Latin American guidelines on hypertension*
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Hypertension is a highly prevalent cardiovascular risk factor in the world and particularly overwhelming in low and middle-income countries. Recent reports from the WHO and the World Bank highlight the importance of chronic diseases such as hypertension as an obstacle to the achievement of good health status. It must be added that for most low and middle-income countries, deficient strategies of primary healthcare are the major obstacles for blood pressure control. Furthermore, the epidemiology of hypertension and related diseases, healthcare resources and priorities, the socioeconomic status of the population vary considerably in different countries and in different regions of individual countries. Considering the low rates of blood pressure control achieved in Latin America and the benefits that can be expected from an improved control, it was decided to invite specialists from different Latin American countries to analyze the regional situation and to provide a consensus document on detection, evaluation and treatment of hypertension that may prove to be cost-utility adequate. The recommendations here included are the result of preparatory documents by invited experts and a subsequent very active debate by different discussion panels, held during a 2-day sessions in Asuncion, Paraguay, in May 2008. Finally, in order to improve clinical practice, the publication of the guidelines should be followed by implementation of effective interventions capable of overcoming barriers (cognitive, behavioral and affective) preventing attitude changes in both physicians and patients.


Keywords: diabetes, diagnosis, epidemiology, hypertension, special populations, treatment

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ADMA, asymmetric dimethylarginine; ARB, angiotensin receptor blocker; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; DALYs, disability-adjusted life years; DBP, diastolic blood pressure; DM, diabetes mellitus; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; IMT, intima–media thickness; LDL, low-density lipoprotein; MS, metabolic syndrome; OGTT, oral glucose tolerance test; PKC, protein kinase C; ROS, reactive oxygen species; SBP, systolic blood pressure; TIA, transient ischemic attack; TOD, target organ damage

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Introduction

Hypertension is a highly prevalent cardiovascular risk factor in the world and particularly overwhelming in low and middle-income countries. Recent reports from the WHO [1] and the World Bank [2] highlight the importance of chronic diseases such as hypertension as an obstacle to the achievement of good health status. It must be added that for most low and middle-income countries, deficient strategies of primary healthcare are the major obstacles for blood pressure control [3]. Furthermore, the epidemiology of hypertension and related diseases, healthcare resources and priorities, the socioeconomic status of the population vary considerably in different countries and in different regions of individual countries. Because of this, the documents from the World Health Organization-International Society of Hypertension [4] and European Society of Hypertension-European Society of Cardiology [5] encourage the development of local guidelines taking into account the above-mentioned conditions.

Considering the low rates of blood pressure control achieved in Latin America and the benefits that can be expected from an improved control, it was decided to invite specialists from different Latin American countries to analyze the regional situation and to provide a consensus document on detection, evaluation and treatment of hypertension that may prove to be cost-utility adequate. That is why members of Hypertension, Cardiology and Diabetes Societies from Latin American countries met to discuss these new recommendations for prevention and management of hypertension and related diseases, and prepare a consensus document in which special attention has been paid to the metabolic syndrome in order to alert physicians about this higher-risk condition, particularly prominent in Latin America but usually underestimated and undertreated. The resulting
document is designed to serve as a guide to physicians assisting patients with hypertension and comorbidities.

The recommendations here included are the result of preparatory documents by invited experts and a subsequent very active debate by different discussion panels, held during a 2-day session in Asuncion, Paraguay, in May 2008. After a formal presentation of the final conclusions reached by each discussion panel, and their approval by all participants, this final document was prepared by an appointed Writing Committee. In order to improve clinical practice, the publication of the guidelines should be followed by implementation of effective interventions capable of overcoming barriers (cognitive, behavioral and affective) preventing attitude changes in both physicians and patients.

Epidemiology, health economics, education

Prevalence

Diabetes mellitus and hypertension are frequently associated, thereby increasing their negative impact on the cardiovascular system [6,7]. More than 80% of the attributed world burden of these diseases is in low and middle-income countries. In Latin America, 13% of deaths and 51% disability-adjusted life years (DALYs) can be attributed to hypertension [1]. The age-adjusted prevalence of hypertension in the adult general population in different countries of Latin America (national surveys or systematic randomized samplings) ranges from 26 to 42% [6–9]. In diabetic populations, the prevalence of hypertension is 1.5–3-fold higher that in nondiabetic populations in the same age segment [6]. In type 2 diabetes, hypertension may already be present at the time of diagnosis or may even precede overt hyperglycemia [6].

The following tables show the prevalence, awareness, treatment and control of hypertension, together with cardiovascular mortality attributed to hypertension (Table 1), and the prevalence of the major risk factors associated with hypertension (Table 2) in various Latin American countries.

### Table 1 Arterial hypertension, sex and cardiovascular mortality

<table>
<thead>
<tr>
<th>Countries</th>
<th>Hypertension prevalence (%)</th>
<th>Hypertension awareness (%)</th>
<th>Treated hypertension (%)</th>
<th>Controlled hypertension (%)</th>
<th>Cardiovascular mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>28.1</td>
<td>54</td>
<td>42</td>
<td>18</td>
<td>23.5</td>
</tr>
<tr>
<td>Brazil</td>
<td>25–35</td>
<td>50.8</td>
<td>40.5</td>
<td>10.2</td>
<td>27.5</td>
</tr>
<tr>
<td>Chile</td>
<td>33.7</td>
<td>59.8</td>
<td>36.3</td>
<td>11.8</td>
<td>30.8</td>
</tr>
<tr>
<td>Colombia</td>
<td>23</td>
<td>41</td>
<td>46</td>
<td>15</td>
<td>30.8</td>
</tr>
<tr>
<td>Ecuador</td>
<td>28.7</td>
<td>41</td>
<td>23</td>
<td>6.7</td>
<td>27.5</td>
</tr>
<tr>
<td>Mexico</td>
<td>30.5</td>
<td>56.4</td>
<td>23</td>
<td>19.2</td>
<td>26.3</td>
</tr>
<tr>
<td>Paraguay</td>
<td>35</td>
<td>31</td>
<td>27</td>
<td>7</td>
<td>34.2</td>
</tr>
<tr>
<td>Peru</td>
<td>24</td>
<td>39</td>
<td>14.7</td>
<td>14</td>
<td>34</td>
</tr>
<tr>
<td>Uruguay</td>
<td>33</td>
<td>68</td>
<td>48</td>
<td>11</td>
<td>56.9</td>
</tr>
<tr>
<td>Venezuela</td>
<td>33</td>
<td>55</td>
<td>30</td>
<td>12</td>
<td>29.5</td>
</tr>
</tbody>
</table>

Columns 2, 3, and 4 percentage values refer to the corresponding hypertensive population (column 1).

