, transverse aortic arch, and high velocity continuous jet in the coarctation site); angiography with MRI (details of coarctation and intercostal vessels). The MRI is the best method for assessment and post-intervention follow-up in young individuals, and does not require preoperative angiography. Invasive angiography is indicated when other imaging methods do not provide visualization of the coarctation, and to older individuals who can have CAD. The definition of significant coarctation requires pre- and post-coarctation pressure gradient > 20 mm Hg.[62]

Patients who do not undergo surgery have a higher incidence of CV events. The treatment is always interventional: endovascular procedure (younger individuals or children) or surgery (hypoplasia of the aortic arch and/or need for coarctation resection). The BP response to interventional treatment depends on the duration of AH prior to surgery and the patient's age. The cure of AH occurs in up to 50% of patients, but AH can reoccur later, especially if the intervention is performed at advanced age. The drugs of choice for both the preoperative period and residual AH after surgery are BBs and ACEIs.

Drug-induced AH

Chart 4 shows the medicines and licit and illicit drugs related to AH development or worsening.

Chart 4 – Medicines and illicit and licit drugs related to AH development or worsening

Drug class	Effect on BP and frequency	Suggested action
Immunosuppressants		
Cyclosporine, tacrolimus	Intense and frequent	ACEI and CCB (nifedipine/amlodipine). Adjust serum level. Reassess options
Anti-inflammatory agents		
Glucocorticoid	Variable and frequent	Salt restriction, DIUs, decrease dose
Non-steroids (1 and 2 cyclo-oxygenase inhibitors)	Occasional, very relevant with continuous use	Observe renal function, use for a short period
Anorexigenic/satiety drugs		
Diethylpropion and others	Intense and frequent	Suspension or dose reduction
Sibutramine	Intermediate, little relevance	Assess BP reduction with weight loss
Vasoconstrictors, including ergot derivatives	Variable, transient	Use for a determined short period
Hormones		
Human erythropoietin	Variable and frequent	Assess hematocrit and dose weekly
Oral contraceptives	Variable, prevalence of up to 5%	Assess method replacement with an expert
Estrogen-replacement therapy (conjugated estrogens and estradiol)	Variable	Assess risk and cost-benefit
GH (adults)	Variable, dose-dependent	Suspension
Antidepressant drugs		
Monoamine-oxidase inhibitors	Intense, infrequent	Approach as adrenergic crisis
Tricyclics	Variable and frequent	Approach as adrenergic crisis
Illicit drugs and alcohol		
Amphetamine, cocaine and derivatives	Acute, intense effect Dose-dependent	Approach as adrenergic crisis
Alcohol	Variable and dose-dependent Very prevalent	See non-pharmacological treatment

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Chapter 13 - Resistant Arterial Hypertension

Definition and epidemiology

Resistant AH (RAH) is defined as uncontrolled office BP despite the use of at least three antihypertensive drugs at appropriate doses, including preferably one DIU, or as controlled BP using at least four drugs.[1-3] Because it does not include the systematic assessment of therapy and adherence, that situation is better defined as apparent RAH (pseudoresistance). Identification of true RAH is fundamental to establish specific approaches.[2] Population-based studies have estimated a 12% prevalence in the hypertensive population.[2] In Brazil, the ReHOT study assesses prevalence and therapeutic choice.[4] Refractory hypertension is defined as uncontrolled BP using at least five antihypertensive drugs,[5] and corresponds to 3.6% of resistant hypertensive individuals. To diagnose RAH, ABPM is required, as well as systematic assessment of adherence. (GR: I; LE: C).

