Guidelines on the management of arterial hypertension and related comorbidities in Latin America

Task Force of the Latin American Society of Hypertension*

THE PROBLEM OF HYPERTENSION AND RELATED COMORBIDITIES IN LATIN AMERICA

Worldwide risk of hypertension and challenges in Latin America

Hypertension is the most frequent chronic noncommunicable disease (NCD) occurring in early productive stage of life and the main risk factor for attributable mortality, years of life lost and years lost for incapacity adjusted by age and disability-adjusted life year [1].

The WHO estimated that hypertension prevalence is around 25% of the world population, predicting that it will increase by 60% by 2025 [2,3].

The population pyramid in Latin America and life expectancy have markedly changed in recent decades [4]. In addition, Latin America has also seen important changes in lifestyle of its population, with spreading of modern cosmopolitan unhealthier diets based on industrialized fast food, rich in saturated fat. Moreover, women have changed their social role model from the traditional one of housewives responsible for their family's diet, to become increasingly members of the working population. The diffusion of motorized public and private transportation and longer days of work have diminished physical activities. Recreation time of children has changed to an indoor cybernetic type of activity, and media promotion of fast food has influenced children's food choices. Though still living in a low and medium-income region, people of Latin America have adopted high-income country lifestyles with the consequence of an increase in cardiovascular risk factors, specially, obesity and hypertension.

Hypertension, global cardiovascular risk and noncommunicable diseases. Challenges in Latin American

With respect to other regions of the world, the implementation of a common policy for cardiovascular prevention in Latin America is confronted with both common and specific challenges.

Among the challenges common to all parts of the world are the growing global burden of morbidity and premature mortality associated with NCDs and the financial constraints and inefficiencies that traditional healthcare models have for coping with chronic diseases.

Specific challenges result from the fact that Latin America is one of the world regions with the greatest disparities in socioeconomic conditions and availability of healthcare. The proportion of people living in poverty is highly variable between different areas of Latin America [2], and a great difference also exists between structure, accessibility,

quality and funding of national health systems. There are 100% public systems such as the Cuban system or predominantly public as in Jamaica, as well as a wide variety of mixed systems such as those in Brazil, Ecuador and Peru. In the region [5], there are big contrasts regarding the equity of medical services; in countries like Bolivia, Peru and Guatemala, only 19.8, 14.3 and 9.3%, respectively, of people with low income have access to medical services.

The challenge of a new chronic care model

Traditional health systems are designed to take care of acute conditions but are not best suited to take care of patients with chronic conditions. As far as hypertension is concerned, the results of the inefficiencies of the current care models are that, despite long-time availability of classes of effective blood pressure (BP)-lowering drugs, the proportion of patients achieving optimal BP goals is disappointingly low. There is also a low perception of the high hidden morbidity associated with NCDs.

Current health services are more oriented to approach critical medical episodes than chronic conditions, which often require less sophisticated interventions, but continuity and integration of care.

Several organizational models for the management of chronic diseases have been proposed, the best known of which is Wagner Chronic Care Model (CCM) [6]. In general, these models focus on patient's empowerment and self-management and active interaction, between the patient and an efficient, accessible and proactive health system.

Although not all components of any CCM have been validated so far nor their applicability to the varieties of the social and geographical realities in Latin America has been tested, it is obvious that the major future task of medical societies, such as the Latin American Society of Hypertension (LASH) and the national hypertension societies existing in each country in Latin America, is that not only of raising the problem, but of collaborating closely with governmental and non-governmental bodies to develop and test new effective models of healthcare for prevention and follow-up of chronic cardiovascular risk factors and diseases. Adopting CCM is important, but, however, it is not enough, as CCM should be a component of a larger model that, by nature, might respond better and in a sustainable manner to the needs of the sick, with the premises of community participation, social justice, intersectorial participation and the responsibility of governments. However, it should also be considered that several components of the CCM have not been sufficiently studied and validated, and that CCM does not seem applicable to all regions.

We believe that the great challenge of any model will always be the optimal integration of all the strengths and preventive opportunities available in society, which transcends the boundaries of the health sector and requires the conscious and unconditional support of all governmental and nongovernmental factors.

Population prevention interventions and policies. WHO 25 × 25 proposal

There is no doubt that the prevention policy in which the greater progress has been made in Latin America is that associated with the Framework Convention on Tobacco Control, whose decisions were adopted by the WHO in 2003 (http://apps.who.int/iris/bitstream/10665/42811/1/9241591013.pdf).

This can be considered the first supranational public policy linked to the prevention of NCDs. On the contrary, there are countries that have fallen behind in implementing this strategy; for example: Cuba, Guyana and Paraguay. Also, the prevention policy on the sodium content in processed foods has been unevenly applied in Latin America, with some notable improvement in Brazil and Argentina. Likewise, in the Action Plan for the Prevention of Obesity in Children and Adolescents (http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=28890&lang=pt), including recommendations on food and physical activity in schools; only Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Peru and Uruguay have achieved significant results.

In general, however, there is less evidence of success for population prevention than for individual prevention strategies. However, several successful interventions in Latin America can be mentioned, such as the People's Pharmacy of Brazil, or Farmácia Popular do Brasil, aimed at providing the Brazilians with inexpensive medicines [7], the Health Has No Price [8], or Saúde Não Tem Preço, focused on the control of diabetes and hypertension; the Veracruz Initiative for Diabetes Awareness Project (file:///C:/Documents%20and%20Settings/aramirez/Mis%20documentos/Downloads/PAHO-VIDA-Diabetes-2010-Eng.pdf) in Mexico, with good results in controlling diabetic patients through self-management and primary healthcare and the Cienfuegos Global Project (http://www.fac.org.ar/revista/00v29n4/congreso/premio1.PDF) in Cuba, in which cross-sectorial and community actions for cardiovascular prevention were integrated in the 1990s and a high control of hypertension was achieved. The last project was part of the Community Actions for Multifactorial Reduction of Non-Communicable Diseases Study (http://www1.paho.org/English/HCP/HCN/IPM/cmn-about.htm), which is an activity of the Integrated Health Services Networks [Redes Integradas de Servicios de Salud (RISS)], an initiative of the Pan American Health Organization (PAHO/WHO). RISS has several points of intersection with chronic care models, but had a low priority on national and global political agendas. But since 2011 significant high-level agreements have been achieved under the auspices of the United Nations and other organizations. In this context, the target of reducing premature mortality from NCDs by 25% by 2025 has been proposed. This goal seems a utopia in Latin America, given the weaknesses and inequities existing in most health systems. However, led by PAHO an action plan of unprecedented scope and government support is being developed, in which several Latin American scientific societies (including LASH) and North American institutions such as the Chronic Disease Center (CDC) are integrated. One of the objectives of this strategy is to ensure the availability and accessibility of a group of key medications. As there is a general agreement about the cardiovascular benefits of lowering BP in hypertension, antihypertensive agents will be included in the programme. This will be a major step forward to achieve the ambitious objectives of the 25 × 25

Project. In addition, the LASH has also implemented a 20×20 project with the aim to increase, by 2020, a 20% the awareness of hypertension in Latin America.

In this way, the purpose of these Guidelines is to provide the essentials tools to effectively diagnose and treat arterial hypertension (AH) and associated diseases in the context of the medical and social conditions existing in Latin America.

