Latin American consensus on hypertension in patients with diabetes type 2 and metabolic syndrome

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The present document has been prepared by a group of experts, members of cardiology, endocrinology and diabetes societies of Latin American countries, to serve as a guide to physicians taking care of patients with diabetes, hypertension and comorbidities or complications of both conditions. Although the concept of 'metabolic syndrome' is currently disputed, the higher prevalence in Latin America of that cluster of metabolic alterations has suggested that 'metabolic syndrome' is a useful nosographic entity in the context of Latin American medicine. Therefore, in the present document, particular attention is paid to this syndrome in order to alert physicians on a particularly high-risk population, usually underestimated and undertreated. These recommendations result from presentations and debates by discussion panels during a 2-day conference held in Bucaramanga, in October 2012, and all the participants have approved the final conclusions. The authors acknowledge that the publication and diffusion of guidelines do not suffice to achieve the recommended changes in diagnostic or therapeutic strategies, and plan suitable interventions overcoming knowledge, attitude and behavioural barriers, preventing both physicians and patients from effectively adhering to guideline recommendations.

Keywords: arterial hypertension, diabetes, Latin American consensus, metabolic syndrome

Abbreviations: ABPM, Twenty-four-hour ambulatory blood pressure monitoring; ACCOMPLISH, Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension; ACCORD, Action to Control Cardiovascular Risk in Diabetes Study; ACEI, angiotensin-converting enzyme inhibitors; ADA, American Diabetes Association; ADVANCE, Action in diabetes and vascular disease# preterax and diamicron mr controlled evalution Study; ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints; ARB, angiotensin receptor blockers; ATP III, Adult Treatment Panel III; BP, blood pressure; CCB, calcium channel blockers; CHD, coronary heart disease; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EMEA, European Medicines Agency; ESH-ESC, European Society of Hypertension-European Society of Cardiology; ESRD, end-stage renal disease; FDAU.S., US Food and Drug Administration; GFR, glomerular filtration rate; Hb A1c, glycosylated haemoglobin; HIC, high-income countries; HOPE, Heart Outcomes Prevention Evaluation; HOT, Hypertension Optimal Treatment Study; IDF, International Diabetes Federation; IFG, impaired fasting glucose; IGTT, impaired glucose tolerance test; LIC, low-income countries; MDRD, Modification of Diet in Renal Disease; OGTT, oral glucose tolerance test; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; PAHO, Pan American Health Organization; PURE, Prospective Urban Rural Epidemiology study; RAAS, renin–angiotensin–aldosterone system; UAE, urinary albumin excretion; UKPDS, United Kingdom Prospective Diabetes Study; UMIC & LMIC, upper middle and low middle income; $VO_{2\ max}$, aerobic capacity; WHO-ISH, WHO-International Society of Hypertension

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INTRODUCTION

Hypertension, diabetes and that cluster of metabolic alterations often referred to as the metabolic syndrome are highly prevalent in Latin America and occur frequently as associated conditions. The development of diagnostic and therapeutic recommendations prepared through the joint work of experts in different areas of medicine is desirable, considering the low rates of control achieved in the real world, and the benefits that can be expected when reasonable objectives are met. Healthcare resources and priorities, the socioeconomic status of the population and the prevalence of hypertension, diabetes mellitus and other related diseases vary considerably in different regions of the world and also in different countries within each region, and even in different areas of individual countries. Recommendations to be usefully translated into practice should consider the particular medical and social features of the region where they should be applied and be cost-effective in terms of local needs and possibilities. For these reasons, the WHO-International Society of Hypertension (WHO-ISH) [1] and European Society of Hypertension-European Society of Cardiology (ESH-ESC) [2] documents have encouraged the development of regional guidelines. Furthermore, acceptance and usage are likely to be greater if local physicians and experts are involved in their development and subsequent diffusion and implementation [3,4].

That is why this document has been prepared by a group of experts, members of cardiology, endocrinology and diabetes societies of Latin American countries, to serve as a guide to physicians taking care of patients with diabetes, hypertension and comorbidities or complications of both conditions. Although the concept of 'metabolic syndrome' is currently disputed, the higher prevalence in Latin America of that cluster of metabolic alterations has suggested that 'metabolic syndrome' is a useful nosographic entity in the context of Latin American medicine. Therefore, in the present document, particular attention is paid to this syndrome in order to alert physicians on a particularly high-risk population, usually underestimated and undertreated.

These recommendations result from presentations and debates by discussion panels during a 2-day conference held in Bucaramanga, in October 2012. Chairs and moderators of the plenary session were Dr Stephen Harrap and Dr Alberto Zanchetti, and all the participants have approved the final conclusions.

The authors acknowledge that the publication and diffusion of guidelines do not suffice to achieve the recommended changes in diagnostic or therapeutic strategies, and plan suitable interventions overcoming knowledge, attitude and behavioural barriers preventing both physicians and patients from effectively adhering to guideline recommendations [5,6].

A great diversity in socioeconomic characteristics is found in Latin American countries, and this is reflected in differences in cardiovascular mortality and morbidity. At variance with what has occurred in the United States and Western Europe, in most Latin American countries, cardiovascular mortality rate has increased during the last decades of the twentieth century and the beginning of the twenty-first century, with the exception of Argentina and Uruguay. Even in the latter countries, however, cardiovascular morbidity and prevalence of cardiovascular risk factors have persisted unchanged or have increased, what has particularly occurred for arterial hypertension, obesity, metabolic syndrome and diabetes [7,8]. Indeed, years before the current increase of cardiovascular illness, lifestyle changes have appeared in the region with changes away from traditional alimentary habits and access to westernized models of nutrition that are likely to have facilitated the genetic expression of these diseases [9]. The pattern of morbidity is further complicated by the phenomenon of a progressive migration of rural inhabitants to urban areas, which increases the urban periphery with low resource individuals, favouring emergent risk factors as acculturation, violence, stress and malnutrition [7].

PREVALENCE OF ARTERIAL HYPERTENSION IN LATIN AMERICA

Cardiovascular risk factors are defined as biological characteristics or lifestyles increasing the probability (risk) of cardiovascular morbidity and mortality [10]. As a cardiovascular risk factor, hypertension usually integrates a cluster of risk factors defined, operationally, as the metabolic syndrome. Among these risk factors, arterial hypertension ranks as the first cause of mortality worldwide, and the third cause of illness-induced disability after malnutrition and risky sex [11].