Associated factors

Causative factors are as follows: higher salt sensitivity, increased blood volume (higher sodium intake, CKD or inappropriate diuretic therapy), exogenous substances that raise BP, and secondary causes (OSAHS, primary aldosteronism, CKD, and renal artery stenosis).[1,3,6] The characteristics of RAH are: more advanced age, African ancestry, obesity, MS, DM, sedentary lifestyle, chronic nephropathy, and LVH.[1,3]

The pathophysiological aspects related to resistance are as follows: (i) sympathetic and RAAS hyperactivity; (ii) vascular smooth muscle proliferation; (iii) sodium retention; and (iv) activation of proinflammatory factors.[1,7] Greater endothelial dysfunction and arterial stiffness are present.[8] In ABPM, there is high prevalence (30%) of WCE and attenuation of nocturnal BP dipping.[9] The prevalence of black ethnicity, DM and albuminuria is higher among refractory hypertensive individuals.[5]

Diagnostic investigation

Pseudoresistance

Pseudoresistance is due to poor BP measurement technique, low adherence to treatment and inappropriate therapeutic regimen.[1,2,10] Studies have shown that 50-80% of the patients fail to adhere to treatment completely or partially.[10-12] The diagnosis of RAH should only be established after inclusion of an appropriate DIU[13] and adjustment of the antihypertensive regimen.[12]

Complementary tests

Blood biochemistry, urinalysis and ECG should be requested at the time of diagnosis, and repeated at least once a year.[1,12] Echocardiogram and retinal exam, when available, should be repeated every 2 to 3 years.

Secondary causes

Secondary causes are common in RAH,[6] OSAHS being the most prevalent (80%, and 50% with moderate-severe apnea),[14] followed by hyperaldosteronism (20%, mainly adrenal hyperplasia)[15] and renal artery stenosis (2.5%).[6] Other secondary causes should only be investigated in the presence of suggestive clinical findings.[6]

ABPM and HBPM

Although the diagnosis of RAH is based on office BP measurement,[1] BP assessment by using ABPM or HBPM is mandatory for the initial diagnosis and clinical follow-up.[1,9,16,17] It is estimated that 30-50% of resistant hypertensive individuals have normal outside-the-office BP levels.[9,12,16] The diagnosis obtained on ABPM defines diagnostic and therapeutic management (Chart 1).[1,12,16]

In true or masked RAH, the medication should be progressively adjusted[16] with the introduction of nocturnal doses of antihypertensive drugs.[18] Patients with controlled BP on ABPM should have their therapy maintained, regardless of the office BP levels. In white-coat RAH, confirmatory ABPM needs to be performed after 3 months, and repeated every six months (if wakefulness SBP ≥ 115 mm Hg) or annually (if wakefulness SBP < 115 mm Hg).[19]

When ABPM is not available, HBPM is a good complementary method. Although it does not assess the nocturnal period and overestimates BP levels, HBPM reaches moderate agreement on the diagnosis,[20] with high specificity and low sensitivity (Chart 2).[17]

Treatment

Non-pharmacological treatment

The NPT is aimed at:

Encouraging lifestyle changes: reduction in salt intake (up to 2.0 g of sodium/day); DASH diet; body weight loss (BMI < 25 kg/m²); physical activity; smoking cessation; and moderate alcohol intake;[1,3,21,22]

Suspending substances that raise BP.[1,3]

Chart 1 – Classification of RAH based on ABPM

Office BP	ABPM	
	Wakefulness BP ≥ 135/85 and/or Sleep BP ≥ 120/70 mm Hg	Wakefulness BP < 135/85 and Sleep BP < 120/70 mm Hg
≥ 140/90 mm Hg	True RAH	White-coat RAH
< 140/90 mm Hg	Masked RAH	Controlled RAH

Chart 2 – Diagnostic investigation of RAH

	Grade of recommendation	Level of evidence
To rule pseudoresistance out		
Adherence to therapy	I	C
Adjustment of the antihypertensive regimen	I	C
Complementary exams		
Blood biochemistry: glucose, creatinine, potassium and lipid panel Urine assessment: albuminuria and proteinuria ECG	I	C
Investigation of secondary causes		
OSAHS Hyperaldosteronism Renal artery stenosis	I	A
ABPM or HBPM		
Assessment of BP control	IIa	C

Pharmacological treatment

The basic principle of the pharmacological treatment is the association of antihypertensive drugs that block most pathophysiological mechanisms of BP elevation. Ideally, the following should be prescribed at full-tolerated dose and at proper intervals: a DIU, a RAAS inhibitor, and a dihydropyridine CCB. In certain situations, such as CAD, CHF and tachyarrhythmias, a BB can replace a CCB in the initial therapeutic regimen with 3 medications.