Epidemiology of hypertension in Latin America

Identifying the incidence of AH is a difficult task, because of its commonly asymptomatic presentation, the limited knowledge among healthy people of the need to have a periodic control of their BP and the difficulties in the access to healthcare.

Epidemiological information is mainly focused on the prevalence of hypertension and many such studies, in different areas of Latin America, are available. Among these studies, the Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) study [9,10], a multicenter observational study including 11 550 individuals of both sexes, aged 25–64, from seven large cities: Barquisimeto (Venezuela), Bogotá (Colombia), Buenos Aires (Argentina), Lima (Peru), México DF (México), Quito (Ecuador) and Santiago de Chile (Chile), showed a prevalence range between 11.7 and 36.7%.

Epidemiological data also showed a high prevalence of the following modifiable risk factors for incident hypertension: unhealthy life style, dyslipidemia, obesity and diabetes. Additional nonmodifiable risk factors contributing to high prevalence of AH were: race, family history and increased life expectancy.

More recently, further epidemiological information has been provided by the PURE (Prospective Urban Rural Epidemiology) study [11,12], carried out in 19 countries worldwide with the aim to study the social factor influencing human habits, cardiovascular disease risk factors and the incidence of noncommunicable chronic diseases. Four countries from Latin America participated with 23 578 individuals between 35 and 75 years. Ambulatory BP monitoring (ABPM) was used to evaluate hypertension prevalence. The prevalence observed was: 50.8% in Argentina, 52.6% in Brazil, 46.7% in Chile and 37.5% in Colombia. Awareness was 57% and from these, 52.8% were receiving treatment and the proportion of individuals under control was 18.3%. Only 36.3% of the studied individuals under treatment had BP below 140/90 mmHg (http://www.fac.org.ar/revista/00v29n4/congreso/premio1.PDF). The problem of low percentage of controlled hypertension among patients is not restricted to Latin America because low percentages are found worldwide, also in developed countries, among patients with much higher income and in countries where health expenditure is higher: This indicates how difficult the BP control problem is. So, strategies are needed at political, educational and medical level to guarantee an easy access to healthcare, antihypertensive drugs and adherence training.

Hypertension is known to be often associated with other cardiovascular risk factors and comorbidities. Many scores are in use to predict the risk of a cardiovascular event according to a number of risk factors [13,14]. In Latin America, not only hypertension prevalence, but prevalence of other risk factors such as ethnicity, obesity, dyslipidemia, tobacco consumption, education and economic levels and prevalence of comorbidities, such as diabetes and metabolic syndrome, are different from those in United States of America or Europe. In applying other regions' or countries' scores the risk is to allot economic and organizational resources different from the needed ones. Chile has developed its own national scores, based on national data, which are used as an instrument for cardiovascular risk control in the Southern Pacific Consensus (Ecuador, Peru and Chile) [15]. It would be desirable that Latin America countries plan to collect their own data and elaborate their own scores.

Diabetes, obesity, dyslipidemia and metabolic syndrome

About 80% of patients with diabetes have concomitant hypertension. Among hypertensive patients, approximately 25% had diabetes. The longer life expectancy associated with an increased percentage of overweight and obesity has exponentially multiplied the cases of metabolic syndrome, diabetes and hypertension in Latin America [16]. The combination of diabetes and hypertension increases the cardiovascular and renal risk, substantially raising the incidence of cerebrovascular disease [17], coronary artery disease [18], retinopathy [19], peripheral artery disease (PAD) [20], erectile dysfunction [21] and renal failure [22].

In individuals with type 1 diabetes, the increase in BP is usually a consequence of diabetic nephropathy. In type 2 diabetes development of hypertension is associated with a series of interacting mechanisms, such as central obesity, insulin resistance, stimulation of both the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), sodium retention, increased oxidative stress and vascular reactivity, reduced baroreflex sensitivity and greater arterial stiffness [23,24]. Obesity is often associated with the obstructive apnea–hypopnea syndrome [25], which, by various mechanisms, involving sympathetic over-stimulation, promotes the BP elevation.

Diabetic nephropathy occurs in 30–40% of patients with diabetes and may contribute to the worsening of hypertension. Diabetic neuropathy often involves the autonomic nervous system. Cardiovascular autonomic neuropathy is associated with a worse prognosis and the risk of fatal outcomes such as arrhythmias and sudden death [26]. Abnormalities of the autonomic function can be demonstrated in 20–40% of patients with diabetes and are often already present upon initial diagnosis of the disease. In the Framingham Heart Study [27] blood glucose levels were inversely related with heart rate (HR) variability; low HR variability being usually considered as a sign of autonomic dysfunction.

Metabolic syndrome

In Latin America, the prevalence of metabolic syndrome appears to be increasing. Several local studies [28–33] have reported that the prevalence in adults ranges from 25 to 45%, with important differences between urban and rural areas, but comparisons are difficult because different definitions of metabolic syndrome were used. The metabolic syndrome was slightly more frequent in women (25.3%)

than in men (23.2%) and the age group with the highest prevalence was that over 50 years. The most frequent components of metabolic syndrome were low HDL-cholesterol levels (62.9%) and abdominal obesity (45.8%). Similar findings were reported in the multicenter CARMELA study on Latin American cities [31].

As mentioned above, the concept of metabolic syndrome is disputed mostly because it is hard to prove that the cardiovascular risk related to the metabolic syndrome is higher than that attributable to the sum of the risk attributed to each of its component. However, the metabolic syndrome is a clinical pattern with easily detectable features, yet largely under-detected, and defines, under a simple term, a cluster of metabolic alterations highly prevalent in Latin America.

Thus, it is a useful instrument to identify individuals at a higher risk of cardiovascular disease as well as of diabetes. It is commonly thought that all components of metabolic syndrome are associated with insulin resistance [34–36]. A recent consensus of the International Diabetes Federation Task Force on Epidemiology and Prevention, the National Heart, Lung, and Blood Institute, the American Heart Association, the World Heart Federation, the International Atherosclerosis Society and the International Association for the Study of Obesity [35] has proposed that the presence of three of the five following criteria can establish a diagnosis of metabolic syndrome:

(1) Increased waist circumference, the definition of which is population and country specific,
(2) Increased fasting serum triglycerides (at least 150 mg/dl), or drug treatment for elevated triglycerides,
(3) Reduced serum HDL-cholesterol (less than 40 mg/dl in men and less than 50 mg/dl in women). Drug treatment for reduced HDL-cholesterol, such as nicotinic acid, is an alternative indicator,
(4) BP in the high-normal or hypertensive range (SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg or current antihypertensive drug treatment),
(5) Elevated fasting glucose (at least 100 mg/dl) or drug treatment for elevated glucose plasma levels.

Several authors consider that central obesity is the main factor in metabolic syndrome and should be present to establish the diagnosis [37]. To define abdominal obesity in Latin America, a recent study [16], which has included capital cities of various countries, has recommended cutoff values of waist circumference of 94 cm for men and 88 cm for women.