Table 1 shows prevalence, awareness, treatment and control of arterial hypertension in Latin America. Prevalence of hypertension [12–14] was similar in Argentina (25–36%), Uruguay (30%), Paraguay (21–30%) and the south of Brazil (31–33%). In Chile [15], differences were found depending on socioeconomic level (lower: 24.5%, higher 17.9%). Differences depending on the living areas were observed in Mexico, when urban (30%) or rural areas (11.7%) were compared [16]. A recent study [17 and Chow *et al.* in preparation], the Prospective Urban Rural Epidemiology (PURE) study, included 153 996 adults (35–70 years) from 628 rural and urban communities from three high-income countries (HICs), 10 upper middle and low middle income (UMIC and LMIC) and four low-income countries (LIC) in various parts of the world. Hypertension was defined when individuals reported treatment for hypertension or had an average blood pressure (BP) greater than 140/90 mmHg from two measures of resting sitting BP using an automated digital device. Overall, 40.7% of participants were found to have hypertension, with 13.3% having a BP of at least 160/100 mmHg and 4.4% a BP of at least 180/110 mmHg. Of those with hypertension, 46.4% were aware of this condition, 40.6% were on pharmacological treatment, but only 13.1% had BP controlled (<140/90 mmHg). The prevalence of hypertension was similar in UMIC (49.6%), HIC (40.7%) and LMIC (39.6%), but lowest in LIC (32.2%). The percentages of awareness (HIC: 49.1%, UMIC: 52.4%, LMIC: 43.5% and LIC: 40.8%; trend = $P < 0.001$), treatment (46.8, 48.3, 36.8 and 31.7%, respectively; trend = $P < 0.001$) and controlled (19, 15.5, 9.9 and 12.7%, respectively; trend = $P < 0.001$) were inversely related to the economic level of the country. Prevalence,

TABLE 1. Awareness, treatment and control rates of arterial hypertension in Latin America

Country	Place	Year of publication	Age (years)	Total number	Hypertensive patients (%)	% Awareness	% Treated	% Controlled
Argentina	La Plata	1988–1989	15–75	6386	32.3	44.0 (42.8–45.2)	33.1 (31.0–35.2)	5.0 (4.3–5.4)
	Rauch	1992	15–75	1523	35.7	36.5 (35.5–37.5)	32.7 (31.1–32.9)	4.0 (2.6–6.0)
	Lujan	1995	18–79	2475	24.6	56.9 (55.7–58.1)	54.2 (53.0–55.4)	23.0 (22.0–24.0)
	Cordoba	1999	15–85	6875	29.9	54.9 (52.4–57.4)	43.0 (40.5–45.5)	13.0 (11.3–14.8)
	Dean Funes	1999	20–70	750	29.7	19.3 (14.4–25.1)	6.7 (3.8–10.8)	–
	Rosario	1999	21–65	2071	31.3	79.7 (78.1–81.3)	47.8 (45.8–49.8)	25.3 (23.3–26.8)
	Rural/Urban	NP	19–99	10415	26.0	50.8 (48.6–53.0)	41.7 (39.6–43.8)	13.0 (11.3–14.8)
	Buenos Aires	2005	25–64	1482	29.0	64.1 (59.9–68.2)	41.6 (37.5–45.8)	18.0 (14.8–21.2)
Brazil	Porto Alegre	1994	>18	1091	29.7	39.1 (33.7–44.6)	13.8 (10.3–18.1)	–
	Sao Paulo (NE)	2001	>18	688	31.5	77.0 (70.7–82.4)	61.8 (54.9–68.3)	17.0 (12.3–22.7)
Colombia	Bogota	2005	25–64	1553	13.5	68.8 (62.5–75.5)	55.0 (48.2–61.8)	30.6 (25.8–35.5)
Chile	Concepción	1988	>14	10139	18.6	65.7 (63.5–67.8	30.0 (27.9–32.2)	7.5 (6.4–8.7)
	Concepción	2004	>15	8472	21.6	66.6 (NR)	59.9 (NR)	30.7 (NR)
	Valparaíso	1999	25–69	3120	11.0	44.0 (42.2–45.8)	22.0 (20.5–23.5)	–
	Santiago	2005	25–69	1655	23.8	61.1 (55.4–64.7)	43.0 (38.8–47.7)	20.3 (16.4–24.2)
Cuba	National	NR	NR	102235	39.7	70.2 (NR)	–	39.7 (39.2–40.2)
Ecuador	National	1999	>18	10605	28.6	41.0 (37.7–43.4)	23.0 (22.3–23.8)	7.0 (6.5–7.5)
	Quito	2005	25–64	1638	8.6	67.6 (60.2–74.9)	51.8 (43.9–59.8)	28.0 (19.9–36.1)
Mexico	Guadalajara	1980	>16	4031	21.5	51.3 (47.9–54.7)	45.6 (42.3–49.1)	7.6 (6.0–9.6)
	Aguas Calientes	1997	>25	6128	26.8	75.0 (73.9–76.1)	37.0 (35.8–39.2)	–
	Durango	1998	>20	5802	21.9	69.1 (67.9–70.3)	–	–
	North (Rural)	2000	25–64	815	6.8	41.0 (37.5–44.5)	–	–
	National	2000	25–64	38377	31.3	43.0 (42.1–43.9)	20.3 (17.9–22.9)	4.9 (3.7–6.3)
	Mexico DF	2005	25–64	1722	11.6	75.7 (70.1–81.2)	65.7 (60.4–70.9)	41.0 (36.2–45.8)
Paraguay	National	1995	18–74	9880	30.4	11.0 (10.4–11.7)	5.5 (5.1–6.0)	0.0
Peru	Lima	2005	25–64	1652	12.5	53.1 (46.5–59.6)	28.8 (24.0–33.5)	12.0 (8.4–15.7)
Uruguay	Minas	NR	>18	560	37.3	78.5 (72.2–83.9)	47.4 (40.4–54.3)	16.3 (11.5–22.0)
Venezuela	Barquisimeto	1994	>20	15000	23.5	61.3 (60.5–62.1)	46.0 (44.4–47.6)	20.6 (19.2–22.0)
	Barquisimeto	2000	≥20	7424	36.8	45.7 (44.7–46.8)	22.9 (21.9–23.9)	4.5 (4.0–5.0)
	Maracaibo	2005	25–64	1848	24.6	72.0 (67.8–76.2)	48.9 (44.2–53.5)	20.7 (17.4–24)

Awareness, treated and controlled refers to patients who are aware of arterial hypertension, under treatment and reached values ≤140/90 mmHg. Data, in these cases, are given as percentual of the hypertensive population (95% CI). CI, confidence interval; NR, not referred.

awareness, treatment and control were higher in urban than in rural communities in LIC and in LMIC, but this did not occur in HIC and UMIC. Overall, 12.5% of treated hypertensive patients received two or more BP lowering medications, with a decreasing trend from wealthier to poorer countries (HIC, 18.1%, UMIC 14.5%, LMIC 14.1%, LIC 1.6%; $P < 0.0001$). Lower level of education was strongly associated with lower rates of awareness, treatment and control in countries of lower economic status, but this was less evident in other countries. Hypertension prevalence was highest in participants with diabetes (63%), and even though awareness was 74.4%, and the percentage of those who received treatment 69.3%, the control rate was only 23.3%. Analysis by region indicated that prevalence of hypertension was highest in Africa (56.6%), followed by Malaysia (46.5%) and South America (46.5%). The South American countries included in the PURE study were Argentina, Brazil, Chile and Colombia. Table 2 shows the characteristics of the individuals studied by country. Awareness, treatment and control of hypertension in the four South America countries averaged 57.0, 52.8 and 18.3%, respectively [Chow *et al.* in preparation].