### Table 2 Prevalence of risk factors associated with hypertension

<table>
<thead>
<tr>
<th>Overweight (%)</th>
<th>Sedentary life (%)</th>
<th>Smoking (%)</th>
<th>Dyslipidemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>19.7</td>
<td>nd</td>
<td>38.6</td>
</tr>
<tr>
<td>Brazil</td>
<td>13</td>
<td>nd</td>
<td>20</td>
</tr>
<tr>
<td>Chile</td>
<td>23.2</td>
<td>90.8</td>
<td>42</td>
</tr>
<tr>
<td>Colombia</td>
<td>47</td>
<td>61</td>
<td>23</td>
</tr>
<tr>
<td>Ecuador</td>
<td>41</td>
<td>34.9</td>
<td>24.8</td>
</tr>
<tr>
<td>Mexico</td>
<td>31</td>
<td>30.8</td>
<td>36.6</td>
</tr>
<tr>
<td>Paraguay</td>
<td>64</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Peru</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Uruguay</td>
<td>59.7</td>
<td>64.3</td>
<td>15.7</td>
</tr>
<tr>
<td>Venezuela</td>
<td>28.1</td>
<td>–</td>
<td>30</td>
</tr>
</tbody>
</table>

nd, Not determined.

Medical economics

Hypertension imposes a huge worldwide economic and social burden because of the associated comorbidities and chronic complications that impair survival and quality of life. Thus, a recent analysis of an international data bank [1] has shown that a very substantial proportion of cardiovascular disease is attributable to high blood pressure.

The global expenditure on antihypertensive treatment is about 50 billion dollars each year [10], more than 90% of which is spent in high-income countries, whereas middle and low-income countries, having a five times greater burden of disease than the corresponding high-income countries, have only access to less than 10% of the global treatment resources. Thus, cost-effectiveness, cost-benefit and cost-utility of the treatment of hypertension in the general population are strongly influenced by the presence of comorbidities and complications [11–13]. Considering the above-mentioned data, the proposal for an intensive treatment of hypertension can be expected to reduce costs and improve survival and quality of life.

Education

In the context of the large and growing disease burden, strategies to improve population health require consistent and comprehensive management of the major risk factors contributing to premature mortality and disability.
Education should be considered an important tool for improving hypertension treatment strategies. To this scope, the recently published WHO/ISH guidelines on preventive cardiology are greatly helping general practitioners in the management of global risk strategies, by the use of pocket guidelines that can be easily obtained in different languages (http://www.who.int/cardiovascular_diseases/guidelines/Pocket_GL_information/en/index.html). Systematic education of hypertensive patients is strongly recommended. Such educational effort should involve patients in their own environment, and provide training in patient education to health teams. Some educational programs for Latin America have been proposed [14]. The promotion of education in the general population and, particularly, among high-risk patients, is greatly advisable. Formal education for children and adolescents should include information about healthy lifestyles.

The following strategies are strongly recommended:

(1) Community educational programs,
(2) Operational strategies to promote lifestyle changes especially in children, teen-agers and young adults,
(3) Educational programs for practitioners and health teams (nurses, nutritionists, etc.),
(4) Hypertension early detection programs, and
(5) Guidelines for optimal control of blood pressure values.

**Clinical characteristics**

**Definition**

Established hypertension is a medical condition implying a higher risk for cardiovascular events and impairment of different organ functions in which the blood pressure is chronically elevated above values considered in the optimal or normal range. Hypertension is frequently associated with comorbidities such as diabetes mellitus, coronary heart disease (CHD), chronic heart failure, stroke, transient ischemic attack (TIA), peripheral vascular disease, chronic renal impairment. Persistent hypertension is considered one of the risk factors for stroke, heart attack, heart failure and arterial aneurysm, and is one of the leading causes of chronic renal failure and dialysis. Even moderate elevation of arterial blood pressure leads to shortened life expectancy. When blood pressure is markedly elevated (mean arterial pressure 50% or more above average) life expectancy is reduced by 30–40%, unless hypertension is appropriately treated [15].

**Blood pressure classification**

After considering the classifications proposed by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [16], the 2007 European Guidelines for the Management of Hypertension [5], and the previous Latin American Consensus on Arterial Hypertension [17], it was decided, as shown in Table 3, to maintain the concept that hypertension is diagnosed when blood pressure values are at least 140/90 mmHg. 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.

Considering that blood pressure is a continuous variable, and that higher are the blood pressure values higher is cardiovascular risk [18,19], it was decided that the patients with blood pressure values between 120/80 and 129/84 mmHg can be considered as normal blood pressure, whereas those with values between 130/85 and 139/89 mmHg as high-normal blood pressure. Blood pressure values lower than 120/80 mmHg are considered as optimal values. However, it should be emphasized that high-normal and normal blood pressure are of a higher risk than optimal blood pressure despite of being in the normal range. By this way, blood pressure values lower than 120/80 mmHg are considered as optimal values. Arterial hypertension is actually classified as: primary, essential or idiopathic when blood pressure is consistently higher than normal with no known underlying cause. It represents 85–90% of all cases of hypertension. Hypertension is defined as secondary when blood pressure is elevated as a result from an underlying, identifiable, often correctable cause (the remaining 10–15% of the total hypertensive patients).

**Resistant or refractory to treatment hypertension**

Resistant or refractory to treatment hypertension is when blood pressure remains above target values despite institution of nonpharmacological treatment and pharmacological treatment including full doses of three or more medications, one of these being a diuretic. These patients must be referred to a specialist or a hypertension center because this type of hypertension is often associated with subclinical organ damage, and has high added cardiovascular risk [20].

**White-coat hypertension**

Also known as isolated office hypertension it is the condition in which blood pressure, measured in the office, is consistently in the hypertensive range, whereas either

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**Table 3** Classification of blood pressure

<table>
<thead>
<tr>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Normal high-normal</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Grade 1</td>
</tr>
<tr>
<td>Grade 2</td>
</tr>
<tr>
<td>Grade 3</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
</tr>
</tbody>
</table>
the ambulatory blood pressure monitoring (ABPM) mean values [21] or home values [22] are always in the normotensive range. Its prevalence is around 10%. Its overall risk is not clearly established [23], but it appears to be associated with more cardiac, renal and metabolic functional and/or structural abnormalities than full normotension [24,25].

**Hidden or masked hypertension**

Also known as isolated ambulatory hypertension, it represents the opposite condition to white-coat hypertension, that is patients have normal office blood pressure, whereas mean ABPM or home blood pressure values are in the hypertensive range. It is found in every one out of seven to eight patients with office normotensive values [25]. The cardiovascular risk in these patients seems to be similar to that of established hypertensive patients [26,27]. Thus, care must be taken to avoid that these patients remain undiagnosed if ABPM or home blood pressure are not measured.

**Isolated systolic hypertension**

Is sustained systolic blood pressure (SBP) at least 140 mmHg with diastolic blood pressure (DBP) less than 90 mmHg. As SBP tends to rise with age, the prevalence of systolic hypertension increases with age and, above the age of 60 years, systolic hypertension represents a common form of hypertension. Impressive evidence has been accumulated on the importance of SBP as a major risk factor for cardiovascular diseases [28].

**Risk stratification**

To manage a hypertensive patient not only blood pressure levels should be considered but also total cardiovascular risk. In order to stratify total cardiovascular risk, the number of risk factors, the presence of target organ damage and of previous or concurrent clinical conditions or outcomes (Table 4) in association with blood pressure grading should be taken into account, as shown in Fig. 1.

