Second Consensus on Treatment of Patients Recently Diagnosed With Mild Hypertension and Low Cardiovascular Risk

Alberto Morales-Salinas, MD, FACC, Michael Hecht Olsen, MD, PhD, DMSc, Richard Kones, MD, PhD, FESC, FAHA, FRSM, FRSH, FCCP, Kazuom Kario, Jiguang Wang, Lawrie Beilin, MD, Michael A. Weber, MD, FACP, FACC, FAHA, Yucichiro Yano, MD, Louise Burrell, MBChB, MRCP, MD, FRACP, FAHA, FRSB, Marcelo Orias, MD, Dzudie A. Cameroon, Carl J. Lavie, MD, FACC, Hector Ventura, MD, John Sundström, Professor, FRSB, Giovanni de Simone, MD, FACC, FAHA, FESC, Antonio Coca, MD, PhD, FRCP, EFESC, Umme Rumana, MD, MBI, and Jaume Marrugat, MD, PhD, FESC

Introduction

The First Consultation on newly diagnosed mild hypertension was published in March, 2017.[1] Mild hypertension was then, and throughout this follow-up paper, defined as a systolic blood pressure of 140-159 mmHg and/or a diastolic blood pressure of 90-99 mmHg. The question considered in the first and extensive publication was: should

Declaration of Competing Interest: All authors state that there is no conflict of interest with respect to finances, other submissions, administratively or otherwise. All authors state that there has been no external funding. All authors state that no part of the manuscript being submitted, nor the entire manuscript has been submitted elsewhere.
Curr Probl Cardiol 2020;45:100653
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2020.100653

adult patients with recently diagnosed mild hypertension at low cardiovascular (CV) risk be treated with anti-hypertensive medications?[1]

This is still a controversial and unresolved question in primary prevention of CV disease (CVD)[1] for several reasons:

a) There are no high-quality levels of evidence, simply because there are no randomized clinical trials or meta-analyses focusing on appropriate definitions of mild untreated hypertension with low cardiovascular risk (CVR).
b) There is no consensus in current guidelines concerning the best method to classify the risk of the patient cohorts included in published studies. Such a classification would allow identification of the risk status of these cohorts and facilitate the extrapolation of the findings of these studies to the real world.
c) Health professionals (methodologists, epidemiologists, clinicians, biostatisticians, and policy experts), and key opinion leaders (principal investigators, as well as the steering and writing committees of clinical trials) often lack full appreciation of (1) the utilities/limitations inherent in the use of risk models, and (2) the appropriate definition of newly diagnosed mild hypertension in low CV risk patients.

The First Consensus suggested that the selection of the risk model depends on the objective of the prediction. The recently published 2020 International Society of Hypertension global hypertension practice guidelines do not address the issue either, and only refer to CV risk in the Section 11 on resources in a brief list of on-line CV risk calculation.[2] Several models can be used to estimate CVR at the individual level. The Systematic Coronary Risk Estimation SCORE is one such model, together with other functions developed or adapted to local population characteristics in some regions.

Cardiovascular death is indisputably the most objective CV outcome in randomized clinical trials, meta-analyses and elsewhere; it is also a reliable indicator of nonfatal CVR.[3] There is appreciable evidence that fatal and non-fatal CV outcomes can be estimated in groups of hypertensive patients based on CV death.[1,3,4,5] However, it is important to remember that case fatalities increase with age and, therefore, the use of CV death as the principal indicator will lead to overtreating the elderly and undertreating the middle aged.