From the data reviewed, it can be concluded that, all over the world, hypertension detection and treatment are poor, and that even the majority of the patients being treated have poor BP control. These findings were common to all countries with different economic levels, although treatment and control were markedly worse in LIC. Thus, systematic efforts for community-wide screening and implementation of simple algorithm based strategies are crucial to reduce the burden of hypertension-related disease.

PREVALENCE OF METABOLIC SYNDROME IN LATIN AMERICA

In Latin America the prevalence of metabolic syndrome components, including arterial hypertension, appears to be increasing. A large body of local studies [18–41] has reported that the prevalence in adults range from 25 to 45%, with important differences between urban and rural areas, but comparisons are difficult because different definitions of metabolic syndrome were used. In patients with myocardial infarction or stroke [27], the prevalence was as high as 75%, regardless of the diagnosed criteria used (International Diabetes Federation, IDF, or Adult Treatment Panel III, ATP III.). In a recent meta-analysis, which included 12 cross-sectional studies in Latin American countries [42], the general prevalence (weighted mean) of metabolic syndrome using the ATP III criteria was 24.9% (range: 18.8–43.3%). 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 high-density lipoprotein

TABLE 2. Characteristics of South America participants by country

Country	Number	Recruited (years)	Rural [*n* = (%)]	Female [*n* = (%)]	Age (years, SD)	SBP (mmHg, SD)	DBP (mmHg, SD)	BP ≥140/90 mmHg [*n* = (%)]	BP ≥160/100 mmHg [*n* = (%)]
Argentina	7483	2006–2009	3894 (52.0)	4603 (61.5)	51 (10.0)	135.6 (21.7)	82.75 (12.5)	3804 (50.8)	2455 (32.6)
Brasil	5566	2005–2009	1300 (23.4)	3076 (55.3)	52 (9.4)	132.33 (23.8)	86.63 (38.0)	2928 (52.6)	2274 (37.5)
Chile	3212	2006–2009	643 (20.0)	2135 (66.5)	52 (9.8)	130.80 (22.2)	82.11 (20.4)	1499 (46.7)	1058 (30.7)
Colombia	7417	2005–2009	3964 (53.4)	4759 (64.2)	51 (9.7)	128.77 (23.3)	81.05 (16.9)	2781 (37.5)	1737 (23.3)

BP ≥140/90 mmHg: self-reported hypertension or values ≥140/90 mmHg; BP ≥160/100 mmHg: self-reported hypertension or values ≥160/100 mmHg. BP, blood pressure. Adapted from Chow *et al.* in preparation.

(HDL)-cholesterol levels (62.9%) and abdominal obesity (45.8%). Similar findings were reported in the multicentre CARMELA study on Latin American cities [21].

PREVALENCE OF DIABETES TYPE 2 IN LATIN AMERICA

In the Latin American urban population, the prevalence of diabetes is between 4 and 8%, being higher in countries or areas with a lower or medium socioeconomic level (Table 3). However, data are scanty and the percentage of patients without confirmation of the diagnosis is around 30–50% and can be higher in rural areas. The CARMELA study [12] conducted in seven Latin American cities during 2005 found that the prevalence of diabetes had almost doubled from values previously reported. Diabetes prevalence was 6.0% in Barquisimeto (Venezuela), 8.0% in Bogotá (Colombia), 6.2% in Buenos Aires (Argentina), 8.9% in Mexico and 7.2% in Santiago (Chile). As in other areas of the world, the growing prevalence of diabetes in Latin America is due, mainly, to changes in lifestyle: lower physical activity, higher caloric intake and increased prevalence of overweight/obesity as well as urbanization.

In diabetic populations, the prevalence of arterial hypertension is 1.5–3 times higher than in nondiabetic individuals with similar age, with a particularly high association in medium and low-income countries [12,43–48].

PREVALENCE OF OVERWEIGHT AND OBESITY IN LATIN AMERICA

The important proportion of individuals with overweight (BMI 25–29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) can be appreciated in different surveys in Latin America [44–61]. In Rosario, Argentina [48], the prevalence of overweight was 40% and that of obesity 29%. In the city of Rio de Janeiro [55], overweight was present in 40% and obesity in 21% of the population studied. In Mexico [43,49], the overweight prevalence ranged from 37% in rural areas to 48% in Mexico DF, and obesity was around 21% (rural: 7%, DF: 29%). In Cuba [54], overweight and obesity together were around 22%. In many studies, obesity and arterial hypertension were strongly associated with a proportion of 40% of individuals with both arterial hypertension and obesity.

TABLE 3. Prevalence of diabetes mellitus in Latin America

Country	%
Argentina	5.0[a]
Bolivia	7.2[b]
Brasil	7.6[c]
Colombia	7.3[b]
Cuba	4.5
Chile	3.9[b]
Jamaica	13.4[a]
México	8.6[b]
Paraguay	6.2[b]
Uruguay	7.0[b]
Venezuela	4.4[b]

% = Population studies published until 2010.
[a]WHO 1980.
[b]WHO 1985.
[c]ADA-WHO 1997.

Estimates of the specific prevalence of obesity have shown a great variability among Latin American populations, ranging from 9.9 to 35.7% [57]. Women [23,33,37,51] and individuals living in urban areas [41] have been identified as the groups predominantly affected. In addition, obesity has been independently associated with low socioeconomic status and poorer educational level [49,53], thus contributing to health inequalities in the region [59,60]. However, there is evidence of a secular trend towards an increase in obesity prevalence in the most economically developed Latin American countries [61].

As with adults, obesity has also become a health problem with children in Latin America, because a high risk of obesity persistence in adult age is associated with development of arterial hypertension [22,50,51].

METABOLIC SYNDROME, DIABETES AND HYPERTENSION: DEFINITION, DIAGNOSIS AND CLINICAL EVALUATION

Metabolic syndrome

As mentioned above, the concept of metabolic syndrome is disputed mostly because it is hard to prove that the syndrome cardiovascular risk is higher than that attributable to the sum of the risks attributed to each of its component. However, metabolic syndrome is a clinical pattern with easily detectable features, yet largely under-detected, and indicates, 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 (CVD) as well as of diabetes. It is commonly accepted that all components of metabolic syndrome are associated with insulin resistance [26,62,63].