Special conditions: stroke, cardiac and kidney diseases. Peripheral artery disease

Stroke
Hypertension is associated with all forms of cerebrovascular disease, including ischemic and hemorrhagic stroke, lacunar infarctions, leukoaraiosis, cognitive impairment and subcortical atherosclerotic encephalopathy [38]. In the INTERSTROKE [39] study, including data from Latin American countries, hypertension occurred in 31.5–45.2%

of patients with a previous ischemic stroke and in 44.5–73.6% of patients with a previous hemorrhagic stroke. In Brazil, Chile and some provinces in Argentina stroke is the principal cause of death. The Global and Regional Burden of Stroke Study [40], estimated that in 2010 there were 16.9 million strokes worldwide, 69% of which were in middle-income and low-income countries. The age-adjusted stroke mortality in Latin America ranges from 37 to 136 per 100 000 inhabitants. This marked difference may be related to differences in genetic background, life style, quality of care or completeness of registries.

There is also a marked variability in stroke prevalence, as reported by various studies. High stroke prevalence was found in an epidemiological survey in Central West Brazil (9.9%) [41] and in Cuba (7.8%) [42],whereas, in the 2nd National Health Survey in Chile, the stroke prevalence was 2.2% in patients older than 14 years and 8% in those older than 65 years [43].

In the Cardiovascular Health Study in USA ischemic stroke was the most prevalent (72.9%), followed by intra-cerebral bleeding (15.2%) and subarachnoid hemorrhage (6%) [44]. In the INTERSTROKE [39] study, the proportion of intracerebral bleeding was higher in the participating Latin America countries than in high-income countries in North America and Europe.

Hypertension has been reported in 75% of the patients with lacunar infarcts. Leukoaraiosis (a rarefaction of the white matter) has been linked with chronic ischemia, aging and hypertension. Multiple brain infarctions and the ischemic lesions in the white matter have been associated with cognitive impairment and dementia. In Latin America, insufficient data on lacunar infarctions are available.

Cardiac diseases
Hypertension is associated with left ventricular (LV) functional and structural abnormalities, including LV hypertrophy. It is also a major determinant of coronary heart disease, heart failure and arrhythmias. In the INTERHEART study [45,46], the hypertension attributable risk for acute myocardial infarction was 23.4% for the overall population and 32.9% for Latin America. Furthermore, hypertension has been reported as an antecedent of heart failure in variable proportions (14–76%) in Latin American patients. Recently, it was reported that hypertensive heart disease was the cause of 21% of heart failure in a study that included 858 Latin American patients from Argentina, Chile, Colombia and Ecuador [47].

A Latin America multicenter echocardiographic study [48] has reported that 30–50% of individuals with mild–moderate hypertension and as many as 90% of those with severe hypertension have LV hypertrophy. Prevalence of diastolic dysfunction in mild-moderate hypertension ranged from 30 to 50%, and in severe hypertension between 65 and 90%. An enlarged left atrium was found in 50% of hypertensive patients. Cardiac damage associated with hypertension appears to be influenced by ethnic factors. For instance, in United States of America, a higher prevalence of LV hypertrophy has been reported in the Hispanic population and even larger proportion has been found in people of Caribbean origin. This has been attributed to

African ancestors with increased salt sensitivity. In Mexican patients, a high prevalence of LV hypertrophy has been related to a high prevalence of obesity and metabolic syndrome [49,50].

Kidney diseases

The kidney has a key role in BP regulation and the pathogenesis of hypertension through control of sodium excretion, the RAAS and body fluid volume regulation [51]. Primary kidney disease is the most frequent cause of secondary hypertension, with renovascular disease representing 0.5–4% of the secondary causes of hypertension [52,53]. Renal artery stenosis can be seen frequently in older patients, as an atherosclerotic lesion, and can also be observed in young individuals, predominantly women, as fibro-muscular dysplasia. Renal artery stenosis does not invariably induce hypertension and in many cases is simply a casual finding in patients with essential hypertension. In other cases, it may induce severe hypertension with heart failure, recurrent pulmonary edema, renal dysfunction and chronic failure. Renovascular hypertension should be suspected in the presence of treatment resistant hypertension, malignant or accelerated hypertension, or an abdominal systo/diastolic murmur [52,53]. Although the study of renal arteries with color Doppler echography is examiner dependent, it can be used as a screening method. However, magnetic resonance angiography or computed tomography angiography must be used as confirmatory study [54,55]. Selective renal artery angiography is the gold standard method and applicable when revascularization is planned [56].

Kidney damage is also a consequence of high BP and hypertensive nephrosclerosis is the second cause of admission to chronic dialysis, after diabetes mellitus. The progression of renal disease appears to be related with the degree of BP control. In Latin America, renal replacement therapy for end-stage renal disease was followed-up in a registry including 20 countries, representing 99% of the region population. The prevalence of renal replacement therapy has increased in Latin America [57] from 119 patients per million in 1991 to 660 patients per million in 2010. The higher rates were observed in Puerto Rico (1366 per million) and in Argentina, Mexico, Uruguay and Chile (between 777 and 1136 patients per million).

Peripheral artery disease

The presence of PAD suggests the presence of an advanced arterial wall damage that may also involve coronary or cerebral arteries, even without clinical signs [58]. As a manifestation of atherosclerotic disease, PAD risk factors are the same as those identified for other vascular areas, with smoking and diabetes mellitus having a stronger association with PAD than with coronary or cerebral-vascular artery disease [59]. Measurement of the ankle-brachial index (ABI) performed with automated devices or with a continuous wave Doppler unit and a sphygmomanometer is strongly recommended [60]. An ABI less than 0.9 is a strong evidence of PAD and advanced atherosclerosis.

No information about prevalence of PAD in Latin America has been reported.

TABLE 1. Blood pressure classification

Classification	SBP (mmHg)	DBP (mmHg)
Normotension		
Optimal BP	<120	<80
Normal BP	120–129	80–84
High-normal BP	130–139	85–89
Hypertension		
Grade 1	140–159	90–99
Grade 2	160–179	100–109
Grade 3	≥180	≥110
Isolated systolic hypertension	≥140	<90

When SBP and DBP values are in different BP categories, the individual should be classified in the higher BP category. BP, blood pressure.

CLASSIFICATION, DIAGNOSIS, AND RISK STRATIFICATION IN ARTERIAL HYPERTENSION

Blood pressure classification

Hypertension is diagnosed when BP values are at least 140/90 mmHg. Above this value, hypertension can be subdivided in grade 1, 2 or 3 [61] as shown in Table 1.

When SBP and DBP values correspond to different grades, the higher grade should be used to classify the patient's hypertension. When SBP is at least 140 mmHg, and DBP less than 90 mmHg, isolated systolic hypertension is diagnosed and hypertension grade is classified according to the SBP values.

Hypertension can be subdivided in:

(1) *Primary, essential or idiopathic hypertension*: when BP is consistently higher than normal with no known underlying cause (around 90–95% of all cases).
(2) *Secondary hypertension*: when BP is increased as the result of an underlying, identifiable, often correctable cause (around 5–10% of the total hypertensive patients).

When office BP and ambulatory or home BP values are considered, four groups can be identified [62–64]:

(1) Patients with normal BP values with both methods (normotensives or sustained normotensives),
(2) Patients with increased BP values with both methods (hypertensive patients or sustained hypertensive patients),
(3) Those with normal BP values in the office and hypertensive values with the ABPM or at home (masked hypertensive patients), and
(4) Those with hypertensive values in the office and normal values with the ABPM or at home (white coat hypertensive patients).