Among traditional risk factors, socioeconomic conditions should be given particular attention in Latin America. Similar emphasis should be given to a low educational level, because of the high percentage of the native population with low opportunities of an adequate education.

Figure 1 does not only include blood pressure values above the conventional 140/90 mmHg cut-off values, but also those considered optimal or normal, or high-normal. At all blood pressure levels, including optimal ones, the total risk increase progressively with the addition of other risk factors, organ damage, diabetes and previous outcomes.

**Diagnostic evaluation of the hypertensive patient**

The time required for the initial evaluation of a hypertensive patient is of at least 30 min. The main objectives of diagnosis are:

1. Confirming the existence of high blood values,
2. Determining the grade of hypertension and the existence of target organ damage,
3. Evaluating the presence of comorbidities,
4. Identifying treatments previously received or currently in use,
5. Quantifying the global risk including its social components,
6. Diagnosing or excluding possible secondary causes of hypertension.

**Clinical history and physical examination**

Not only the grade of hypertension should be defined but also the time at which hypertension was diagnosed. Information on age, sex and race should be recorded. The physical exam must include measurement of height, weight, waist, hip and calculation of waist to hip ratio and body mass index (BMI), the evaluation of pulses, heart rate, blood pressure values, heart auscultation, search of carotid, thoracic or periumbilical bruits and a funduscopic examination. Search should be made for associated risk factors and possible complications such as peripheral edema, angina pectoris, dyspnea, headache, ectopic heart beats.

Blood pressure measurements must be performed in accordance with the American Heart Association

### Table 4 Factors to be taken into account to quantify cardiovascular risk

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Subclinic TOD</th>
<th>Clinical events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, sex (male)</td>
<td>Left ventricular hypertrophy</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Microalbuminuria</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>High total cholesterol</td>
<td>Creatinine &gt; 1.3 mg/dL</td>
<td>Stroke</td>
</tr>
<tr>
<td>Tobacco smoking, impaired glucose tolerance, diabetes*</td>
<td>Increased carotid IMT</td>
<td>Peripheral arterial disease</td>
</tr>
<tr>
<td>Family history of cardiovascular events</td>
<td>Hypertensive retinopathy (grades III/IV)</td>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>Increased vascular stiffness</td>
<td>Chronic renal disease</td>
</tr>
<tr>
<td>High LDL cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High triglycerides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight/obesity (BMI &gt; 25 kg/m²), Menopause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social/economic position**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; HDL, high-density lipoprotein; IMT, intima–media thickness; LDL, low-density lipoprotein; TOD, target organ damage. * According to the American Diabetes Association, International Diabetes Federation. ** Homeless, primary degree education, jobless.
recommendations, in two different positions (sitting and standing), with the aim to discover orthostatic hypotension (decreases greater than 20 mmHg in SBP and/or 10 mmHg in DBP), especially frequent in older patients [29]. When SBP and DBP values correspond to different grades, the higher grade should be used to define the patient’s hypertension.

Home blood pressure measurements, performed by instructed persons with either a mercury sphygmomanometer or preferably by automatic or semiautomatic validated devices, are an important tool for the control and follow-up of hypertensive patients. Upper normal values are similar for home and day-time ABPM, that is 135/85 mmHg [30].

Laboratory examinations
The main objectives are to detect other cardiovascular risk factors, to assess target organ damage and to identify secondary causes of hypertension. A complete blood count, fasting plasma glucose, blood urea nitrogen, serum and urinary creatinine, serum electrolytes, uric acid, total high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, liver function tests, T3, T4 and TSH, added to a complete urinanalysis, estimated glomerular filtration rate (from serum creatinine with the Modification of Diet in Renal Disease Study Equation for Estimating Glomerular Filtration Rate with Standardized Serum Creatinine Values (MDRD) formula), and an electrocardiogram must always be performed at the first visit.

Recommended examinations
Vascular, cardiac and renal ultrasound and Doppler examinations are recommended to evaluate left ventricular mass and to identify subclinical atherosclerosis in different vascular territories, renal arterial stenosis or kidney alterations. Measurement of the pulse wave velocity is helpful to assess large artery stiffness. Microalbuminuria (in a 24-h urine collection or as albumin/creatinine ratio) is highly recommended.

Ambulatory blood pressure monitoring
The method, which does not replace conventional measurements, gives more detailed information on mean 24-h, daytime or night-time values [31,32]. The 24-h mean values are more closely related to target organ damage and outcomes than office values. ABPM is indicated when:

1. White coat hypertension is suspected,
2. Hidden (masked) hypertension is suspected,
3. Normal blood pressure is accompanied by total high risk,
4. Evaluation of the 24-h blood pressure profile (dipping, nondipping, etc.) is desirable,
5. Refractory hypertension is suspected,
6. Hypotensive or hypertensive episodic events are looked for,

Risk related to blood pressure values. DM, diabetes mellitus; MS, metabolic syndrome; RF, risk factor; TOD, target organ damage.
(7) Autonomic dysfunction is present,
(8) Target organ damage progresses or does not regress
despite apparently good control of blood pressure.

Finally, the flowchart of Fig. 2 can be followed to evaluate hypertensive patients in whom possible causes of secondary hypertension are searched for.

**Metabolic syndrome, diabetes mellitus 1 or 2 and hypertension**

**Definition of metabolic syndrome**
The metabolic syndrome is an entity with easily detectable features and prognostic relevance, yet largely under-recognized, that may become a diagnostic target to identify subjects at increased cardiovascular risk [33–36]. The International Diabetes Federation (IDF, https://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf) considers abdominal obesity as one of the major cardiovascular risk predictor. However, since there are no data on normal cut-offs for abdominal circumference and visceral fat in Latin American populations, the use of the South Asian data is suggested until more specific data become available. Some small studies support this proposal [37–39]. Cooperative studies are under way and the new information may give more reliable information in this regard. Although evidence about cardiovascular benefits of intervention is still lacking [40], it makes sense, from a clinical and epidemiological standpoint, to focus on this population for the primary prevention of diabetes mellitus.

Definitions of metabolic syndrome range from the more stringent definition based on insulin resistance (World Health Organization) to that only based on clinical criteria [National Cholesterol Education Program (NCEP) [41]]. The NCEP definition has been adopted in hypertension guidelines [5], presumably favoring a higher sensitivity to identify populations at risk but at the cost of decreased specificity in detecting true insulin resistance [5,6]. An additional asset of the NCEP definition is clinical simplicity, as it may be applied almost anywhere despite the limited resources available in Latin America. However, the IDF classification seems to be more appropriate for Latin America populations than the other classifications in terms of the ethnic differences [37,38]. The prevalence of metabolic syndrome varies in terms of the classification criteria, age, sex, race and socioeconomic status, but it is approximately 25–50% in Latin America according to IDF criteria [37]. Recent estimates of the prognostic value of metabolic syndrome showed relative risk ratios for cardiovascular events or mortality ranging from 2.0 to 3.3, whether or not diabetes mellitus is included [36,42].