The 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 [62] has proposed that the presence of three of the five following criteria make the diagnosis of metabolic syndrome:

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

Several authors consider that central (abdominal) obesity is the main factor in metabolic syndrome and should be included in the diagnosis. To define abdominal obesity in Latin America, a recent study [64], which has included capital cities of various countries, has recommended cut-off values of waist circumference of 94 cm for men and 88 cm for women. However, a number of independent studies have indicated that the cut-off points suggested by the IDF (90 cm for men and 80 cm for women) are better related with the presence of the other components of the metabolic syndrome in the Latin American population [27,28,30,34,36]. Although no cohort studies are available in Latin America evaluating the relation of waist circumference cut-off points with future development of diabetes or CVD, it is expected that, as with most risk factors, the relation is continuous, and any cut-off is based on arbitrary conventions. The choice of the authors of this consensus document is to use the IDF cut-off values. The risk factors that are associated with a higher risk of metabolic syndrome are listed as follows:

(1) Family history of type 2 diabetes mellitus;
(2) Gestational diabetes mellitus;
(3) Macrosomy
(4) Low birth weight
(5) Childhood undernutrition
(6) High perinatal mortality and/or early CVD in first-order relatives;
(7) Sedentary habit;
(8) Diet rich in animal fat;
(9) Ethnicity;
(10) Low socioeconomic status;
(11) History of dislipidemia, obesity and hypertension;
(12) Hyperandrogenism in women; and
(13) Achantosis nigricans.

The diagnosis of metabolic syndrome may be helpful in primary prevention of diabetes mellitus, hypertension and CVD. Detection is expected to increase awareness of cardiometabolic risk in both physicians and patients and consequently to reinforce motivation, for adequate changes in lifestyle and weight reduction. Evidence for drug treatment is lacking, but when BP and plasma glucose are above the accepted threshold defining hypertension and, respectively, diabetes, antihypertensive and antidiabetic treatments should be initiated.

Type 2 diabetes

The criteria for diagnosis of type 2 diabetes mellitus, adopted and recommended by the Latin American Consensus, are listed as follows:

(1) Fasting glucose at least 126 mg/dl in two successive readings
(2) At least 200 mg/dl 120 min after oral glucose tolerance test
(3) At least 200 mg/dl at any time in the presence of symptoms

The American Diabetes Association (ADA) criteria for diabetes diagnosis [65] were adopted, but the importance of the oral glucose tolerance test (OGTT) as a more specific diagnostic tool was considered. The recently revived term 'prediabetes', and a lower threshold for glucose intolerance [an impaired fasting glucose (IFG: 100–125 mg/dl) and/or impaired glucose tolerance test (IGTT: 140–199 mg/dl)] may improve diabetes detection [66,67], but cost-effectiveness of this strategy in terms of treatment implementation and prevention of complications is yet unknown [68], and therefore, the ADA classification has been preferred [65].

Hypertension: classification and diagnosis

After considering the classifications proposed by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [69], the 2007 ESH-ESC guidelines on hypertension management [70], the 2009 Reappraisal of the European guidelines [71] and the previous Latin American Consensus on Arterial Hypertension [10], it was decided, as shown in Table 4, to maintain the concept that hypertension is diagnosed when BP values are at least 140 or 90 mmHg in the physician's office or health clinic. Above this value, hypertension can be subdivided in grade 1, 2 or 3. This classification also applies to isolated systolic hypertension, which must be diagnosed and treated especially in older patients. Elderly patients aged over 80 years should be diagnosed as hypertensive when BP is at least 150/90 mmHg. In elderly patients, BP should also be measured in the upright position to detect a possible excessive orthostatic decline.

TABLE 4. Classification of blood pressure and hypertension recommended by the Latin American Consensus

Blood pressure	Value (mmHg)
Optimal	<120/80
Normal	120/80–129/84
High normal	130/85–139/89
Grade 1 hypertension	140/90–159/99
Grade 2 hypertension	160/100–179/109
Grade 3 hypertension	≥180/110
Isolated systolic hypertension	≥140/<90

TABLE 5. Hypertension, blood pressure criteria

Hypertension	Office or clinic blood pressure ≥140/90 mmHg (average of three measurements/visit, three visits)
	24-h ABP ≥130/80 mmHg, daytime ABP ≥135/85 mmHg
	Home or self-measurement BP ≥135/85 mmHg
White-coat hypertension	Office or clinic hypertension and home or ambulatory normotension
Masked hypertension	Office or clinic normotension with home or ambulatory hypertension

ABP, ambulatory blood pressure.

Arterial hypertension is actually classified as primary, essential or idiopathic, when BP is consistently higher than normal with no known underlying cause. It represents over 90% of all cases of hypertension. Hypertension is defined as secondary, when BP is elevated as a result of an underlying, identifiable and often correctable cause (the remaining 10% of the hypertensive patients).

Diagnosis of hypertension should be based on at least three different BP measurements, taken on, at least, two separate office or clinic visits. Arterial hypertension should be diagnosed when BP is at least 140 and/or 90 mmHg. Although office or clinic values are those upon which diagnosis and treatment should be usually based, there are additional methods of BP measurement that are useful in several cases. Twenty-four-hour ambulatory BP monitoring (ABPM) is more closely related to prognosis than office BP [72,73], and two subgroups of hypertensive patients can be detected, when office and ambulatory BP are found divergent: white-coat hypertensive patients (office hypertension and ambulatory normotension) and masked hypertensive patients (office normotension along with ambulatory hypertension). Upper cut-off values for hypertension diagnosis by ABPM are indicated in Table 5.

There are clinical situations in which ABPM may be helpful for the diagnosis of hypertension, for example when white-coat hypertension is suspected, when patients with marked hypertension have no signs of target organ damage and when there are marked differences in BP values measured at different visits. There are also indications for home BP measurements, which are known to increase treatment compliance. Only validated automatic devices should be used, and the patient instructed to do the measurements in the seated position, after several minutes of rest, ideally both in the morning and evening. During treatment, measurements should be done before antihypertensive drugs are taken in the morning.

To manage a hypertensive patient, not only BP levels should be considered but also total cardiovascular risk. In order to stratify total cardiovascular risk, the number of cardiovascular risk factors, the absence or presence of target organ damage and of previous or concurrent clinical conditions or outcomes, including the metabolic syndrome and diabetes, should be taken into account together with BP grading, as summarized in Table 6.

Hypertension in patients with diabetes

As a result of impaired autonomic function and extensive organ damage, higher BP variability, marked orthostatic responses and impaired nocturnal BP reductions are common features in diabetic individuals [72]. These features have diagnostic, prognostic and therapeutic implications: the number of BP measurements for decision-making should be higher, detection of orthostatic hypotension should be a routine procedure, and home and, especially, ambulatory BP measurements are strongly recommended in diabetic individuals, whenever possible. Updated information on this topic is available [73], and training in the interpretation of data is advisable.

Recommendations on diagnostic evaluation in patients with hypertension and diabetes are summarized in Table 7. The diagnostic follow-up recommendations are listed as follows:

(1) HbA1c (every 4 months)
(2) Blood glucose self-monitoring (every 24–48 h)
(3) Yearly: fundus, ECG, microalbuminuria, basic laboratory tests
(4) Every 2 years: echocardiogram and ECG stress test (possible silent ischemia)

TABLE 6. Risk stratification in patients with metabolic syndrome, hypertension and diabetes type 2

	Normotension			Hypertension		
Other risk factors or diseases	Optimal	Normal	High normal	Grade 1	Grade 2	Grade 3
No RF	Mean risk	Mean risk	Mean risk	Low added risk	Moderate added risk	High added risk
1–2 RF or social conditions of risk	Low added risk	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
≥3 RFs or social conditions of risk, TOD or MS/DM	Moderate added risk	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Clinical-associated condition	High added risk	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

DM, diabetes mellitus; MS, metabolic syndrome; RF, risk factor; TOD, target organ damage.