Diagnosis

Office BP measurements should be performed using an auscultatory or oscillometric semiautomatic sphygmomanometer, validated and calibrated periodically. Today, the mercury sphygmomanometer is used less frequently and in

some countries its use is forbidden to avoid possible contamination.

The measurement of BP must be done in both arms with the patient in the sitting position for several minutes and, if a difference more than 10 mmHg occurs regularly, the arm with higher pressure should be used for future measurements. Measurements should be done at least twice, and if a difference greater than 4 mmHg is observed, a third measurement must be performed. To assess the presence of orthostatic hypotension, defined as a reduction of SBP at least 20 mmHg or DBP at least 10 mmHg from seated values, it is recommended to measure BP one and 3 min after assumption of the standing position. Heart rate should always be measured [65,66].

The diagnosis of hypertension requires further confirmation. To this purpose, there are three methods to verify the diagnosis:

Office or clinic measurement

It is recommended that the diagnosis of hypertension be based on at least two BP measurements per visit and on at least, two consecutive visits separated by 1 week. Hypertension is diagnosed when the average BP calculated is at least 140 or at least 90 mmHg at both visits [67].

Out of office measurement

The other two methods are known as out of office BP measurements [63,64]. They are recommended because they provide a large number of measurements, away from the medical environment, and are more reliable than the office (or clinic) measurements [68]. Apart from being used to confirm a diagnosis of AH or normotension, out of office measurements enable the diagnosis of either white coat hypertension or masked hypertension.

Home blood pressure monitoring

The measurements of BP by the patient or a member of the family with an automatic or semiautomatic validated device is a highly recommended approach. It is important to provide verbal and/or written instructions to the patient. For diagnostic evaluation, BP should be measured daily on at least 4 days, or preferably 7 consecutive days, twice daily, in the morning and in the evening, after 5 min of rest in the seated position. Home BP is the average of these readings, with exclusion of the monitoring measurement in the first day [68,69].

Ambulatory blood pressure monitoring

Twenty-four-hour average ambulatory BP has been consistently shown to have a stronger relationship with morbid or fatal events than office BP [62]. A validated instrument should be used, and at least three to four measurements per hour should be obtained during daytime and three measurements per hour during the night. Cutoff values defining AH are different when BP is taken in the doctor's office or clinic and out of office. Cutoff values are given in Table 2.

BP measurements with a sphygmomanometer or automatic or semiautomatic devices, in the office, clinic or pharmacy are the most widely available ways to evaluate

TABLE 2. Definitions of hypertension by different types of blood pressure measurement

	SBP (mmHg)		DBP (mmHg)
Office BP	≥140	Or	≥90
Home BP	≥135	Or	≥85
Ambulatory BP			
Daytime	≥135	Or	≥85
Night-time	≥120	Or	≥70
24 h	≥130	Or	≥80

BP, blood pressure.

BP in Latin America. So this way of measuring BP values should be considered in the routine approach.

The use of ABPM, though indisputably providing very valuable information, heavily depends on the social and economic context. In Latin America, the use of ABPM is highly limited, especially for low-income and medium-income people, because public and private health providers do not cover the cost of the procedure.

Home BP monitoring seems more easily applicable in Latin America both for hypertension diagnosis and follow-up of treatment, provided validated devices are used. However, the cost of devices and measurement expertise are aspects that must be taken into account when prescribing this procedure.

Search for hypertension-related subclinical organ damage

The most frequent types of subclinical organ damage in hypertension concur to the assessment of total cardiovascular risk. So, quantifying the organ damage in all hypertensive patients would certainly add precision to the management of hypertension. However, considering the difficult social and economic conditions of many Latin American countries and the evidence presented in the 'TREATMENT OF HYPERTENSION' section, that all hypertensive patients should receive antihypertensive treatment independently of absence or presence of organ damage, it is recommended that routine search of subclinical organ damage be limited to the following: serum creatinine, electrocardiographic (and eventually echocardiographic) signs of LV hypertrophy. If diabetes is present, the urinary albumin-to-creatinine ratio should also be measured. Table 3 provides accepted echocardiographic cut-offs for definition of LV hypertrophy and diastolic dysfunction.

TABLE 3. Echocardiogram measurements for left ventricular hypertrophy and diastolic dysfunction

Measurements	Abnormal
Left ventricular mass index (g/m^2)	>95 (women), >115 (men)
Relative wall thickness	>0.42
Septal velocity (e') (cm/s)	<8
Lateral wall velocity (e') (cm/s)	<10
Left atrial volume (ml/m^2)	≥34
Left ventricular filling pressure (e/e')	≥13

TREATMENT OF HYPERTENSION

General principles

Since 1996, a large number of trials comparing BP-lowering drugs with placebo (or no treatment) in hypertensive patients, complemented by trials of more versus less intense BP lowering, have shown that antihypertensive treatment can significantly reduce the incidence of fatal and nonfatal events associated with hypertension [70]. They also provided overwhelming evidence that lowering high BP is the core approach to reduce the increased burden of cardiovascular and renal disease associated with hypertension [70].

Middle-income and low-income regions, as most of Latin American countries, have a five times greater burden of disease than high-income countries, with access to less than 10% of the global economic treatment resource. There is a massive amount of evidence linking socioeconomic status with the conventional risk factors for hypertension [1,2,71,72]. A low socioeconomic status is known to be associated with a high health risk lifestyle as a consequence of poor dietary habits and high prevalence of smokers and alcohol consumers [9–11,31,45]. A recent world systematic survey of socioeconomic status and hypertension, including Latin-America countries, such as Brazil and Argentina, provided evidence of an increase in the risk of hypertension among the lowest socioeconomic categories for income, occupation and education [11]. Among these three categories of risk, education appears to be the strongest predictor of hypertension burden. Therefore, priority attention in therapeutic management of hypertension should be given to those individuals with social risk conditions such as homelessness, poverty, lack of education or unemployment, which are at the highest risk of fatal events and often receive no treatment whatsoever.

Blood pressure treatment initiation and targets

Treatment initiation

The current opinions of the LASH on treatment threshold and target have been updated in a document recently published [73]. These opinions are briefly summarized below. Most of the randomized controlled trials, providing evidence of the benefits of antihypertensive treatment, investigated patients in whom baseline SBP was at least 160 mmHg, who could currently be classified as grade 2 or 3 hypertensive patients, or patients under background antihypertensive treatment at the time of randomization, who could likely be classified at least as grade 2 hypertensive patients. Therefore, previous guidelines [74–77] favoring treatment of grade 1 hypertensive patients at low–moderate cardiovascular risk recognized that direct evidence derived from specific trials was poor and the recommendation to treat these patients was based on expert opinion only. Since then, more solid evidence has been provided. A meta-analysis of BP-lowering has been done only including those trials in which the average baseline BP values (in absence of background antihypertensive treatment) were within the grade 1 hypertension range (SBP: 140–159 mmHg and DBP: 90–99 mmHg) and cardiovascular risk was low-to-moderate (10 years cardiovascular death risk lower than 5% in the placebo group) [78]. This meta-analysis has shown that, in these patients, BP-lowering drug treatment significantly reduced relative and absolute risk of stroke, coronary events and all cause mortality [78] and has therefore provided. a stronger support to the recommendation to initiate drug treatment in grade 1 hypertensive patients at low to moderate risk than the arguments that could be used in previous guidelines [73]. Furthermore, the recent results of the Heart Outcomes Prevention Evaluation 3 [79] trial also showed that antihypertensive treatment is associated with a reduction of major cardiovascular events compared with placebo, in patients with a basal SBP more than 143.5 mmHg and at intermediate cardiovascular risk.