The correct use of DIUs to ensure control of volemic expansion is essential, and more than half of the patients can meet the BP target with DIU optimization.[13] Chlorthalidone is superior to hydrochlorothiazide.[23] For stage 4 or 5 CKD patients, loop DIUs should be used and administered at least twice a day. Spironolactone, an aldosterone antagonist, is the choice for the fourth drug in patients with true RAH, enabling a mean reduction of 15-20 mm Hg in SBP, and of 7-10 mm Hg in DBP, at doses of 25-50 mg/day.[24] However, up to 20-30% of the patients might not tolerate its use, because of renal function worsening, hyperpotassemia, gynecomastia or mastalgia. In such cases, amiloride can be used (5-10 mg/day), but with an apparently lower BP response.[25] The use of clonidine as the fourth drug is being assessed in the Brazilian ReHOT study, considering the sympathetic and RAAS activity measurements as possible predictors of the best therapeutic response to clonidine and spironolactone, respectively.[4]

In patients not reaching BP control on ABPM after the addition of spironolactone, BBs (mainly those with vasodilating effect) are the fifth drugs, if not contraindicated. Central alpha-agonists (clonidine and alpha methyldopa), direct vasodilators (hydralazine and minoxidil), or central agonists of imidazoline receptors are usually used as the sixth and seventh drugs. In addition, associations of multiple DIUs (thiazide DIUs, loop DIUs and spironolactone), especially in the presence of edema, or dihydropyridine and non-dihydropyridine CCBs can be used in the most critically ill patients.

Chronotherapy guided by ABPM, with the nocturnal administration of at least one antihypertensive drug, could improve BP control and reverse the unfavorable non-dipping pattern in those patients, in addition to reducing CV morbidity and mortality (Chart 3).[18]

New therapeutic strategies

New strategies are being developed, but are still experimental. Although safe, they are not better than the conventional treatment, and should only be used in truly resistant patients (Chart 4).

Direct and chronic stimulation of carotid sinus baroreceptors

The Rheos system is a programable device, like a pacemaker, surgically implanted, consisting in a generator of impulses that activate the carotid baroreceptors via radiofrequency. The Rheos Pivotal Trial has not detected significant long-term benefits.[26]

Renal sympathetic denervation

Percutaneous transluminal renal sympathetic denervation through a catheter has been mainly assessed in the SYMPLICITY studies conducted in RAH patients. Recent meta-analyses[27,28] have not confirmed the initially promising results.

Use of CPAP

The antihypertensive effect of CPAP is controversial. However, as an auxiliary treatment in patients with OSAHS, mainly those who tolerate its use for more than 4 hours/night, there is evidence that it can help to reestablish the dipping pattern.[29]

Chart 3 – Treatment of resistant arterial hypertension

Intervention	Grade of recommendation	Level of evidence
Adopt lifestyle changes	I	B
Optimize treatment with 3 drugs: chlorthalidone*, ACEI or ARB, and CCB†	I	B
Add spironolactone as the 4th drug	IIa	B
Add BB as the 5th drug†	IIb	C
In sequence, add centrally acting sympatholytic drugs or direct vasodilators	IIb	C
Prescribe the night administration of one or more drugs	IIb	B
Check and improve adherence to treatment	I	C

Chart 4 – New therapeutic strategies for resistant arterial hypertension

Intervention	Grade of recommendation	Level of evidence
Stimulation of carotid sinus baroreceptors (Rheos device)[26]	IIb	B
Renal sympathetic denervation[27,28]	IIb	B
Use of CPAP[29]	IIb	B
Central arteriovenous anastomosis (coupler device)[30]	IIb	B

Central iliac arteriovenous anastomosis

The ROX Control HTN study[30] has shown promising results with significant reductions in BP levels and in hypertensive complications of patients with central iliac arteriovenous anastomosis with the coupler device.