We should also emphasize that some trials have not provided direct information about when to initiate antihypertensive treatment because they included patients taking antihypertensive drugs at baseline.[1]

More than thirty epidemiological, clinical, psychosocial, and public health elements were identified in the First Consensus that favor early antihypertensive pharmacological treatment in adults with recently diagnosed mild hypertension and low CVR.[1]

Most people have other risk factors or co-morbidities in association with hypertension. However, some patients do have hypertension without any other risk factors. For that subgroup, the First Consultation used the term "isolated" hypertension.[1]

To avoid potential confusion with other types of hypertension,[6,7] the Second Consultation now refers to this subgroup as "solitary" hypertension (Table 1). Also, the Second Consultation re-defines solitary hypertension as: uncomplicated hypertension with blood pressures (BP) between 140-159 and/or 90-99 mmHg with low absolute total CVR (using any of the available risk models), and without any other major CVR factors (age: male >55 years or female >65 years, smoking, dyslipidemia, diabetes mellitus, obesity, postmenopausal status in women, and a family history of premature CV disease).

The First Consultation focused on consideration of the recommendations of the 2013 European hypertension guidelines.[4] The 2018 European (ESC/ESH)[8] and American (ACC/AHA)[8] guidelines expressed some

Table 1. Features of recently diagnosed mild hypertension with low CVR, and mild solitary hypertension compared

Variables	Mild hypertension with low CVR[1]	Mild solitary hypertension[1]
Blood pressure thresholds	SBP 140-159 and/or DBP 90-99 mm Hg (according to the First Consensus[1])	SBP > 140-159 and DBP < 90 mmHg (according to the First Consensus[1])
Low absolute CVR is an inclusion criterion	Yes	Yes
Additional major CVR factors are exclusion criteria	No	Yes
Evidence of hypertension-mediated organ damage is an exclusion criterion	Yes	Yes
Cardiovascular disease is an exclusion criterion	Yes	Yes
Antihypertensive treatment at baseline is an exclusion criterion	Yes	Yes

Notes: Although both the First and Second Consensus statements recommend the SCORE model for the analysis of research studies,[1] for individual levels one can use any of the available risk models (eg, Framingham or the ACC/AHA Pooled Cohort Equations, or models adapted to or developed with local populations).[9]

new views concerning the treatment of patients with mild hypertension. These recommendations have motivated this Second Consultation which focuses on newly diagnosed mild hypertension with low CVR.

To further clarify the concept, comparing the characteristics of mild hypertension with low CVR with solitary hypertension may be helpful (Table 1). Patients with solitary hypertension will always be a subgroup of those with mild hypertension.

Objectives

(1) To analyze what has been changed in the management of adults with mild hypertension and low CVR in the 2018 ESC/ESH and 2017 ACC/AHA guidelines compared with the previous guidelines;
(2) To identify the main barriers to the management of patients with mild hypertension and low CVR;
(3) To update the recommendations of the First Consensus.

Methods

The initial version of this manuscript was elaborated (by AMS, MHO, and RK) based on the changes proposed by the 2018 ACC/AHA and ESC/ESH guidelines on hypertension, as well as other papers pertinent to this topic. This Second Consensus was submitted to selected experts from all continents and major societies of hypertension or CV prevention. The review was periodically updated according to the suggestions of the experts during the different stages of evaluation from March 20, 2019 to May 2020, until a consensus emerged. This document does not represent the official position of any societies or official organization.

There has been no financial support for this work.

Results

What has been changed in the management of adults with mild hypertension and low CVR in the 2018 ESC/ESH[7] and 2017 ACC/AHA[8] guidelines?

As presented in Table 2, a comparison between the levels of evidence classifications used by the ESC/ESH[8] and ACC/AHA[9] guidelines is a useful first step.

The 2018 ESC/ESH guidelines:

Table 2. Comparison between the levels of evidence in the 2 guidelines

Level of evidence	ESC/ESH[8]	ACC/AHA[9]
A	Data from multiple RCT or meta-analysis	High quality of evidence: from more than one RCT. Meta-analysis of high-quality RCT. One or more RCT corroborated by high quality registries studies.
B	Data from single RCT or large non-randomized studies.	Randomized (R): Moderate quality of evidence from one or more RCT. Meta-analysis of moderate quality RCTs. Non-randomized (NR): Moderate quality of evidence from one or well-designed, well-executed studies, observational studies or registries. Meta-analysis of such studies.
C	Consensus of expert and/or small studies, retrospective studies and registries.	Limited data (LD): Randomized or non-randomized observational or registries of studies with limitation of design or execution. Meta-analysis of such studies. Psychological or mechanistic studies in human subjects. Expert opinion (EO): Consensus of expert opinion based on clinical experience.