TABLE 7. Recommended diagnostic evaluation of hypertensive patients with diabetes mellitus

Basic or minimal investigations	Clinical history and physical examination
	Blood pressure measurement (according to AHA)
	ECG
	Laboratory tests: fasting glucose and HbA1C, serum creatinine, lipid profile, liver enzymes, Na^+, K^+
	Microalbuminuria (according to ADA)
	Fundoscopy (when abnormal consult an ophthalmologist)
Optional investigations	ABPM
	ECG stress test (men >40 years, postmenopausal women)
	Doppler echocardiogram

ABPM, ambulatory blood pressure monitoring; ADA, American Diabetes Association.

In terms of total cardiovascular risk (see Table 6), the presence of diabetes is usually considered to imply a high level of risk, but it is reasonable to believe that cardiovascular risk is different in recent or long-term diabetes, in absence or in presence of complications. In normotensive patients with diabetes, there is no evidence that BP-lowering drugs are of any benefit.

RENAL AND CARDIOVASCULAR COMPLICATIONS IN DIABETIC HYPERTENSIVE PATIENTS

Patients with diabetes and hypertension are at an increased risk of renal disease, coronary heart disease (CHD), stroke and heart failure. The association with comorbidities such as dyslipidemia, prothrombotic state and autonomic dysfunction [74] contributes to an increase in morbidity and mortality.

Diabetic nephropathy

The prevalence of nephropathy in patients with type 2 diabetes is 30–50% [75]. Three stages are described [76], which are reported as follows:

(1) Incipient nephropathy, lasting about 10 years with supranormal glomerular filtration rate (GFR), accompanied after about 5 years by increased urinary albumin excretion (UAE: 30–300 mg/day for microalbuminuria). The presence of increased UAE identifies diabetic patients at a higher risk of developing progressive kidney damage and CVD.
(2) Clinical evident nephropathy, characterized by a UAE over 300 mg/day (overt proteinuria), a normal or moderately reduced GFR and hypertension. If untreated, these patients are at a high risk of progressing to end-stage renal disease (ESRD). Without intervention, this condition may progress faster, and 50% of patients could reach ESRD in 10 years and 75% in 20 years. Conversely, therapeutic interventions in both types of diabetes slow the rate of GFR decline. It has been reported that 20–40% of individuals with UAE could progress to macroalbuminuria and 20% of them to ESRD.
(3) Progressive renal insufficiency with overt proteinuria (300 mg/day) and a markedly reduced GFR (<30 ml/min). Macroalbuminuria identifies diabetic patients with substantial histological kidney damage and predicts a linear decline in GFR.

For screening the onset and progression of diabetic nephropathy, it is mandatory to test UAE every year at the onset of diabetes 2 and to estimate GFR from serum creatinine by using one of the current validated formulae [Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)].

Coronary heart disease

Type 2 diabetic patients with hypertension have a 1.9 times higher risk of CVD than hypertensive patients without diabetes [77]. Factors such as elevated fibrinogen levels, particularly during poor glycaemic control, elevated levels of plasminogen activator inhibitor-1 and increased platelet aggregation may be responsible [78]. These diabetes-related alterations may increase the risk of thrombosis at the site of plaque disruption and also the risk of reinfarction after thrombolytic therapy or revascularization. Furthermore, cardiac arrhythmias are frequently seen as a consequence of the autonomic dysfunction. Evaluation of CHD should include an exercise stress test followed, if positive, by a myocardial perfusion study (Single-photon emission computed tomography).

Left ventricular dysfunction and heart failure

Diabetes is a major risk factor for left ventricular dysfunction and heart failure. In the Glasgow Monica study, the incidence of left ventricular dysfunction was higher in diabetic patients (29%) than in nondiabetic individuals (7%) [79]. In the Framingham Study, relative risks for clinical heart failure were 3.8 in men and 5.5 in women with diabetes compared with those without diabetes [80]. In diabetic patients with glycosylated haemoglobin (HbA1c) less than 7.0% the rate of heart failure was 4.2 per 1000 patient years, and this rate increased to 9.2 per 1000 patients yearly when HbA1c was over 10% [80]. The poor prognosis of these patients has been explained by an underlying diabetic cardiomyopathy exacerbated by hypertension and ischaemic heart disease [81].

The high prevalence and significant morbidity and mortality of heart failure dictate early identification of risk factors and clinical signs. A careful history may help in detection of symptoms of heart failure (dyspnoea on effort, orthopnoea, nocturnal cough and easy fatigability), although patients with left ventricular systolic dysfunction may not report symptoms [82]. Therefore, the diagnosis of

heart failure in the diabetic and hypertensive patient may require further testing. Although an electrocardiogram and a radiograph may be helpful, Doppler echocardiography is needed to visualize the cardiac structural and functional changes underlying heart failure and is the recommended test whenever heart failure is suspected. As heart failure is a predictor of sudden cardiac death, 24-h Holter ECG is recommended to screen for arrhythmias.

Stroke

The rates of stroke and stroke-related disability are higher in diabetic patients than in nondiabetic individuals [83]. The risk of fatal versus nonfatal stroke is higher, the higher the level of HbA1c even many years before the outcome [83–85].

TREATMENT OF HYPERTENSION IN DIABETIC PATIENTS

Nonpharmacological treatment of hypertension in diabetes mellitus

Dietary plan

Carbohydrates will account for 55–60% of the total calories intake (TCI), minimizing refined simple carbohydrates (sugar, honey, fructose, molasses, and so on), while increasing complex carbohydrates (vegetables, fruits and whole grains). The use of noncaloric sweeteners is allowed, but those with low sodium content should be selected.

Proteins will account for 0.8–1 g/kg of ideal body weight. Animal proteins are to be preferred due to their high biological value, but legumes and cereals should be included to add proteins and fibre.

Fibre should be taken approximately 30 g/day, preferably soluble fibre.

Fat will account for no more than 30% of the TCI, with saturated (dairy fat and by-products) 10% or less, polyunsaturated (vegetable oils, dried fruits, fish) 10% and monounsaturated (avocado, olives, chicken, pork) greater than 10%.

Vitamins and trace elements should be taken as recommended for the general population.

Minerals should include sodium 2–3 g (4–6 g sodium chloride), and convenience foods should be avoided. It is advisable to know the sodium content of drinking water in the region, as it may vary widely, as it does in bottled water. Efforts should be made to meet the recommended intake of calcium, especially in hypocaloric diets, through an adequate choice of foods. Consider circumstances that may interfere with calcium absorption (malabsorption syndrome, foods rich in phytohaemaglutinins, drugs, and so on). Potassium needs can usually be met by increasing dietary vegetables and fruits.