Whether the recommendation to initiate antihypertensive treatment when hypertension is still in the grade 1 range also extends to the elderly is widely debated. On the contrary, randomized controlled trials of BP lowering in the elderly (variably defined as older than 60, 65 or 70 years) were limited to individuals with grades 2 and 3 hypertension. However, it is the Task Force opinion that the very favorable results of all these trials make it prudent to initiate antihypertensive therapy also in elderly grade 1 hypertensive patients provided they are in good physical conditions and do not present important adverse reactions to treatment, such as excessive or orthostatic hypotension, dizziness and physical or mental deterioration.

Blood pressure targets of treatment

Another debated problem is that of the BP values that should be achieved by treatment to optimize fatal and nonfatal event prevention. Very few trials, mostly in small groups of patients and with small numbers of incident outcomes and hence with low statistical power, have specifically investigated the possible benefits of lowering SBP and DBP below given cutoffs. Only recently, the Systolic Blood Pressure Intervention Trial (SPRINT) [80], which enrolled 9361 patients without diabetes, showed that BP-lowering treatment aiming at a SBP lower than 120 mmHg, significantly reduced the composite of major cardiovascular events and all cause of death compared with a less intense treatment aiming at SBP lower than 140 mmHg. It should be noted, however, that in the more intensely treated group, there was an increased number of episodes of hypotension, syncope and acute renal failure, which even exceeded the number of cardiovascular events prevented. Furthermore, the point has been raised that the method of BP measurement in this study (automatic device in absence of a doctor or a nurse) was quite different from that used in all other trials and is likely to provide BP values considerably lower than those traditionally measured in the doctor's office or clinic (and even lower than ambulatory BP values) [81].

Therefore, the best evidence currently available on target BP values is based on meta-analyses stratifying BP-lowering trials according to the BP levels achieved by active (or more active) treatment: between 140 and 150 mmHg, between 130 and 140 mmHg and below 130 mmHg. A meta-analysis of 34 trials on 138 412 individuals, also including SPRINT data has shown that lowering SBP to values between 130 and 140 mmHg significantly reduced relative and absolute

risks of all the major cardiovascular events and mortality [82]. Lowering SBP below 130 mmHg also significantly reduced relative risk of most outcomes, but the absolute cardiovascular risk reduction is definitely smaller and the risk of permanent discontinuation for adverse events significantly greater [83].

In conclusion, the general evidence-based recommendation can be given to aim at SBP values below 140 mmHg (between 140 and 130 mmHg) and DBP values below 90 mmHg in all hypertensive patients independently of their level of cardiovascular risk. Also, SBP values below 130 mmHg appear safe, but the further benefits of a more intense SBP reduction are rather small and must be balanced with the risk of excessive side effects. In individual cases the physicians will be guided by the extent and relevance of treatment-related adverse effects [83].

Treatment strategies: lifestyle changes

Lifestyle measures should be instituted, whenever appropriate, in all hypertensive patients, including those who require drug treatment. The purpose is to lower BP, to control other risk factors and, if pharmacological treatment is required (as frequently is), to reduce the number or the doses of antihypertensive drugs. Lifestyle measures are also advisable in patients with normal and high normal BP to reduce the risk of developing hypertension and target organ damage. The lifestyle measures that are widely recognized to lower BP and/or cardiovascular risk, and that should be considered are:

(1) Weight reduction (and weight stabilization)
(2) Reduction of excessive alcohol intake
(3) Physical activity
(4) Reduction of sodium intake (<6 and >3 g)
(5) Increase of dietary K^+ intake
(6) Increase in fruit and vegetable intake and decrease in saturated and total fat intake
(7) Smoking cessation.

BMI and abdominal circumference are reliable clinical markers in cardiovascular prevention. Optimal BMI for the hypertensive population is between 18.5 and 25 kg/m². According to a recent study (cited in the 'Diabetes, obesity, dyslipidemia, and metabolic syndrome' section), the upper limit for an adequate abdominal circumference in Latin America is 94 cm for men and 88 cm for women [16].

Physical activity is an important complement to diet for weight and BP reduction. All hypertensive patients living a sedentary life, and particularly those with additional risk factors should be encouraged to do physical exercise for at least 30 min daily and at least 5 days a week [84]. A percentage of isometric exercise must be included since sarcopenia and muscular strength has been shown to be an important risk factor for cardiovascular diseases [85].

Because long-term compliance with lifestyle measures is low and the BP response highly variable, patients under nonpharmacological treatment should be followed-up closely to appropriately decide the moment where to start with pharmacological treatment.

Because of the high prevalence of obesity and metabolic syndrome in Latin America [28–33] public health systems should be engaged in leading strategies campaigns to increase physical activity, reduce salt intake and quit smoking. In Argentina, the Health Department has promoted a very active campaign for salt reduction in industry food, which has been considerably successful.

Treatment strategies: pharmacological treatment

Choice of antihypertensive drugs

The large number of randomized placebo-controlled trials testing the effects of BP lowering by drugs on cardiovascular morbidity and mortality (and the quantitative assessment of the extent of these beneficial effects by meta-analysis) [70] has been mentioned in the 'General principles' section. The question as to whether the beneficial effects of BP lowering differs according to the class or classes of drugs employed has also been approached by a large number of randomized trials comparing head to head similar BP reductions produced by different classes of drugs. A recent meta-analysis [86] has identified 50 trials with 52 two-drug comparisons, including as many as 247 006 hypertensive patients: provided that BP was equally reduced by the two treatments, the meta-analysis has shown that differences between antihypertensive drug classes are quantitatively minor, and limited to specific cardiovascular events, the effects of the various drug classes on the composite of major cardiovascular events being quite similar. Therefore, antihypertensive treatment can be based on the use of five major classes of drugs, each of which has been widely used both in placebo-controlled and head-to-head comparative trials: diuretics (chlorthalidone, indapamide or thiazides), calcium channel blockers (CCB), angiotensin-converting-enzyme-inhibitors (ACE-I), angiotensin receptor blockers (ARB) and β-blockers. All these drug classes are suitable for the initiation and maintenance of antihypertensive treatment alone or in combination (Fig. 1).