**Definition of diabetes mellitus in Latin America**
A growing body of evidence support the view that, like blood pressure, fasting plasma glucose is a continuous variable increasing the risk of cardiovascular disease, independent of the fact that plasma levels reach or do not reach the cut-off point used to establish the diagnosis of diabetes [43,44]. The diagnostic criteria for diabetes (confirmed fasting plasma glucose of at least 126 mg/dl or plasma glucose of at least 200 mg/dl 2 h after an oral glucose load) were chosen because they identified individuals at high risk of retinopathy. Recently, the terms of
dysglycemia or prediabetes have been proposed to define a condition in which the levels of fasting glucose range between 100 and 125.9 mg/dl or the value of plasma glucose 2 h after an oral glucose load of 75 g is between 140 and 199.9 mg/dl. It has been demonstrated that the risk of developing diabetes mellitus and CVD is increased in patients with prediabetes [45], especially in populations of developing countries [14,46], who are prone to develop insulin resistance associated with epigenetic adaptations to the rapid economic transition and with changes in the lifestyle experienced by these populations [14,47].

The population prevalence of diabetes mellitus in Latin America is 5–9%, being lower in rural areas and higher in areas over an altitude of 3000 m, where around 100 000 individuals live. Prevalence of prediabetes is similar to that of diabetes mellitus. The prevalence of hypertension in the diabetic population is 1.5-fold to 3-fold higher than among nondiabetic patients in the same age segment [6]. Prevalence of hypertension in diabetes is close to 30%; it develops many years after the onset of diabetes, usually as a consequence of diabetic nephropathy [48,49]. On the contrary, in type 2 diabetes, hypertension may be present at the time of diagnosis or may even precede overt hyperglycemia [50]. In newly diagnosed type 2 diabetics, the prevalence of hypertension is around 60%. In type 2 diabetes, it is difficult to determine whether hypertension is secondary to diabetes, since patients are usually older and more frequently obese than nondiabetic patients. Because in western populations the prevalence of diabetes increases with age and degree of obesity [51], a higher frequency of hypertension could be expected. However, after adjusting for age and overweight/obesity, the prevalence of hypertension was still 1.5-fold higher in diabetic patients relative to nondiabetic patients [52]. In certain ethnic groups [53], diabetic nephropathy could be the primary cause of hypertension in type 2 diabetes, as is the case among Pima Indians and African-American individuals. Patients with diabetes and hypertension are at a high risk for both macrovascular disease (coronary artery, cerebrovascular and peripheral vascular disease), and microvascular (renal failure, retinopathy). Although the relation between diabetic neuropathy and high blood pressure remains unclear, some epidemiologic evidence suggests that hypertension may facilitate the development of neuropathy [6].

Complications of diabetes

Diabetic nephropathy

The prevalence of nephropathy is 20–30% in patients with type 1 diabetes mellitus, and 30–50% in those with type 2 diabetes mellitus [54]. Three stages are described.

Incipient nephropathy

Incipient nephropathy features a supranormal glomerular filtration rate (GFR) for about 10 years, followed by an increased urinary albumin excretion (30–300 mg/day) for about 5 years. Presence of increased urinary albumin excretion in both type 1 and type 2 diabetes mellitus identifies patients at risk for progressive renal disease, and is considered an independent predictor of cardiovascular disease. Twenty to forty percent of individuals with abnormal microalbuminuria are reported to progress to frank albuminuria, and 20% of them to end-stage renal disease (ESRD).

Clinical nephropathy

Clinical nephropathy is characterized by more than 300 mg/day urinary albumin excretion and hypertension in almost 100% of patients. In type 1 diabetes mellitus, 80% of patients may develop albuminuria greater than 300 mg/day within 10–15 years, and many of them will progress to ESRD. Without intervention, progression to this condition may be faster; in fact, 50% of patients will have developed ESRD in 10 years and 75% in 20 years [55]. On the contrary, therapeutic interventions in both types of diabetes mellitus can slow down GFR decline.

Progressive renal insufficiency

Progressive renal insufficiency may be defined as macroalbuminuria (≥300 mg/day) and a reduced GFR (<30 ml/min per 1.73 m²). Macroalbuminuria identifies diabetic patients with substantial histological damage and predicts a linear decline in GFR. Newly diagnosed type 2 diabetes mellitus patients should be screened for albuminuria on a yearly basis. In type 1 diabetes mellitus patients, albuminuria should be searched for after 5–7 years from diagnosis, since increased urinary albumin excretion rarely occurs earlier in the course of the disease.

The management of diabetes and hypertension in patients with nephropathy mandates strict glucose and blood pressure control. The target for glycosylated hemoglobin A1c (HbA1c) should be less than 6.5–7%, since this has been shown to delay progression from microalbuminuria to macroalbuminuria [5]. The recommended blood pressure goal is less than 130/80 mmHg, and less than 120/75 mmHg in patients with proteinuria more than 1 g and/or reduced GFR.

Randomized intervention trials have demonstrated that the management of hypertension in patients with diabetic nephropathy should include blockade of the renin–angiotensin system [56–58] with agents such as angiotensin-converting enzyme inhibitors (ACEIs, greater evidence in type 1 diabetes mellitus) or angiotensin receptor blockers (ARBs, greater evidence in type 2 diabetes mellitus). If the blood pressure target is not achieved, other drugs should be added, such as diuretics (thiazides), calcium antagonists or β-blockers. The combination of three or more drugs is often necessary to meet blood pressure targets. Although there are
data favoring the combined use of ACEIs and ARBs in patients with type 2 diabetes mellitus and proteinuria, the recently published results of this combination in the large ONTARGET trial [59] call for caution, and require a careful reappraisal of this approach.

Patients with diabetic nephropathy require dietary protein restriction in addition to the pharmacological treatment since a reduced dietary protein intake (0.6 g/kg per day) may delay the progression to ESRD [60].

**Cardiovascular complications**

Patients with diabetes and hypertension are at increased risk for cardiovascular diseases such as CHD, heart failure, stroke, peripheral vascular disease. Comorbidities, including dyslipidemia, prothrombotic state and autonomic dysfunction, may contribute to poorer outcomes, thereby increasing morbidity and mortality. The incidence of cardiovascular disease in men and women with diabetes mellitus 2 is up to three to four times higher that in unaffected individuals. Furthermore, diabetes mellitus is associated with a cardiovascular disease mortality rate that exceeds 70%, and people with diabetes mellitus 2 are two to three times more likely to die from cardiovascular disease than people with no history of diabetes mellitus, even after controlling for other cardiovascular risk factors [61,62]. They are also at high risk of renal failure, limb amputation, cognitive decline, premature death, retinal disease leading to blindness and erectile dysfunction.

**Coronary heart disease**

Several factors account for the increased risk, including increased fibrinogen levels (particularly during poor glycemic control), increased levels of plasminogen activator inhibitor-1, and increased platelet aggregation [63]. Screening for CHD should include exercise stress testing and myocardial perfusion single-photon emission computed tomography imaging, when necessary.