Prognosis

A retrospective cohort study performed from a North American registry indicates that, after beginning the antihypertensive treatment, the apparent RAH incidence (uncontrolled BP with 3 medications) is 0.7/100/patients-year, and those patients' relative risk for CV events is 1.47 (95% confidence interval: 1.33-1.62).[31] A prospective study with 556 resistant hypertensives (follow-up of 4.8 years) has shown that uncontrolled ABPM and lack of nocturnal dipping are important markers of CV risk.[32] The apparent RAH condition is considered of independent risk for the occurrence of CV events. (GR: IIa; LE: C). Performing ABPM is recommended to establish the prognosis of hypertensives with true RAH. (GR: IIa; LE: C).

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Chapter 14 – Hypertensive Crisis

Definition

The terms HU and HE were proposed as an operational classification of HC in 1993 by the V *Joint National Committee on Detection Evaluation and Treatment of High Blood Pressure*.[1] The HUs are symptomatic clinical situations in which there is significant BP elevation (arbitrarily defined as DBP ≥ 120 mm Hg) without acute and progressive TOD.[2,3] The HEs are symptomatic clinical situations in which there is significant BP elevation (arbitrarily defined as DBP ≥ 120 mm Hg) with acute and progressive TOD.[2,3]

Patients complaining from headache, atypical chest pain, dyspnea, acute psychological stress, and panic syndrome associated with high BP levels characterize neither HU nor HE, but rather a pseudo hypertensive crisis. Treatment comprises the optimization of antihypertensive drugs and raising awareness about treatment adherence.

Classification

Chart 1 shows the classification of HE, and Chart 2 differentiates HU from HE regarding diagnosis, prognosis and management.

Major epidemiological, pathophysiological and prognostic aspects

Epidemiology

Hypertensive crisis accounts for 0.45-0.59% of all hospital emergency treatments, while HE accounts for 25% of all cases of HC, ischemic stroke and APE, which are the most frequent HEs.[4-6]

Chart 1 – Classification of hypertensive emergencies

HYPERTENSIVE EMERGENCIES
Cerebrovascular - Hypertensive encephalopathy - Intracerebral hemorrhage - Subarachnoid hemorrhage - Ischemic stroke Cardiocirculatory - Acute aortic dissection - APE with left ventricular failure - AMI - Unstable angina Renal - Rapidly progressive AKI
Severe adrenergic crises Crisis of PHEO Excessive dose of illicit drugs (cocaine, crack, LSD)
Pregnancy hypertension Eclampsia Severe preeclampsia "HELLP" syndrome Severe hypertension at the end of pregnancy

APE: acute pulmonary edema; AMI: acute myocardial infarction; AKI: acute kidney injury; PHEO: pheochromocytoma.

Pathophysiology

Increased intravascular volume and PVR, or reduced production of endogenous vasodilators seem to precipitate greater vascular reactivity, resulting in HC.[7] Self-regulation is compromised, particularly in the cerebral and renal vascular beds, resulting in local ischemia, which triggers a vicious circle of vasoconstriction, myointimal proliferation and target-organ ischemia.[8]

Prognosis

Survival up to 5 years is significantly higher in individuals with HU than with HE.[4,9] Absence of nocturnal dipping associates with higher risk for TOD and consequent endothelial dysfunction, a situation involved in acute BP elevation.[10]

Complementary clinical and laboratory investigation

Clinical and laboratory investigation should properly assess BP and TOD. Initially, BP should be measured in both arms, preferably in a calm environment, and repeatedly until stabilization (minimum of 3 measurements). Data on the patient's usual BP should be rapidly collected, as well as information on situations that can raise it (anxiety, pain, salt), comorbidities, use of antihypertensive drugs (dosage and adherence) or drugs that can increase BP (anti-inflammatory drugs, corticoids, sympathomimetic drugs, alcohol). A systematic approach helps to check for the presence of acute and progressive TOD:

Cardiovascular system: chest, abdominal or back pain or discomfort; dyspnea, fatigue and cough. Assessment of HR, heart rhythm, pulse changes, gallop rhythm, cardiac and vascular murmurs, jugular venous distension, and pulmonary, abdominal and peripheral congestion. Exams requested based on clinical findings and availability: ECG, electrocardiographic monitoring, O2 saturation, chest X ray, echocardiogram, myocardial necrosis markers, blood cell count with platelets, LDH-C, CT angiography and MRI.

Nervous system: dizziness, headache, impaired vision, hearing or speech, consciousness or coma level, agitation, delirium or confusion, focal deficits, neck stiffness, convulsion. Exams: tomography, MRI and lumbar puncture.

Renal and genitourinary system: changes in urine volume, micturition frequency or urine aspect, hematuria, edema, dehydration, abdominal masses and murmurs. Exams: urinalysis, serum creatinine, serum urea, Na+, K+, Cl-, blood gas analysis.

Retinal exam: papilledema, hemorrhages, exudates, vascular changes, such as spasms, pathological arteriovenous crossings, arterial wall thickening and silver- or copper-wire aspect.

General treatment of hypertensive crisis

The treatment of HU should begin after a period of clinical observation in a calm environment, which helps to rule out the cases of pseudocrisis (treated with only rest or use of painkillers or tranquilizers). Captopril, clonidine and

Chart 2 – Differences in the diagnosis, prognosis and management of hypertensive urgency and emergency

Urgency	Emergency
Markedly high BP level DBP > 120 mm Hg	Markedly high BP level DBP > 120 mm Hg
Without acute and progressive TOD	With acute and progressive TOD
Oral drug combination	Parenteral medication
No risk of imminent death	Risk of imminent death
Early ambulatory follow-up care (7 days)	ICU admission

ICU: intensive care unit.

BBs are oral antihypertensives used to gradually reduce BP in 24-48 hours. The use of drops of rapid-release nifedipine capsules to treat HU should be banned, because it is neither safe nor effective, and causes rapid and marked BP reductions, which can result in tissue ischemia. The use of nifedipine for preeclampsia is currently debatable.

The treatment of patients with HE is aimed at rapid BP reduction to prevent the progression of TODs. Patients should be admitted to the ICU, on IV antihypertensives and be carefully monitored to prevent hypotension. The general recommendations for BP reduction for HE are:[2]

- ↓ BP ≤ 25% in the 1st hour;
- ↓ BP 160/100-110 mm Hg in 2-6 hours;
- BP 135/85 mm Hg in 24-48 hours.

However, HEs should be approached considering the impaired system or target organ. Thus, each type of HE (CV, cerebral, renal or other) should be previously characterized before beginning specific antihypertensive therapy.

Hypertensive emergency in special situations

Chart 3 shows the medications used for HE.

Stroke

Arterial hypertension is the major risk factor for stroke, especially hemorrhagic stroke. The diagnosis is based on complete neurological exam. To assess the severity of the condition, the National Institute of Health Stroke Scale (NIHSS) should be used. Brain CT and MRI allow defining the type of stroke and territory involved, and, usually, 85% of the strokes are ischemic, and 15%, hemorrhagic.[11] For incipient infarctions, MRI is more sensitive than CT.

Hemorrhagic stroke12

1 – For patients with SBP between 150 and 220 mm Hg and with no treatment contraindication, acute SBP reduction to 140 mm Hg is safe and can be effective to improve the functional outcome. (GR: IIa; LE: B) (in 1 hour with IV infusion of antihypertensives and BP monitoring 5/5 min) (GR: I; LE: A).

2 – For patients with SBP > 220 mm Hg, consider aggressive BP reduction with continuous IV infusion and frequent BP monitoring. (GR: IIb; LE: C).