However, there are specific conditions in hypertension that may make specific classes of drugs preferable as possible first choice:

(1) ACE-Is or ARBs in patients with metabolic syndrome or type 2 diabetes, because metabolic variables are not affected or may even be improved by these agents,
(2) ACE-Is or ARBs in patients with renal dysfunction and microalbuminuria or proteinuria, because these agents slow progression to chronic renal failure and dialysis,
(3) ACE-Is or ARBs in patients with systolic or diastolic LV dysfunction,
(4) ACE-Is, ARBs and CCBs in patients with LV hypertrophy, because these agents facilitate LV hypertrophy regression,
(5) β-blockers in patients with coronary heart disease,
(6) CCBs (dihydropyridines) or diuretics in elderly hypertensive patients with isolated systolic hypertension and in hypertensive patients of African descent,
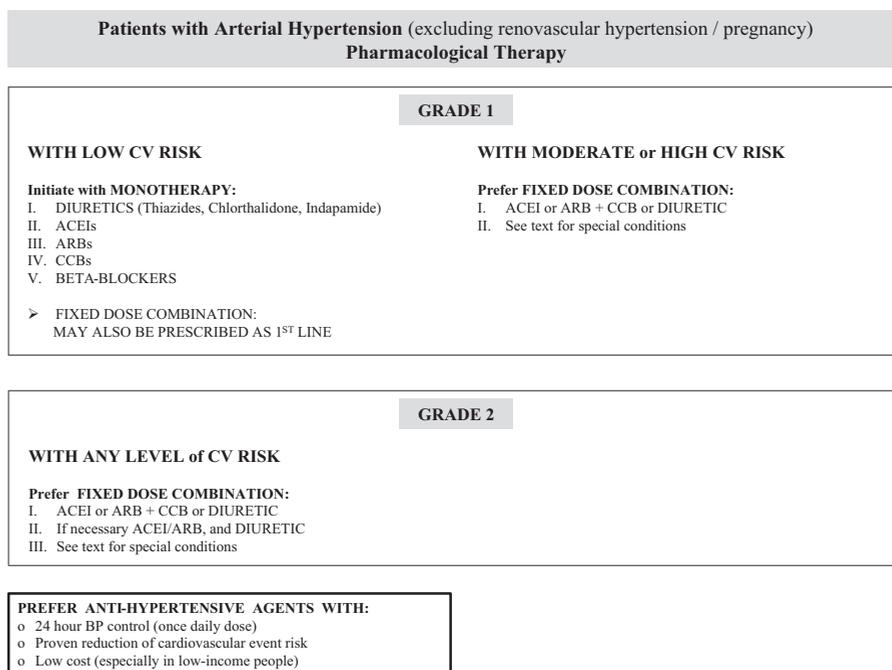
Patients with Arterial Hypertension (excluding renovascular hypertension / pregnancy)
Pharmacological Therapy

GRADE 1

WITH LOW CV RISK

Initiate with MONOTHERAPY:
I.   DIURETICS (Thiazides, Chlorthalidone, Indapamide)
II. ACEIs
III. ARBs
IV. CCBs
V.   BETA-BLOCKERS

➢ FIXED DOSE COMBINATION:
   MAY ALSO BE PRESCRIBED AS 1ST LINE

WITH MODERATE or HIGH CV RISK

Prefer FIXED DOSE COMBINATION:
I.   ACEI or ARB + CCB or DIURETIC
II. See text for special conditions

GRADE 2

WITH ANY LEVEL of CV RISK

Prefer FIXED DOSE COMBINATION:
I.   ACEI or ARB + CCB or DIURETIC
II. If necessary ACEI/ARB, and DIURETIC
III. See text for special conditions

PREFER ANTI-HYPERTENSIVE AGENTS WITH:
o 24 hour BP control (once daily dose)
o Proven reduction of cardiovascular event risk
o Low cost (especially in low-income people)

FIGURE 1 Pharmacological therapy.

(7) Alpha blocking agents, in patients with prostatic hypertrophy,

(8) Chlorthalidone, indapamide or thiazides in African Americans, elderly hypertensive patients or low-income people, who cannot afford the cost of other drugs,

(9) Diuretics, ACE-Is, β-blockers (metoprolol, bisoprolol, carvedilol or nebivolol) and aldosterone antagonists, in hypertensive patients with heart failure,

(10) ACE-Is and β-blockers, in post MI patients,

(11) Diuretics (slow release indapamide) possibly associated with an ACE-I in the prevention of recurrent stroke,

(12) Patients with peripheral vascular disease (in addition to smoking cessation and regular aerobic exercise) may be prescribed CCBs to lower BP without exacerbation of symptoms,

(13) ACE-Is or ARBs, in patients with recurrent atrial fibrillation; β-blockers or verapamil in sustained atrial fibrillation

(14) Mineralocorticoid receptor antagonists, mainly spironolactone and/or an alpha blocker, in resistant hypertension.

In addition, the following criteria should be considered in the choice of a specific drug in each individual patient:

(1) The adverse or side effects of the drugs, because these are the most important cause of noncompliance; drugs are not equal in terms of adverse effects, particularly in individual patients,

(2) The duration of effects of the drugs: compounds which exert their antihypertensive effect over 24 h with once a day administration should be preferred because a simple treatment schedule always favors compliance,

(3) The previous favorable or unfavorable experience of the individual patient with a given class of compounds,

(4) The effect of drugs on cardiovascular risk factors in relation to the cardiovascular risk profile of the individual patient,

(5) The presence of subclinical organ damage, clinical cardiovascular disease, renal disease or diabetes, which may be more favorably treated by some drugs than others,

(6) The presence of other disorders that may limit the use of particular classes of antihypertensive drugs,

(7) The possibilities of interactions with drugs used for other comorbidities,

(8) The cost of drugs, either to the individual patient or to health providers (cost considerations should never predominate over efficacy, tolerability and protection for the individual patient).

Monotherapy and combination therapy

How antihypertensive treatment should be initiated and how quickly the desirable target BP values should be attained is widely debated. Traditionally, guidelines recommended limiting initial treatment to lifestyle measures in grade 1 and 2 patients for several months or weeks, according to the level of the total cardiovascular risk (low or moderate) before adding drugs. The Task Force shares the opinion recently expressed by a group of international experts [87] that drug treatment can be delayed for some time only in grade 1 patients with no other risk factors and therefore at low relative and absolute cardiovascular risk, because delaying drug treatment to a time when

cardiovascular risk is higher and organ damage is present may be associated with a higher cardiovascular residual risk [88] and limit the full benefits of drug treatment. These considerations also influence the question whether drug treatment should be started with monotherapy or combination therapy. Individuals with grade 1 and low or moderate cardiovascular risk can be started with monotherapy and combined therapy considered if BP control in not achieved. Combination therapy is recommended as initial therapy for individuals with hypertension grade 2 or 3, independently of risk stratification. For grade 1 hypertensive patients with high and very high cardiovascular risk, combination therapy is also recommended as initial treatment. When combination therapy is chosen, fixed dose combination preparations should be used whenever possible, as they are associated with higher adherence to treatment [89].

After starting pharmacological BP treatment, the patient could be evaluated every 4–6 weeks to consider drug prescription modifications. Doses may be increased or drugs may be added to achieve BP control.

The most suitable combinations are those that include an ACE-I or ARB with a diuretic or a CCB. In the ACCOMPLISH trial [90], the combination of an ACE-I with a CCB was found superior to the combination of the same ACE-I with hydrochlorothiazide in protecting against cardiovascular morbidity and mortality in high cardiovascular risk patients, including patients with diabetes or coronary artery disease. However, when three drugs are needed, a diuretic should necessarily be part of the prescription in a triple therapy.