There is no consistent evidence of the risks or benefits of moderate chronic coffee consumption (2 cups/day).

Alcohol consumption is directly related to BP levels and the prevalence of hypertension in different populations. There is also evidence that alcohol abuse blunts the effect of antihypertensive drugs. Alcohol consumption by diabetic patients should be discouraged, or a maximum of 30 g/day allowed to men and 15 g/day to women.

Meals should be distributed as three or four meals, and one or two snacks during the day should be preferred, depending on the patient's schedule and pharmacological treatment of diabetes mellitus. Ethnical preferences and socioeconomic status should also be considered.

Physical activity

A sedentary lifestyle and the lack of physical activity are strong predictors of cardiovascular mortality, independent of BP and other risk factors. The intensity of the recommended exercise should be individualized according to the clinical condition. When the planned activity does not exceed 60% of maximum oxygen consumption (VO_2 max, e.g. walking), a clinical examination will suffice. When a more intense activity is planned, a more extensive screening of possible diabetic complications should be carried out. Special attention must be paid to silent (or compensated at rest) heart disease, proliferative retinopathy, incipient nephropathy, peripheral vascular disease, peripheral and autonomic neuropathy and osteoarthropathy, especially of the lower limbs, which may cause feet lesions. An individual, three-times-a-week-programme must be prepared, including moderate intensity recreational-like aerobic activity (equivalent to 3–5 Metabolic equivalents) in the form of sports or domestic exercise, lasting from 20–60 min per session, preceded by a previous 5 to 10-min warm-up, and followed by 5 to 10-min relaxation. The patient must be instructed on the appropriate clothing to prevent feet lesions, such as cotton socks and sport shoes. Self-monitoring of blood glucose before and after exercise may help preventing hypoglycemia and allow the patient to verify the beneficial effects of exercise on glycaemic control [86–88]. Intense exercise is contraindicated for patients with active proliferative retinopathy, clinical nephropathy or neuropathy.

Pharmacological treatment

The benefits of reducing BP in diabetic patients have been clearly shown by the results of the Hypertension Optimal Treatment (HOT) [89] and United Kingdom Prospective Diabetes Study (UKPDS) [90] studies among others [91–95]. Diabetic patients may require more intense treatment to achieve the same BP levels as nondiabetic individuals. Thus, almost every diabetic patient will need, in addition to nonpharmacological measures, a combination treatment to achieve BP treatment goals, as earlier as possible.

The target SBP to be achieved to guarantee an optimal protection from cardiovascular outcomes to hypertensive patients with diabetes has been an issue of intense debate, recently. Although a number of guidelines in the past [1,2,69,70] had recommended a lower target of less than 130/80 mmHg in diabetic patients (and generally in high-risk patients) than in low–moderate risk hypertensive patients (<140/90 mmHg), a recent reappraisal of the available evidence [71,96] has demonstrated that no one of the randomized trials of antihypertensive treatment in diabetic patients with hypertension has ever achieved mean SBP

values below 130 mmHg, and the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) [97] trial has shown no further reduction of cardiovascular outcomes but a higher incidence of adverse effects in the diabetic patients randomized to achieve an SBP of less than 120 as compared with an SBP of less than 140 mmHg (average values actually achieved 119 and 133 mmHg). A number of meta-analyses [98,99] have attempted to correlate cardiovascular outcomes with achieved BPs and have found no further benefit or worsening of cardiovascular outcome incidence at lower BP, with the possible exception of the incidence of stroke [99].

In summary, it appears that in hypertensive patients with diabetes, an SBP target of less than 140 mmHg can be recommended as in nondiabetic hypertensive individuals. However, values just above 130 mmHg (as achieved in ACCORD [97] and ADVANCE [100]) appear safe and may be more effective in reducing or preventing microalbuminuria [100]. As to target DBP, the results of the HOT [89] and UKPDS [90] studies indicate that values between 80 and 85 mmHg are beneficial.

As to patients with diabetic nephropathy, previous guidelines have commonly recommended BP targets 130/80 and less than 120/75 mmHg in case of proteinuria. A recent review [101] has shown that these recommendations are not supported by trial results and are only based on findings from long-term, nonrandomized follow-up of trials. It appears prudent, therefore, to recommend the same BP targets to diabetic patients with and without nephropathy.

Five classes of antihypertensive agents [diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs)] have been used in randomized trials that have shown that BP lowering significantly reduces cardiovascular, cerebrovascular and renal outcomes in hypertensive patients with diabetes as well as without diabetes [102], and therefore, all of them can be chosen in patients with hypertension and type 2 diabetes. However, when selecting to initiate treatment with monotherapy, drugs blocking the renin–angiotensin–aldosterone system (RAAS), ACEIs or ARBs, should be preferred because of their greater antiproteinuric effect. ARBs are commonly better tolerated, and this is a relevant issue in patients with hypertension in whom adherence is essential. As a general rule, a long-acting agent providing BP reduction over the 24 h should be indicated in order to use possibly a single daily administration. Recently, regulatory agencies [US Food and Drug Administration (FDA) and European Medicines Agency (EMEA)] have approved ramipril as ACEI and telmisartan as ARB for patients with high cardiovascular risk (i.e. hypertensive patients with type 2 diabetes) on the basis of Heart Outcomes Prevention Evaluation (HOPE) [94] and Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) [103] trials.

In most patients with type 2 diabetes and hypertension, the desirable BP target cannot be achieved with monotherapy and treatment must include two or more agents. If before treatment SBP/DBP is far from target values, it is recommended to initiate with a two-drug combination, a fixed combination of an ACEI or ARB with a dihydropyridine CCB or a diuretic. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [104] has shown greater benefits with an ACEI/CCB rather than an ACE/diuretic combination, but these interesting data need to be confirmed. When three drugs are needed, an ACEI or ARB along with a CCB as well as either a thiazide or indapamide diuretic should be used. In patients with a GFR less than 30 ml/min, thiazide diuretics should be replaced by a loop diuretic (such as furosemide) at appropriate doses. The association of ACEI and ARB, as well that of an ACEI or ARB with a renin inhibitor (aliskiren) have a greater antiproteinuric effect, but the association of ACEI and ARB failed to show greater outcome reduction in ONTARGET [103] and actually had more adverse effects, and ALTITUDE [105], a trial in diabetic patients testing the association of aliskiren with an ACEI or ARB, was prematurely interrupted for more adverse effects of the association. Therefore, the association of two different drugs interfering with the renin–angiotensin system, at full doses, is at present discouraged.

Diuretics and beta-blockers, particularly in association, increase insulin resistance and may facilitate onset of diabetes in predisposed individuals, and therefore this association should possibly be avoided in hypertensive patients with prediabetes or the metabolic syndrome. Vasodilating beta-blockers, such as nebivolol and carvedilol, appear not to impair insulin sensitivity, and nebivolol has recently been shown not to worsen glucose tolerance even when added to a thiazide diuretic [106]. Therefore, vasodilating beta-blockers should be preferred in those conditions in which there are compelling reasons for administering a beta blocker (ischaemic heart disease, heart failure, tachyarrhythmia, and so on).