The management of CHD is similar for hypertensive patients with or without diabetes mellitus. Smoking cessation should be strongly encouraged. Treatment targets include re-establishment of coronary flow and myocardial perfusion, plaque stabilization, prevention of recurrent ischemia, limitation of left ventricular (LV) remodeling, suppression of arrhythmias and secondary prevention. Treatment should include β-blockers. Antiplatelet therapy with aspirin [64] is the mainstay of treatment for diabetic patients with CHD, and is also recommended during and after acute myocardial infarction. It is important to achieve an adequate glycemic control as early as possible, since blood glucose levels on admission are an independent predictor of early and late mortality of patients with myocardial infarction [65]. Statins should be administered to protect vulnerable plaques even in patients with a normal lipid profile [65].

**Left ventricular dysfunction and heart failure**

Diabetes is a major risk factor for LV dysfunction and heart failure. In the Glasgow Monica study, the incidence of LV dysfunction was higher in diabetic patients (29%) compared with nondiabetic patients (7%) [66]. In the Framingham study [67], the relative risk for clinical heart failure in patients with diabetes was 3.8 in men and 5.5 in women, relative to nondiabetic patients. The prevalence of heart failure in elderly diabetic patients has been recently reported to be 39% [68]. The rate of heart failure was found to be 4.2/1000 patients/year for diabetic patients with HbA1c less than 7.0%, and to increase to 9.2/1000 patients/year for those with HbA1c greater than 10% [69]. Diabetic and hypertensive patients often develop the so-called ‘diastolic heart failure’, that is, heart failure with preserved systolic ejection fraction [70]. The high prevalence of heart failure and the significant morbidity and mortality associated with it mandate the early identification of risk factors and clinical signs to allow the appropriate treatment. Although an electrocardiogram and X-rays may be helpful, two-dimensional and pulsed Doppler echocardiography is recommended whenever heart failure is suspected in order to visualize the changes in heart structure and function that underlie heart failure. A 24-h electrocardiographic monitoring is also important to screen for arrhythmias, since heart failure is a proven predictor of sudden cardiac death.

Large clinical trials have documented the benefits of drugs blocking enhanced neuro-hormonal systems (sympathetic and renin–angiotensin) in attenuating cardiac remodeling, improving ventricular function, and reducing morbidity and mortality. Treatment should include a diuretic (furosemide), an ACEI or ARB and a β-blocker, unless contraindicated. Spironolactone can also be considered in absence of severe renal dysfunction.

**Stroke**

The rates of stroke-related disability are higher in diabetic than in nondiabetic patients [71]. The risk of fatal vs. nonfatal stroke is associated with higher levels of HbA1c many years before the event [72]. Hence, blood pressure and glycemic control, together with other proven therapies such as aspirin and statins [73], are warranted for stroke prevention.

**Prevention of cardiovascular disease in diabetic patients**

To prevent cardiovascular disease in patients with diabetes mellitus and hypertension, strict control of glycemia [74,75] and blood pressure is fundamental. The Diabetes Control and Complications Trial (DCCT) in people with type 1 diabetes found that a 6-year period of intensive glycemic control (HbA1C 7.2 vs. 9.0%) led to a 42% reduction in cardiovascular outcomes after 11 more years of passive follow-up. Interestingly, during passive follow-up, glycemic control was not different between the groups [74]. In type 2 diabetes mellitus the evidence is less clear:
the UK Prospective Diabetes Study (UKPDS) [75] showed only benefit in preventing microvascular disease by reducing HbA1c to 7.0 vs. 7.9%, and three recent trials (ACCORD [76], ADVANCE [77] and DIGAM 1–2 [78]) lowering HbA1c to below 7% failed to reduce macrovascular disease significantly, although ADVANCE reported a small but significant improvement in microvascular outcomes. However, these studies indicated that the cardiovascular risk of a diabetic patient is directly related to the duration of diabetes, and the efficacy of hypoglycemic therapy in reducing cardiovascular risk might be affected by the duration of diabetes [79]. Early intensive treatment should be encouraged in diabetic patients, especially in those at high risk of developing cardiovascular disease, as are the hypertensive diabetic patients.

Risk of diabetes in hypertension

Epidemiologic evidence suggests that hypertension is a risk factor for the development of diabetes. One prospective study found that people with hypertension had a 2.4 higher incidence of diabetes than people without hypertension [80]. One explanation for the increased risk of diabetes in hypertension is activation of the renin–angiotensin system. Both angiotensin II-mediated pancreatic vasoconstriction [81] and aldosterone-mediated hypokalemia [82] inhibit glucose-induced insulin release from the beta cell. In addition, angiotensin II and insulin share signal transduction pathways. Thus, insulin activates protein kinase C (PKC) through the tyrosine phosphorylation of insulin receptor substrate type 1 and 2 (IRS-1 and IRS-2) and stimulates the mitogen-activated protein (MAP)-kinase pathway signaling, whereas angiotensin II inhibits PKC signaling that alters the intracellular signaling of insulin, producing insulin resistance [83]. Blockade of the renin–angiotensin system reduces the contraregulatory hormone norepinephrine [84], improves peripheral insulin sensitivity [85], and prevents the development of diabetes in people with hypertension, heart disease, or heart failure, and reduces glucose levels [86–88]. For these reasons the recommendation of the 2007 European Guidelines for the Management of Arterial Hypertension recommend that in hypertensive patients with metabolic syndrome and type 2 diabetes ARB or ACE inhibitors [5] should be used as first antihypertensive drugs. In Latin American populations similar recommendations should be given for this kind of patients, especially in face of their higher proneness to develop insulin resistance at lower levels of abdominal obesity [89,90], a condition with epidemic characteristics in Latin America [91], and associated with changes in vascular function independently of other cardiovascular risk factors [92].
periodically. The lifestyle measures that are widely recognized to lower blood pressure and/or cardiovascular risk, and that should be considered are:

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

Body mass index and abdominal circumference are reliable clinical markers in cardiovascular prevention. Optimal BMI for the hypertensive population is between 18.5 and 25 kg/m². Likewise, an adequate abdominal circumference is less than 90 cm in male and less than 80 cm in women [37–39,98], but no tables of normality values based on epidemiological studies of sufficient power are available in Latin America.

Aerobic exercise is an important complement of diet for weight and blood pressure reduction. It should be implemented in all hypertensive patients and particularly in those with additional risk factors for at least 30 min daily.

Because long-term compliance with lifestyle measures is low and the blood pressure response highly variable, patients under nonpharmacological treatment should be followed up closely.