Diuretics and traditional β-blockers (i.e. without vasodilating action), especially in combination between them, are not first choice in patients with metabolic syndrome or at high risk of diabetes, but vasodilating β-blockers such as carvedilol and nebivolol, and slow release indapamide may be suitable. Combination of two blockers of the renin–angiotensin system, such as an ACEI or an ARB, should be avoided as they have been shown to be associated with an excess of adverse events, particularly acute renal failure [91,92].

Resistant or refractory hypertension

There is a number of hypertensive patients whose BP remains above target values despite institution of nonpharmacological and pharmacological treatment including full doses of three or more medications, one of these being a diuretic, and possibly including an antialdosterone agent. These cases are defined as treatment resistant or refractory hypertension. Their prevalence has been reported to be of around 10% of treated hypertensive patients. However, a precise diagnosis requires 24-h ABPM to exclude white-coat hypertension and careful control of adherence to treatment (failure of treatment adherence is probably the most frequent cause of resistant hypertension). The prevalence of resistant hypertension is likely to decrease with a more frequent use in these patients of aldosterone antagonists, which appear to be very effective. Renal denervation has also been employed with beneficial effects. However, confirmation of these results from ongoing controlled trials is required. Carotid sinus stimulation has also been recommended in these patients.

Overcoming treatment barriers

To achieve the major goals of antihypertensive treatment, that is reducing cardiovascular and renal morbidity and mortality and increasing quality of life, treatment should be initiated promptly (possibility before significant organ damage develop), be effective (achieving prescribed targets) and sustained (targets should be attained lifelong). To achieve these goals, there are difficulties worldwide, which are specifically high in Latin America.

In isolated or far away small populations in Latin America, physicians are not present. Effort should be done to treat health personnel who can help in those areas by using telemedicine support or diagnostic and therapeutic procedures from a distance. In addition to proper attention by doctor or nurse or health personnel, antihypertensive treatment also requires patient empowerment (awareness and knowledge of treatment benefits), active participation of the family, in particular, and the society, in general, and a proper approach of health decision-makers to complete the virtuous circle of efficient, equitable, sustainable and sustained access to good quality medical practice to an appropriate prescription and full adherence and persistence of patients to prescribed lifestyle changes and drugs [93].

Indeed, despite the large number of effective hypertensive drugs available and the overwhelming evidence of the benefits of BP control, the current rates of BP control are very low worldwide. Data from the PURE study [12] showed that, in only 20–30% of hypertensive patients, BP was lower than 140/90 mmHg. Although several factors are responsible for this situation, clinical inertia and low patients' adherence account for most of this failure. Poor adherence to treatment represents a major barrier to hypertension treatment. It is estimated that approximately 40% of patients will discontinue treatment within 2 years of initiation. This percentage may increase to 61% within 10 years. Despite the lack of detailed information in Latin America, the main reasons for poor adherence can be ascribed to socioeconomic factors and the insufficient number of drugs freely available for BP target achievement. Different approaches have been proposed to improve adherence: educational and training programs, improving patient's knowledge regarding the goals of BP control and active participation of governments. There are clearly many barriers to success in countries of all income levels. Progress in overcoming this issue will require a comprehensive understanding of the barriers and facilitators to implementing changes [93].

Recent systematic reviews have identified barriers to the control of hypertension at two different levels: at the service level (related to characteristics of individual providers and patient experience with front line services) and at the health system level (related to financial, organizational and governance issues). Examples of barriers at the service level included difficulties with transportation, inappropriate opening hours, and difficulties in making clinic appointments, inaccessible healthcare facilities, and lack of insurance and high costs of treatment [94]. Improvement in the availability and affordability of key medicines is an important challenge that was recently approached by the WHO, which expects to achieve a target of 50% in the use of key medicines by 2025. To reach this goal, these medicines need to be made widely available and affordable. The

PAHO is the other organization involved in improving the availability and affordability of medications to control chronic NCDs and their risk factors and, particularly, treatment and control of hypertension. The PAHO recognizes that in the last two years new and important evidence has been published in relation to the treatment of hypertension, including clinical trials and meta-analysis of high quality, as well as new guidelines and consensus documents. For this reason, the PAHO has considered it is important that the list of the antihypertensive drugs included in the Strategic Fund of the PAHO be updated on the basis of a review of available evidence. With this objective, the PAHO has signed an agreement with the LASH for the elaboration of a technical report about medications that could have a priority in the PAHO Strategic Plan for free supply of drugs in populations with very low income in Latin America.

SPECIAL POPULATIONS

Hypertension in diabetes

Benefits of blood pressure reduction

Hypertension control is a priority target for the reduction of cardiovascular and renal risk, particularly in patients with type-2 diabetes mellitus, as first shown by the Hypertension Optimal Treatment (HOT) study [95] and, shortly thereafter, by the United Kingdom Prospective Diabetes Study (UKPDS) [96]. In the HOT study [95], antihypertensive treatment aiming at DBP less than 80 mmHg markedly and significantly reduced the risk of major cardiovascular events and total mortality, when compared with treatment strategies aiming at DBP less than 85 or less than 90 mmHg. In the UKPDS study [96], more versus less intensive BP-lowering (achieved SBP/DBP values of 144/87 mmHg resulted in a 24% reduction of any endpoint related to diabetes, 32% reduction of diabetes related deaths, 44% of strokes and 37% reduction of microvascular complications of diabetes. The beneficial results of antihypertensive treatment in diabetes have been subsequently confirmed by a number of randomized trials.

Blood pressure targets

There is some controversy about SBP and DBP targets in patients with diabetes. DBP levels currently recommended (<85 mmHg) are based on the HOT trial [95], showing that, among hypertensive patients with diabetes, the greatest reduction in cardiovascular events occurred in those randomized to DBP levels less than 80 mmHg (values attained 82 mmHg). The SBP target currently recommended (SBP values between 140 and 130 mmHg) is based on the fact that most of the randomized trials showing benefits from BP-lowering in patients with diabetes rarely reduced SBP below 140 mmHg and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [97], found that SBP values below 120 mmHg were not associated with cardiovascular outcome rates lower than in the control group, whose SBP goal was below 140 mmHg. Although in ACCORD [97], stroke was significantly reduced by attaining the lower SBP target (<120 mmHg), the number of strokes was rather small and the group randomized to the lower SBP target had much higher rates of severe adverse events, such as hypotension, hypokalemia and increased serum creatinine. The main result of the ACCORD trial [97] are consistent with data from the Swedish register study showing that among patients with diabetes those with SBP less than 130 mmHg had the same incidence of cardiovascular events as those with SBP less than 140 mmHg [98]. Finally, a quite recent meta-analysis of all trials including hypertensive patients with diabetes [99] has shown a marked reduction in cardiovascular events is achieved when SBP is reduced to values between 130 and 139 mmHg, and no or little further benefit is obtained by lowering SBP below 130 mmHg.

In conclusion, although earlier guidelines used to recommend low SBP/DBP targets in patients with diabetes (below 130/80 mmHg), since 2013 most guidelines [74,75,77] recommend SBP less than 140 mmHg and DBP less than 90 or 85 mmHg. Whether lower BP targets may be beneficial in younger people with diabetes with recent disease, and higher targets should be reserved for people with diabetes over 60 years of age and established cardiovascular disease is at present undecided.