In patients with renal and/or cardiac dysfunction, cardiac function may be improved by the administration of mineralocorticoid receptor antagonists (spironolactone, eplerenone), which have been shown to be effective in resistant hypertension. However, serum levels of potassium and GFR should be closely monitored in patients with renal disease using a RAAS inhibitor and an aldosterone antagonist.

Alpha blockers have been shown to improve insulin resistance and might be used as an additional agent in hypertensive patients with type 2 diabetes, not achieving BP target, although they are not recommended as monotherapy except in hypertensive patients with prostatic hypertrophy. Table 8 indicates antihypertensive agents to be preferred for drug management of hypertensive patients with type 2 diabetes and special conditions.

SPECIAL POPULATIONS

Hypertension and diabetes in Afro-Latin Americans

People in Latin America belong to different ethnicities [107]. The prevalence of the various ethnicities in each Latin American country is characterized by a mixture of races, ethnicities and cultures as in no other continent.

Despite the large number of black people in Latin America, there is no epidemiologic study on the prevalence

TABLE 8. Drug use recommendations for hypertensive patients with diabetes type 2 and special conditions

Coronary heart disease and/or left ventricular dysfunction	ACEI/ARBs, beta-blockers, aldosterone antagonists
Isolated systolic hypertension in the elderly	Calcium channel blockers, diuretics, ARBs
Angina pectoris	Calcium channel blockers, beta-blockers often in association
Chronic renal disease	ACEI or ARBs, especially in presence of microalbuminuria or overt proteinuria
Peripheral artery disease	Calcium channel blockers
Patients with atrial fibrillation	Beta-blockers, ARBs, ACEIs, nondihydropyridine calcium channel blockers
Left ventricular hypertrophy	ACEI, ARBs, CCBs
Benign prostatic hypertrophy	Alpha blockers

ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CCB, calcium channel blocker.

of hypertension and diabetes in this population, and no studies have investigated dietary intake, physical activity, body build associated with hypertension and diabetes in a sufficiently large sample of this racial group using consistent methodologies. Most of the information results from studies conducted in the USA including black people who had migrated from Latin America and the Caribbean to USA [108,109] or USA-born youth of Latin and Caribbean origin [32].

Thus, the first recommendation of the Latin American Consensus is to encourage academic and governmental organizations in Latin America to support epidemiological, clinical and therapeutic research in African-Latin American people to investigate whether the results of USA studies also apply to African descendants living in Latin America. Up to now, the only available study assesses the importance of arterial hypertension in a rural district of black people living in the province of Esmeraldas in Ecuador [110], where 4284 of the 8876 adults living in the area were screened. Hypertension was found in 1542 (36%) of them, only four (0.3%) of whom were well controlled by treatment. In the 2.5 years of follow-up, CVD was the major cause of death in the adult population. Furthermore, four of five of the individuals who died by CVD had a history of hypertension. Thus, the prevalence of uncontrolled hypertension in this study was much higher than that reported in the USA studies.

Until a suitable number of data are collected in Latin America, the Consensus recommends adopting the recent recommendations of the International Society of Hypertension in Blacks [111]. According to the latter document among black people, there is a clear geographical difference in the prevalence of hypertension: 14% in Western Africa, 26% in Caribbean and 33% in USA. These differences are tentatively attributed to differences in diet and lifestyle. In USA, black women are more sedentary, have a high caloric intake and are more obese already in the preadult period [112,113]. Genetic and environmental factors, such as low socioeconomic status, high dietary sodium and/or low dietary potassium intake, and low birth weight because of maternal malnutrition, have been associated with poor renal development and lower number of nephrons, predisposing to arterial hypertension and early kidney dysfunction [114,115].

The cardiorenal complications related to arterial hypertension and type 2 diabetes (stroke, left ventricular hypertrophy, cardiac failure, chronic or end-stage renal failure) occur more often in black than in white people. Hypertensive blacks have 4–20 times higher risk of progressing to dialysis than whites with similar BP levels, and mortality in African-American men is three times higher (49%) than in non-Hispanic whites in USA (16%), and two and a half times higher in black women (37%) than in non-Hispanic (14%) white women [116].

The choice between antihypertensive monotherapy and drug combination depends on the presence or absence of comorbidities, and the specific efficacy of the drugs to be used. Comparative studies have shown that black hypertensive patients have a better response to thiazide diuretics (hydrochlorothiazide or chlorthalidone) and CCBs than to ACE inhibitors, angiotensin II receptor blockers or beta-blockers [117,118]. The best control is always obtained if sodium intake is reduced. Furthermore, blacks are more prone to present angioneurotic oedema in response to ACEIs than white people [119]. Therefore, in blacks, monotherapy should be based on either a diuretic or a CCB, and when combination therapy is decided, this should include a CCB and/or a diuretic along with a RAAS blocker, preferably an ARB.

Hypertension and diabetes in the Andes population

The Latin American populations living in the Andes Mountains share similar characteristics and historic patterns of colonization as native Indians living at lower altitudes, being mostly Amerindians or mestizos. Those people living at a high altitude (over 3000 m above sea level) represent a special group in whom the prevalence of hypertension and diabetes is scarcely known. A population-based study [120] included 1878 adults living in the Peruvian Andes. The prevalence of hypertension was 15.7% [95% confidence interval (CI), 14.0–17.4), did not differ by sex and increased steeply with age, particularly in women. Awareness, treatment and control rates were 47.9, 39.5, and 14%, respectively. DBP increased until age 50 years and reached a plateau thereafter, whereas mean arterial pressure continued to increase with age even after age 50. The predominant type of hypertension was systolic-diastolic (41.7%; 95% CI, 35.1–48.5) or isolated diastolic. Isolated systolic hypertension accounted for only 29.3% of cases (95% CI, 23.9–35.4) and was responsible for a minority of cases in all age groups before age 70. That diastolic hypertension is predominant in the Andes Mountains over 3000 m above sea level has recently been confirmed in another study [121], which has found that more than 50% of this population was unaware of their hypertensive condition. This study also showed that the prevalence of

hypertension was similar in the coast, sierra and jungle areas of Peru [120,121].

Hypertension and diabetes in the elderly

The PanAmerican Health Organization (PAHO)/WHO report on demographic data from Latin America [122] has shown that people older than 60 years represent 14% of the total population in Argentina, 10% in Brazil, 13% in Chile, 8% in Colombia, 9% in Ecuador, 7% in Paraguay, 8% in Peru, 18% in Uruguay, 8% in Venezuela and 8% in Mexico.

Elderly people, defined as individuals older than 65 years, have an increased risk of arterial hypertension, specially isolated systolic hypertension [123,124], implying an additional cardiovascular risk because pulse pressure higher than 65 mmHg is associated with greater stiffness of the large arteries wall and increased cardiovascular morbidity and mortality [124]. ABPM during 24 h is considered a useful tool to optimize the clinical evaluation of elderly hypertensive patients [125,126], in whom abnormal nocturnal BP falls and morning BP surges have been claimed to be associated with cerebrovascular disease [127,128], although these findings have been recently disputed [129].