Initiation of blood pressure-lowering therapy

Initiation of blood pressure-lowering therapy should be decided on two criteria: the level of SBP and DBP and the level of total cardiovascular risk. Drug treatment should be initiated promptly in grade 3 hypertension as well as in grade 1 and 2, when total cardiovascular risk is high or very high. In grade 1 or 2 hypertensive patients with moderate total cardiovascular risk drug treatment may be delayed for a few weeks and in grade 1 hypertensive patients without any other risk factor for several months. However, it is important to pay particular attention to those individuals who are at risk because of their social environment (homeless, poor, the uneducated, or the unemployed), in whom a prompter initiation of therapy should be considered and a close monitoring of health is mandatory. When initial blood pressure is in the high-normal range the decision on drug intervention heavily depends on the individual clinical condition. In the case of diabetes, history of cerebrovascular, coronary, or peripheral artery disease, the recommendation to start blood pressure-lowering drugs finds some support in the results of controlled trials. Patients in the normal blood pressure range but at very high cardiovascular risk because of associated clinical disease should be advised to implement intense lifestyle measures. In these patients blood pressure should be closely monitored and drug treatment considered in the presence of increasing blood pressure or worsening of the clinical condition.

Selection of antihypertensive drugs

The main benefits of antihypertensive therapy are due to lowering of blood pressure per se. Five major classes of antihypertensive agents – thiazide diuretics, calcium antagonists, ACE inhibitors, angiotensin receptor blockers, and β-blockers – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination [5]. β-blockers, especially in combination with a thiazide diuretic, should not be used in patients with the metabolic syndrome or at high risk of incident diabetes. In these patients carvedilol, nebivolol, or slow-release indapamide may be suitable [99–101]. Renin inhibitors, such as aliskiren, although not yet available in all countries, have been shown to be effective antihypertensive agents [102]. However, results of outcome trials are still awaited, and the cost/benefit ratio of these agents is still unknown. In many patients more than one drug is needed, so fixed combinations might be useful in order to improve compliance and increase successful control of blood pressure [103].

The choice of a specific drug or drug combination, and the avoidance of others should take into account the following:

1. The previous favorable or unfavorable experience of the individual patient with a given class of compounds.
2. The effect of drugs on cardiovascular risk factors in relation to the cardiovascular risk profile of the individual patient.
3. The presence of subclinical organ damage, clinical cardiovascular disease, renal disease or diabetes, which may be more favorably treated by some drugs than others.
4. The presence of other disorders that may limit the use of particular classes of antihypertensive drugs.
5. The possibilities of interactions with drugs used for other comorbidities.
6. The cost of drugs, either to the individual patient or to the health provider.

Cost considerations, however, should never predominate over efficacy, tolerability, and protection for the individual patient.

Continuing attention should be given to side-effects of drugs, because these are the most important causes of noncompliance. Drugs are not equal in terms of adverse effects, particularly in individual patients. Drugs which exert their antihypertensive effect over 24 h with a once-a-day administration should be preferred because a simple treatment schedule favors compliance [104].
In hypertensive patients with moderate or high cardiovascular risk and specific accompanying conditions, the following pharmacological interventions are recommended:

1. ACE inhibitors or ARBs in patients with metabolic syndrome or type 2 diabetes because metabolic parameters are not affected or may even be improved.
2. ACE inhibitors or ARBs in patients with renal dysfunction and microalbuminuria or proteinuria because these agents slow down progression to chronic renal failure and dialysis.
3. ACE inhibitors or ARBs in patients with systolic and diastolic left ventricular dysfunction even if asymptomatic.
4. ACE inhibitors, ARBs, and calcium channel blockers in patients with left ventricular hypertrophy because these agents facilitate left ventricular regression.
5. Beta blockers in patients with CHD.
6. Calcium channel blockers (dihydropyridines) in elderly hypertensive patients and African Americans hypertensive patients.
7. \( \alpha \)-Adrenergic blocking agents in patients with prostatic hypertrophy.
8. Thiazides and chlortalidone in African American hypertensive patients, elderly hypertensive patients, or low-income people who cannot afford the cost of other drugs.
9. In hypertensive patients with heart failure diuretics, ACE inhibitors, bisoprolol, carvedilol or nebivolol, and spironolactone.
10. In postmyocardial infarction patients ACE inhibitors and beta blockers.
11. Recurrency of stroke is better prevented with diuretics (slow-release indapamide) and ACE inhibitors.
12. Patients with peripheral vascular disease should be encouraged to quit smoking and perform aerobic exercise. Calcium channel blockers are suitable to lower blood pressure without exacerbation of symptoms.
13. ACE inhibitors or ARBs in patients with recurrent atrial fibrillation. Beta blockers or verapamil in sustained atrial fibrillation.

**Special populations**

**Hypertension in children**

**Definition of hypertension in children**

Hypertension in pediatrics is defined by percentile tables related to sex, age, and height provided in the Report from the Working Group on High Blood Pressure in Children and Adolescents [105]. Normal blood pressure is defined when blood pressure, depending on sex, age, and height, is under the 90th percentile, high-normal blood pressure when blood pressure is over the 90th and under the 95th percentiles in three or more occasions. Adolescents with blood pressure values at least 120/80 mmHg should be considered as prehypertensive. White-coat hypertension is defined when blood pressure values are equal or over the 95th percentile and in the normal range out of the office. For diagnosis confirmation, ABPM or home blood pressure is required.

**Blood pressure measurement**

The demonstrated link between childhood blood pressure values and essential hypertension in adult life supports the recommendation that blood pressure must be routinely measured in the pediatric physical evaluation. The old concept that hypertension in children and adolescents is predominantly secondary is untrue. Thus, it is recommended that blood pressure must be measured since the first days of life and at least once in a year even in children, especially in the obese ones, as hypertension is closely related to obesity in children [106–111].

Measurement of blood pressure is mandatory in diseases or conditions accompanied by higher risk of arterial hypertension, such as renal diseases, diabetes, insulin resistance, long-term steroid therapy, nonsteroidal anti-inflammatory drugs, oral contraceptives, cyclosporine, neurofibromatosis, new borns with pathological umbilical vessels, Turner syndrome, corrected aortic coarctation, hemolytic–uremic syndrome, unexplained congestive heart failure, dilated myocardiopathy, and seizures of unknown cause.

Blood pressure measurements should follow these recommendations:

1. The child must be sitting in a chair that enables him to have the arm supported. If this is not possible, the child must sit on mother’s lap.
2. No measurement of blood pressure must be performed if the child is crying or moving the arm from which the measurement is to be performed.
3. To choose the correct arm-cuff, the arm circumference must be measured at mid distance between the acromium and olecranon. The air bladder, not the cuff, must cover 80% of the arm circumference.

<table>
<thead>
<tr>
<th>Table 5 Recommended cuff length for blood pressure measurement</th>
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<tbody>
<tr>
<td><strong>Inflatable bladder</strong></td>
</tr>
<tr>
<td>Newborn</td>
</tr>
<tr>
<td>Breast feeding</td>
</tr>
<tr>
<td>Child</td>
</tr>
<tr>
<td>Adult</td>
</tr>
<tr>
<td>Obese</td>
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<td>Thigh</td>
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Calculated to cover at least 80% of the arm circumference.

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ence and 2/3 of the olecranon–acromion distance. In case of unavailability of the correct cuff, the next size can be used. If only an adult cuff is available, the thigh of the children can be used with the child lying, performing the auscultation in the popliteal fossa.