Ischemic stroke13

1- For patients with no indication for thrombolytic therapy and initial BP > 220/120 mm Hg, BP should not be reduced more than 15-20%, maintaining DBP as 100-110 mm Hg in the first 24 hours.

2- The ideal BP level to be attained is not known, but there is consensus that no antihypertensive treatment should be instituted during the initial care, except if SBP is > 220 mm Hg or DBP is > 120 mm Hg. (GR: I; LE: C).

3- Consider the possibility of using thrombolytics after BP control. For patients with indication for thrombolytic therapy and initial BP > 185/110 mm Hg, BP should be reduced to < 185/105 mm Hg for, at least, the first 24 hours after the thrombolytic agent. (GR: I; LE: B).

Acute coronary syndromes

Coronary syndromes can be accompanied by BP elevation, because of a reflex of the ischemic myocardium. The increased PVR increases myocardial oxygen demand because of the increased left ventricular wall tension.

The IV nitrates reduce PVR, improve coronary perfusion and have an important systemic vasodilator effect, reducing preload and myocardial oxygen consumption. SNP is not indicated because of the coronary flow steal mechanism caused by generalized coronary vasodilation.[2,3]

Unstable angina / non-ST elevation MI / ST elevation MI14,15

To treat AH, persistent ischemia and HF, IV nitroglycerin is indicated in the first 48 hours. Its use should not exclude other interventions that have proven to reduce mortality, such as BBs or ACEIs. Nitroglycerin is, however, contraindicated in the presence of recent use of phosphodiesterase inhibitors (previous 24 to 48 hours). (GR: I; LE: B).

The IV use of BBs is indicated for individuals with AH who have no signs of HF, clinical evidence of low cardiac output, increased risk for cardiogenic shock or other contraindications relating to beta blockade. (GR: IIa; LE: B).

Acute pulmonary edema

Approximately one third of the patients admitted with APE and HE have preserved left ventricular function. Myocardial

Chart 3 – Medications used via parenteral route to treat hypertensive emergencies

Medications	Administration route and dosage	Beginning	Duration	Indications	Adverse events and precautions
SNP (arterial and venous vasodilator, stimulates cGMP formation)	Continuous IV infusion 0.25-10 mg/kg/min	Immediate	1-2 min	Most hypertensive emergencies	Cyanide poisoning, severe hypotension, nausea, vomiting. Careful in kidney and liver failure and high intracranial pressure. Protect from light
Nitroglycerin (arterial and venous vasodilator, nitric oxide donor)	Continuous IV infusion 5-15 mg/h	2-5 min	3-5 min	Coronary insufficiency, left ventricular failure with APE	Headache, reflex tachycardia, tachyphylaxis, flushing, metahemoglobinemia
Metoprolol (selective BB)	5 mg IV (repeat 10/10 min, if necessary up to 20 mg)	5-10 min	3-4 h	Coronary insufficiency, acute aortic dissection (in combination with SNP)	Bradycardia, advanced atrioventricular block, HF, bronchospasm
Esmolol (ultra-rapid selective BB)	Attack: 500 µg/kg intermittent infusion 25-50 µg/kg/min ↑ 25 µg/kg/min every 10-20 min. Maximum 300 µg/kg/min	1-2 min	1-20 min	Acute aortic dissection (in combination with SNP), severe postoperative hypertension	Nausea, vomiting, 1st-degree atrioventricular block, bronchospasm, hypotension
* Phentolamine (alpha-adrenergic blocker)	Continuous infusion: 1-5 mg Maximum 15 mg	1-2 min	3-5 min	Excess of catecholamines	Reflex tachycardia, flushing, dizziness, nausea, vomiting
* Trimethaphan (SNS and PSNS ganglionic blocker)	Continuous infusion: 0.5-1.0 mg/min. ↑ 0.5 mg/min up to maximum of 15 mg/min	1-5 min	10 min	Excess of catecholamines Acute aortic dissection	Tachyphylaxis
Hydralazine (direct vasodilator)	10-20 mg IV or 10-40 mg IM 6/6 h	10-30 min	3-12 h	Eclampsia	Tachycardia, headache, vomiting. Worsening of angina and infarction. Careful in high intracranial pressure
* Diazoxide (vasodilator of arteriolar smooth muscle)	Infusion 10-15min 1-3 mg/kg Maximum 150 mg	1-10 min	3-18 h	Hypertensive encephalopathy	Retention of sodium, water, hyperglycemia and hyperuricemia
* Fenoldopam (dopaminergic agonist)	Continuous infusion 0.1-1.6 µg/kg/min	5-10 min	10-15 min	AKI	Headache, nausea, flushing
* Nicardipine (CCB)	Continuous infusion 5-15 mg/h	5-10 min	1-4 h	Stroke, hypertensive encephalopathy, left ventricular failure with APE	Reflex tachycardia, phlebitis, avoid in patients with HF or myocardial ischemia
* Labetalol (alpha/beta-adrenergic blocker)	Attack: 20-80 mg 10-10 min Continuous infusion 2 mg/min (maximum 300 mg/24h)	5-10 min	2-6 h	Stroke, acute aortic dissection (in combination with SNP)	Nausea, vomiting, atrioventricular block, bronchospasm, orthostatic hypotension
* Enalapril (ACEI)	Intermittent infusion 1.25-5.0 mg 6/6h	15 min	4-6 h	Left ventricular failure with APE	Hypotension, kidney failure
Furosemide (loop DIU)	20-60 mg (repeat after 30 min)	2-5 min	30-90 min	Left ventricular failure with APE, hypervolemia	Hypopotassemia