All trials that have demonstrated the benefits of BP lowering in the elderly have aimed at an SBP target of less than 150 mmHg [96], and this should be considered as the evidence-based target for elderly hypertensive patients, but in the otherwise healthy elderly a target similar to that recommended for younger hypertensive patients ($\leq$140 mmHg) can be considered. There is also evidence of benefits in reducing SBP to less than 150 mmHg in hypertensive patients aged 80 years and older [130]. Frail or complicated individuals should be treated with particular attention not to worsen their general health conditions.

In the elderly individuals, the pharmacological treatment must be initiated gradually to guarantee good tolerability and quality of life. Sexuality (sexual dysfunction), sleep and functional status must be considered in the clinical evaluation of this population [10].

Various clinical trials have demonstrated the benefits of reducing isolated systolic hypertension [131–133], by using diuretics or CCBs. Other trials in elderly hypertensive patients, a number of whom with isolated systolic hypertension, have also used ACE inhibitors and angiotensin receptor inhibitors, and these classes of drugs can also be used in the elderly, both as monotherapy and in combination.

In those patients with associated cardiovascular risk or comorbidities, the drug of choice must be selected in accordance with the concomitant illness, as inidcated in Table 8. Long-lasting acting drugs are preferable in face of a better compliance and a sustained 24-h antihypertensive action.

THE ROLE OF ENVIRONMENT AND EPIGENETICS IN METABOLIC SYNDROME, HYPERTENSION AND DIABETES IN LATIN AMERICA

The increasing incidence of metabolic syndrome, diabetes type 2 and CVDs in Latin America seems to be associated to environmental influences and ethnic characteristics [134]. This raises the possibility that genetic predisposition associated with particular ethnic groups might interact with environmental factors to explain different incidence of disease. There has been considerable interest in the special influence of in-utero and early-life environmental exposure. This is represented in the Developmental Origins of Disease hypothesis that emphasizes the critical periods in early life during which body structure and function can be set for life. More recently, the early effects of environment have been conceived in terms of epigenetics.

Epigenetics is the science that explains the variation of gene expression in response to changes in environmental conditions. This term includes any process that alters gene activity without changing the DNA sequences and leads to rapid but reversible modifications of DNA (e.g. methylation) or chromatin that can be transmitted to daughter cells. DNA methylation of a regulatory region for a specific gene can inhibit gene expression. Chromatin is the nuclear complex consisting of DNA wrapped around histone proteins that can be modified by acetylation to influence gene expression [135].

The mechanisms that control epigenetic processes are not yet completely understood, but it is clear that heritable DNA variation might alter the sensitivity to certain environmental triggers or change the nature of the epigenetic responses to a given exposure. In the Latin American context, the question is whether regional and ethnic variation in epigenetic processes or simply differences in the environmental exposures explain diversity in the metabolic syndrome.

It is well known that in Latin America, the maternal and childhood undernutrition has been an important problem that not yet has been resolved in an important percentage of the poor populations [136]. In Latin America, a high prevalence of arterial hypertension has been found in children, adolescents and adults with nutritional stunting [137–144]. One study in Brazil [137] that investigated arterial pressure in a random sample of adolescent slum residents with stunting (10–16 years, $n = 56$) showed an elevated percentage of these individuals to have an arterial pressure above the 90th and 95th percentiles, adjusted for height, and were at a risk for hypertension. Considering the group of patients as a whole, the prevalence of diastolic arterial hypertension was 21% (95% CI, 10–32-%). The prevalence of cases with a systolic or diastolic arterial pressure above the 90th percentile was 51% (95% CI, 37–65). Another study done in the northeast of Brazil [138] with 416 adults (18–60 years), also slum residents, showed that arterial hypertension was prevalent in 28.5% of the population (women, 38.5%; men, 18.4%). The SBP and DBP increased according to the reduction in stature, and hypertension was more prevalent in women who were obese and short (50%) than in those who were obese but not short [odds ratio (OR), 1.98; 95% CI, 1.22–2.96]. Recently, another survey [139] investigated whether the health conditions of mothers who had a short stature were different from those without stunting or that of their offspring. A short maternal stature was independently associated with obesity, abdominal

obesity and increased arterial pressure. Furthermore, short maternal stature was associated with a low birth weight and stunting in children. In Colombia, it was demonstrated that children 11 years old with a medium BMI of 21 kg/m^2, the higher tertile, presented an increase of 10 mmHg in relation to children with a medium BMI of 15 kg/m^2, the lower tertile [140]. Also in Brazil, Franco *et al.* [141] reported changes in the sympathoadrenal and renin–angiotensin systems in children small for their gestational age. They investigated the plasma levels of ACE, angiotensin and catecholamines in 8 to 13-year-old children to determine correlations between the plasma levels and both birth weight and BP. Circulating noradrenaline levels were significantly elevated in small gestational age girls compared with girls born with a weight appropriate for their gestational age. In addition, angiotensin II and ACE activity were higher in small gestational age boys. There was a significant association between the circulating levels of both angiotensin II and ACE activity and SBP. Another study in Brazil [142] showed that ACE activity is increased, together with an increase in systolic and diastolic pressure in children with stunting independent of birth weight.

Although in Latin America the prevalence of type 2 diabetes mellitus in individuals who were undernourished in early life is not known, it is known that poor countries with an accelerated process of urbanization are particularly vulnerable and have been experiencing a considerable increase in diabetes prevalence [143]. Deleterious changes have been reported in glucose metabolism in Mexican children suffering from undernutrition in infancy. The study examined the effects of undernutrition in the first year of life on glucose tolerance and plasma insulin and found that early undernutrition in the extra-uterine period, independent of the birth weight, was associated with hyperinsulinemia and a reduced sensitivity to insulin, which worsened as BMI increased in adult life [143].

So, it is interesting to speculate that the increased rates of hypertension, metabolic syndrome and type 2 diabetes mellitus, observed in Latin America, could be the result of the discrepancy between the nutritional environment during foetal and early life and the adult environment. This discrepancy causes a mismatch between the foetal programming of the subject and the adult circumstances created by the imposition of new lifestyles [144]. The conflict between the earlier programming and the later presence of abdominal obesity may have produced a higher sensitivity of this population to develop a state of low-degree inflammation, insulin resistance and, consequently, an epidemic of hypertension, metabolic syndrome and diabetes. The relative roles played by genetic and environmental factors and the interaction between the two are still the subjects of great debate and merit further research.

The recommendation of the Latin American Consensus is to stimulate academia to develop research aimed to establish the epigenetic mechanisms explaining the relationship between maternal malnutrition, early growth restriction and the later occurrence of abdominal obesity and CVD in Latin America.

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Conflicts of interest

There are no conflicts of interest.

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