From 6–7 years of age a small adult cuff can be used.

**Diagnostic evaluation**  Children with marked and persistent arterial hypertension should be evaluated for secondary hypertension. Inquiry should be made about newborn diseases and history of urinary infection, feeding habits, energetizer drinks, and illicit drugs. Physical exam should include heart rate, peripheral pulses, vascular and cardiac bruits, and blood pressure in both arms and legs. ABPM or home blood pressure readings may help to confirm the diagnosis and to discard white-coat hypertension, which is frequent in adolescents [112,113], thus avoiding unnecessary studies. The 24-h ABPM classification related to sex and age could be performed by using tables reported elsewhere [114].

Blood count, serum and urinary creatinine, serum uric acid, serum and urinary electrolytes, acid–base evaluation, plasma renin activity, serum aldosterone, fasting glycemia, serum lipids, a full urine test with microalbuminuria, cardiac and renal Doppler ultrasound should be performed whenever there is a consistent suspicion of secondary hypertension.

Special tests according to type of suspected secondary hypertension can be considered, such as renal scintigraphy before and after ACEI, magnetic angio-resonance and/or aorto-renal arteriography (renovascular disease), urinary catecholamines and metanephrine (pheochromocytoma), aldosterone : renin ratio, cortisol plasma levels (primary hyperaldosteronism or Cushing disease).

**Prevention**  Pediatricians should measure blood pressure as part of the physical examination in all children. Physicians in charge of adult hypertensive patients or adult cardiac patients should measure blood pressure in their patients’ offspring also, since hypertension presents familiar aggregation [115]. Lifestyle changes should be elicited in the entire family, these greatly contributing to the primary prevention of hypertension and cardiovascular morbi-mortality. Healthy eating changes and increased physical activities should be promoted in schools, in view of actively antagonizing the overweight and obesity epidemics induced by trash food intake and sedentarism due to the time spent at the computer and in front of the television. Obesity is one of the major components of the metabolic syndrome that also include other cardiovascular risk factors like arterial hypertension, insulin resistance, and dyslipidemia [107,116]. High salt intake through processed foods and sugar intake in sweetened beverages also contribute to weight gain [117]. A reduced salt intake is a simple measure to prevent weight gain. A greater intake of vegetables and fruits, foods with high potassium content, may also help to prevent a blood pressure increase. Recommendations should be given against active or passive exposition to tobacco smoking, since there is a straight relationship between parental and children’s smoking habits. Childhood is a specific window in which prevention of hypertension and cardiovascular risk factors should be started.

**Treatment**  Nonpharmacological treatment is the major measure to lower blood pressure in children. It is similar to that recommended above for prevention of hypertension.

Pharmacological treatment should not start before 4–6 months of an unsatisfactory response to lifestyle changes, when target organ damage is present and in patients with secondary hypertension.

Clinical studies with antihypertensive drugs in children are not numerous nor large, but they have provided some information about doses and safety of drugs. Treatment should be started with a single drug, all classes (ACEIs, ARBs, beta blockers, calcium antagonists, and diuretics) being suitable. Small doses should initially be used and subsequently titrated until blood pressure control is reached. In case of failure, a second drug can be added in order to avoid too large doses of any single drug.

**Cautions when treating hypertension in children**  Avoid the use of ACEIs and ARBs in female adolescents at risk of pregnancy (specific contraindication). Beta blockers can cause some reduction in physical performance and diuretics increase the risk of electrolyte disturbances.

**Hypertension in pregnancy**  In pregnancy hypertension has a prevalence of about 5–10%, and is more prevalent in high-risk pregnancies, such as those with a previous history of preeclampsia or chronic severe hypertension, or in primiparous women. In Latin America a higher prevalence of hypertension in pregnancy has been documented than in high-income countries [118]. Therefore, special attention is given to this topic in the present guidelines. Indeed, most of the complications of hypertension in pregnant women are preventable, and the best prevention is based on early detection of hypertension through a careful measurement of blood pressure.

**Definition and classification**  Hypertension in pregnancy is defined as blood pressure values of at least 140/90 mmHg in two or more readings at a 4-h interval [119]. Proteinuria in pregnancy is defined as urinary protein excretion of at least 300 mg/24 h. Among the different hypertensive syndromes in pregnancy particular attention is called to preeclampsia because of its prevalence in Latin America.
Preeclampsia is frequently associated with fetal complications. It starts through an anomalous placentation before the 20th week [120], and usually presents clinically after the 28th week, with an increase in blood pressure, proteinuria, and hyperuricemia. Edema, impaired renal function, hemolysis and platelet aggregation, attributed to endothelial dysfunction secondary to placental ischemia, can also occur. Endothelial dysfunction may release different toxins into the maternal blood, such as cytokines, reactive oxygen species (ROS), asymmetric dimethylarginine (ADMA), antibodies against angiotensin II receptors, and so on [121]. Factors favoring the abnormal placentation are: first pregnancy before age 18 years or after 40 years age, previous history of preeclampsia (especially if before the 32nd week [122]), history of spontaneous abortion or severe intrauterine growth retardation, pregnancy resulting from assisted fertilization, multiple pregnancies, close familiar (mother, sister) history of preeclampsia, Rh isoimmunization, subclinical infections, chronic arterial hypertension, renal failure, obesity, autoimmune diseases. Differences between developed countries in the causes of preeclampsia and in the strategies to prevent it have been described [123]. Inflammation secondary to vaginal and urinary subclinical infection [124,125], periodontal disease [126], insulin resistance [127] are considered as possible risk factors for the development of preeclampsia. Therefore, it is important that pregnant women with the above-mentioned risk factors be carefully followed to detect hypertension and proteinuria early, prevent severe complications requiring hospitalization, and, if necessary, perform cesarean delivery to preserve mother and child.

**Prevention**

**Low-dose aspirin**  The efficacy is lower than initially expected [128] and its use is still controversial. Nevertheless in patients at high risk of preeclampsia early aspirin administration (100 mg/day from the 8th week until 2 weeks before probable delivery) may delay onset of preeclampsia.

**Calcium supplementation**  An inverse relationship has been shown between calcium intake and preeclampsia [129]. Although a number of trials of calcium supplementation have failed to consistently show benefits, some low and middle-income populations of Latin America have low calcium diets and in these groups beneficial effects on preeclampsia and prematurity delivery have been obtained by giving a 1 g daily supplement of calcium [130–132].

**Subclinical infections**  Because of the strong relationship between urinary and periodontal infections and preeclampsia [133], it is imperative to search for and treat bacteriuria, urinary, and/or vaginal and periodontal infections in pregnant women.

**Diagnostic studies**

Biochemical tests during pregnancy should include blood count, glycemia, serum electrolytes, creatinine and uric acid, urinalysis and 24-h proteinuria. These measurements must be repeated at the 20th, 28th, 32nd, and 36th weeks and more frequently when hypertension or complications are present. Pregnant women at high risk of preeclampsia may be advised to have a uterine arterial Doppler ultrasound at weeks 10–12 and 20–28.