**Not available in Brazil. SNP: sodium nitroprusside; cGMP: cyclic guanosine monophosphate; SNS: sympathetic nervous system; PSNS: parasympathetic nervous system; APE: acute pulmonary edema; AKI: acute kidney injury; HF: heart failure; ACEI: angiotensin-converting-enzyme inhibitor; DIU: diuretic.*

ischemia can also be involved in the pathophysiology of the APE associated with HE.[16,17] The HE with APE findings should be controlled in an ICU setting, with parenteral medication, monitoring and gradual BP decrease.[18]

Acute aortic dissection

Acute aortic dissection should always be considered in patients with precordial pain and BP elevation. Progression of the dissection is related to the BP level and ventricular ejection velocity.[19] Target SBP (120 mm Hg) should be achieved in 20 minutes. The isolated use of SNP is not ideal, because it increases HR and the aortic ejection velocity, and can worsen the dissection. Thus, SNP should be associated with a BB. In case of intolerance to SNP or contraindication to BBs, trimethaphan should be used.

Use of illicit substances

Illicit substances that raise BP, such as cocaine, crack, amphetamines and ecstasy, have sympathomimetic action.[20] Crack and cocaine increase the risk for stroke and acute coronary insufficiency.[21] In addition to increasing HR and BP, ecstasy have other effects, mainly serotoninergic syndrome, and can cause rhabdomyolysis and AKI.[22] A complicator of those intoxications is the concomitant ingestion of high doses of caffeine, present in energetic beverages, nicotine and alcohol. Those intoxications have in common the high level of plasma noradrenaline.[23] The treatment includes the use of BBs, alpha-blockers and CCBs.[24]

Rapidly progressive acute kidney injury

Acute and progressive renal function impairment is observed in patients admitted to hospital emergency units.[25] Individuals with greater renal function impairment have important cardiac dysfunction and greater loss of renal function during episodes of marked BP elevation, which is accompanied by high in-hospital mortality rates.[26] Rapidly progressive AKI is defined as a sudden renal function worsening in 48 hours, with specific classification criteria: RIFLE (*Risk, Injury, Failure, Loss, End-Stage Kidney Disease*) and AKIN (*The Acute Kidney Injury Network*).[27] Treatment includes hydralazine, loop DIUs and BBs. In case of no result, SNP can be considered until dialysis is performed.

The management for preeclampsia and eclampsia is reported in Chapter 9.

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