Proteinuria

Normal albuminuria is defined as urinary albumin excretion of less than 30 mg every 24 h and microalbuminuria as daily urinary albumin excretion of 30–300 mg in 24 h (which corresponds to 20–200 μg/min). Presence of microalbuminuria should be searched in all patients with type 1 diabetes since 5 years from diagnosis of diabetes and in those with type 2 diabetes soon after diagnosis of diabetes. Measurement of albuminuria can be performed in a random urine sample and values must be confirmed in, at least, 2–3 collections within 3–6 months. In random urine samples, normal albuminuria is defined as values less than 17 mg/l (equivalent to less than 30 mg/24 h, 30 mg/g creatinine or 20 μg/min) and microalbuminuria (incipient diabetic nephropathy) is defined as values between 17 and 174 mg/l (equivalent to 30–300 mg/24 h, 30–300 mg/g creatinine or 20–200 μg/min) and full proteinuria (established diabetic nephropathy) is defined as values above 174 mg/l (equivalent to more than 300 mg/24 h, more than 300 mg/g creatinine or higher than 200 μg/min). In addition to being an early sign of kidney damage in diabetes, microalbuminuria also is a sensitive marker of endothelial vascular damage, with an established association between the level of proteinuria and the incidence of cardiovascular mortality [100–103].

Antihypertensive treatment

Reduction of clinical outcomes in patients with type 2 diabetes has been demonstrated in studies using several classes of drugs. In the vast majority of people with diabetes, an association of antihypertensive drugs to achieve the target BP goals is required. However, because the largest evidence of the beneficial effects of BP-lowering in hypertensive patients with diabetes on cardiovascular and, particularly, renal outcomes has been obtained by blockade of the RAAS [90], the use of agents blocking this system should always be part of the antihypertensive treatment strategies in people with diabetes, except when renal function is markedly reduced.

Hypoglycemic drugs with blood pressure-lowering effect

New hypoglycemic drugs have been evaluated on cardiovascular outcomes in multicenter trials

(1) Glitazones,
(2) Incretins, both glucagon-like peptide 1 analogs and dipeptidyl-peptidase-4 (DPP-4) inhibitors and
(3) Sodium–glucose cotransporter-2 (SGLT-2) inhibitors.

All these new classes have been widely scrutinized for their cardiovascular safety.

Glitazones

These agents have been found to be associated with a relevant increase in body weight, peripheral edema, increased risk of heart failure and, probably limited to rosiglitazone, increased risk of coronary events.

Glucagon-like peptide 1 analogs

Liraglutide was shown to have superiority over placebo for a composite cardiovascular endpoint, BP and weight reduction [104]. DPP-4 inhibitors are also new compounds for the treatment of type-2 diabetes with a slight BP effect. However, some possible increase in heart failure risk has been reported with saxagliptin and alogliptin [105,106].

Sodium-glucose co-transporter-2 inhibitors

Empaglifozin was found to reduce cardiovascular mortality, but not nonfatal myocardial infarction and stroke when compared against placebo [107]. All the three new classes of agents and particularly the SGLT-2 inhibitors empaglifozin and canaglifozin appear to reduce SBP/DBP [108].

Hypertension in pregnancy

Hypertension in pregnancy, with a prevalence of 5–15%, continues to be the major cause of maternal and perinatal morbi-mortality worldwide. Severe preeclampsia has a prevalence around 3–5% and requires a multidisciplinary perinatal medical team to preserve maternal and fetal health. The earlier detection of maternal risk factors previous to and during pregnancy is the clue to identify and prevent this complication [109,110].

Hypertension during pregnancy is defined as BP values higher than 140/90 mmHg when measured twice in the same arm, with an interval of 15 min. DBP is a better predictor for adverse events during pregnancy and in the perinatal period than SBP [111,112]. DBP values higher than 90 mmHg are associated with an increase in perinatal morbidity. Severe hypertension during pregnancy is defined as BP values higher than 160/110 mmHg. Severe SBP increases are associated with a greater risk of maternal stroke.

Proteinuria, preferably in 24 h samples, should be measured in all pregnancies with associated risk factors or AH. Severe preeclampsia is diagnosed when AH is associated with 24-h urinary protein excretion higher than 4 g and is usually accompanied by reduced renal function (plasma creatinine increase, oliguria) and clinical symptoms of organ damage, such as headache, visual alterations and pulmonary edema. All these symptoms can be associated with intrauterine growth restriction, oligoamnios, placental abruption, eclampsia and HELLP syndrome [113].

All hypertensive drugs are able to pass the placental blood barrier so the choice of antihypertensive drugs is restricted to those for which evidence was obtained of fetal safety [114].

When SBP is at least 160 mmHg and/or DBP at least 110 mmHg, BP reduction is mandatory as it has well established maternal benefit by reducing the risk of stroke [114,115]. However, the use of antihypertensive drugs appears not to reduce perinatal mortality, premature delivery or placental abruption [114,115]. Maternal BP should not be reduced abruptly since a deficit in the utero-placental perfusion pressure might induce acute fetal stress [109,110].

The suggested drugs to be used are: methyl DOPA, labetalol, nifedipine or amlodipine. These drugs can be administered in the first third of pregnancy. Drugs interfering with the renin–angiotensin system (ACE-Is or ARBs) are definitively forbidden and should not be prescribed to women who are planning a pregnancy or are pregnant. The unique treatment for preeclampsia is delivery, either induced or by cesarean section, but magnesium sulfate can be considered to prevent maternal convulsive events, before and after the delivery [109,110].

Low-dose aspirin (100 mg) has been recommended to prevent preeclampsia with controversial results. As a prudent measure, it may be recommended in women at high risk of eclampsia, to be taken before pregnancy or before the 6th week of pregnancy until delivery. Data supporting the administration of heparin in patients with thrombophilia and/or preeclampsia are still lacking. Similarly, no evidence supports the use of multivitamin preparations containing vitamins D, C or E or rest to prevent eclampsia [114]. The WHO recommendation of calcium supplementation should be implemented to prevent preeclampsia, only in areas in which calcium intake is low [115].

Hypertension in Afro-descendents

The prevalence of hypertension is greater than in other ethnics groups [116] with increased cardiovascular and renal morbidity and mortality [117].

Most information for this ethnic group comes from studies in the United States. Reliable studies in Latin America investigating prevalence of hypertension in people of African descent are few. More studies are obviously needed.

Treatment of hypertension in this group of patients must be intense and prompt because many of these patients have an early development of organ damage [117,118].

CCBs and diuretics can be used as first line treatment, frequently in combination. The use of β-blockers and drugs interfering with the renin–angiotensin system (ACE-Is or ARBs) should be considered as second line therapy, in combination with either a diuretic or a CCB or both.

Hypertension in Andinean populations

The Andinean population consists of individuals living at altitudes higher than 1000 m over seaside level. The

adaptation to hypoxic natural environmental conditions induces cardiovascular compensatory mechanisms and a higher sensitivity to insulin. Hypertension prevalence in the Andinean population is lower than in non-Andinean populations [4,119]. Data from Peru report the prevalence of hypertension in individuals, older than 40 years, living over 3000 m is 11.3% compared with the 20.7% in those living at lower altitude.

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