In women with a history of preeclampsia before the 32nd week, or of recurrent abortions, hematological abnormalities are two to three times more frequent than in the general population [134,135]. A search for anticardiolipin antibodies, homocysteine, antithrombin III deficit, lupus inhibitor, activated C protein resistance, protein S deficit, helps in the identification of women that, in a future pregnancy, may require aspirin or heparin to prevent complications. Likewise, in any pregnant woman with high fasting plasma glucose an OGTT should be performed.

**Treatment**

Pharmacological treatment must be started when blood pressure is at least 150/100 mmHg. Treatment can be initiated orally, and the patient recontrolled after 48–72 h.

Based on 40 years experience and 7.5 years follow-up of children of treated mothers, alpha methyl-DOPA (500–2000 mg/day) is the drug of first choice. Second-line drugs are labetalol (100–400 mg/day), long-acting nifedipine (30–60 mg/day), and hydralazine (50–200 mg/day) [136].

Drugs with absolute contraindications are renin inhibitors, ACE inhibitors, and ARBs [137,138]. Relative contraindications are beta blockers (mostly atenolol), because of reduced placental perfusion and untoward effects in the newborn (reduction in weight, bradycardia, and hypooglycemia) [139]. Diuretics are also relatively contraindicated, unless when cardiac failure is present, because pregnancy is characterized by reduced plasma volume, which may be further reduced by diuretic therapy.

Emergency hospitalization and treatment (often intravenously) is required when DBP is at least 110 mmHg or remains above 100 mmHg despite treatment, proteinuria is greater than 1 g/24 h, there is the HELLP syndrome or eclampsia. Even in emergency situations blood pressure must be reduced gradually during the first 24 h. Recommended drugs are: labetalol – initial dose 20 mg i.v., with subsequent doses at 10-min intervals, if necessary, up to a maximal dose of 220 mg; long-acting nifedipine – if the patient is conscious, 10 mg every 30 min orally, with a maximal dose of 40 mg (magnesium sulfate can be associated although some reduction in uterine contractility has
Eclampsia is characterized by seizures. It evidently of gestational time. Interruption of pregnancy is recommended independently of gestational time; when this is more than 36 weeks, pregnancy should be interrupted. When gestational time is less than 36 weeks, corticoids should be administered to induce pulmonary maturation, and pregnancy interrupted after 48 h.

**Complications of hypertension in pregnancy**

**HELLP syndrome** HELLP is an abbreviation of the main findings [140]: hemolytic anemia, elevated liver enzymes, and low platelet count. This, together with eclampsia, is the most frequent cause of maternal death. It can follow a severe preeclampsia or represent the first manifestation of the disease. The three diagnostic criteria are microangiopathic anemia with hyperbilirubinemia, increased lactic acid dehydrogenase and hepatic enzymes, and thrombocytopenia. The patient must be hospitalized, possibly in an intensive care unit, and antihypertensive drugs are needed, those with low breast milk excretion should be used, such as methyl dopa, nitrrendipine, captopril, or enalapril [144]. Special caution must be taken with diuretics since a reduction in breast milk production can be induced; diuretics are also excreted in breast milk and can cause electrolytic alterations in the newborn.

**Recommendation for follow-up of women and children after a hypertensive pregnancy**

**Breast feeding** Blood pressure less than 150/100 mmHg does not require treatment and salt restriction can be the only measure to normalize blood pressure. If antihypertensive drugs are needed, those with low breast milk excretion should be used, such as methyldopa, nitrrendipine, captopril, or enalapril [144]. Special caution must be taken with diuretics since a reduction in breast milk production can be induced; diuretics are also excreted in breast milk and can cause electrolytic alterations in the newborn.

**Long-term maternal blood pressure control** All women presenting hypertension during pregnancy should have their blood pressure followed up subsequently, since they are prone to show or develop continuing hypertension. Furthermore, a number of retrospective studies have shown an increased cardiovascular risk in women with preeclampsia and intrauterine undernutrition [145–147].

**Child blood pressure control** Several epidemiological studies have shown a strong association between low birth weight and prevalence of hypertension and cardiovascular diseases in adulthood. These findings support the concept that cardiovascular diseases may start in intrauterine life [148]. Therefore, children of mothers with a hypertensive pregnancy should have their blood pressure controlled up to adulthood.

**Hypertension in the elderly** Hypertension is known to be one of the most important treatable risk factors in patients older than 65 years. Isolated systolic hypertension which is very frequent in the elderly [149] carries an additional risk because the increased pulse pressure (>65 mmHg) has been found to be associated with increased cardiovascular morbidity and mortality [150]. The elderly are prone to orthostatic hypotension and pseudo hypertension due to a reduced arterial compliance, therefore blood pressure measurements must also be done with the patient in the erect posture. Twenty-four hour ABPM may also be a valuable adjunct to the clinical evaluation [151,152].

**Diagnosis** In elderly hypertensive patients, especially those resistant to treatment, renovascular hypertension due to abdominal aorta atherosclerosis must be searched for. Doppler ultrasound examinations of the renal artery and abdominal aorta are a useful screening tool.

**Treatment**

In the elderly, blood pressure should be reduced to a target similar to that recommended for younger people, that is below 140/90 mmHg. This goal, however, is more difficult to achieve. In the elderly, blood pressure decrease must be gradual to ensure good tolerability and guarantee a good quality of life.

A number of large trials (SHEP, STOP, MRC, Syst-Eur, and Syst-China [153–157]) provided strong evidence of the benefits of lowering blood pressure in older patients either with systolic–diastolic or isolated systolic hypertension, showing decreases in stroke (25–47%), coronary events (13–30%), heart failure (29–55%), and cardiovascular death (17–40%), in actively treated vs. placebo-treated patients. The recent HYVET trial [93], which included 3800 patients older than 80 years randomized to either placebo or active treatment with indapamide and perindopril, showed that even in these very elderly patients blood pressure reduction is associated with a significant reduction in fatal and nonfatal stroke (30%), stroke deaths (39%), all-cause mortality (21%), cardiovascular deaths (23%), and heart failure deaths (64%).

**Pharmacological treatment** When selecting antihypertensive drugs for older people, the frequent presence of comorbidities and, consequently,
of multiple drug intake, must be taken into account, and the risk of pharmacological interactions considered. To avoid excessive or sudden falls in blood pressure, due to impaired pharmacokinetics, overestimation of blood pressure values, the postprandial and orthostatic hypotension, reduced blood flow autoregulation, and so on, agents must be started at low doses, and doses adjusted every 4–6 weeks after evaluating side-effects. The first-step drugs in older people without complications are diuretics and calcium antagonists, as more frequently used in randomized trials, but favorable data are also available for other agents (see HYVET results for the use of ACEI in combination with a diuretic). In elderly hypertensive patients with associated risk factors, hypertensive complications, or comorbidities, drugs must be chosen depending on the comitant disease. Long-acting drugs are preferred due to better patient compliance (an aspect particularly valuable in the elderly in whom a simplified drug delivery is recommended) and a smoother antihypertensive effect.

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