Comments: Treatment initiation for patients with 140-159 and/or 90-99 mmHg at low-moderate CVR, alongside lifestyle changes; recommendation upgraded from Class II in the previous guidelines[4] to Class I currently.[8]

Drug treatment for patients with BP between 140-159 and/or 90-99 mmHg at low-moderate CVR is based on the Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial[9] and Sundstrom meta-analysis.[11] The CV mortality at 10 years in HOPE-3[10] and Sundstrom meta-analysis[11] were 4.8% (7.1% in the upper tertile of baseline systolic BP) and 6.2%, respectively. Therefore, these studies are not applicable to patients with mild hypertension and low CVR according to SCORE categories: (1) **Low**: CV mortality <1% at 10 years, (2) **moderate**: CV mortality ≥1% and <5% at 10 years, (3) **high**: CV mortality ≥5% and <10% at 10 years, and (4) **very high**: CV mortality ≥10%.[7]

The ESC/ESH guidelines acknowledged that there is controversy about whether younger adults (age <50 years) with uncomplicated mild hypertension should be treated because of the obvious difficulty in conducting conventional clinical outcome trials in younger adults, in whom the outcomes only occur after many years.[7] However, these guidelines also noted that despite the absence of clinical trial evidence demonstrating benefits of antihypertensive treatment in younger adults with uncomplicated mild hypertension, treatment with BP-lowering drugs might still

be considered prudent based on the linear relationship between elevated BP and long-term CV events and mortality in observational studies. Moreover, there is evidence that young adults with mild hypertension are at risk of major CV events. Given the effectiveness of treating older patients with mild hypertension, it appears to be a very reasonable extrapolation to treat younger adults, perhaps to systolic BP targets of <130 mmHg if tolerated (Tables 3 and 4).

The 2018 ACC/AHA guidelines:

Comments: The new ACC/AHA classification defined grade 1 hypertension as systolic and diastolic BP of 130-139/80-89 mmHg and grade 2 as BP ≥140/90 mmHg. The rationale for this categorization and management of hypertension is mainly based on the HOPE-3,[10] the meta-analysis from Sundstrom,[11] and on the independent systematic review and meta-analysis provided by the Evidence Review Committee.[12]

Although many of the key recommendations in the ACC/AHA guideline were independent of the Systolic Blood Pressure Intervention Trial (SPRINT),[13] there has been an assumption by some observers that the SPRINT findings underscored the selection of blood pressure target recommendations in these guidelines. On closer examination, however, SPRINT is not relevant to the question of how or whether to treat mild hypertension: (1) the trial did not provide direct information regarding

Table 3. Recommendations regarding the management of patient with BP between 140-159 and/or 90-99 mmHg and low CVR[2,8]:

Lifestyle interventions are recommended to determine if this will normalize BP (Class II, Level B).[2,8]
In patients with BP between 140-159 and/or 90-99 mmHg at low−moderate-risk and without evidence of hypertension-mediated organ damage, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention (Class I, Level A).[8]

Note: CVR according to SCORE.[4,8]

Table 4. New recommendations regarding the management of patient with BP between 140-159 and/or 90-99 mmHg and low CVR[9]:

Use of BP-lowering medication is recommended for primary prevention of cardiovascular diseases in adults with no history of cardiovascular disease and with an estimated 10-year ASCVD risk <10% and systolic BP ≥ 140 mmHg or a diastolic BP ≥ 90 mmHg. Class 1, level C-LD

Note: CVR according to atherosclerotic cardiovascular disease (ASCVD).[9]

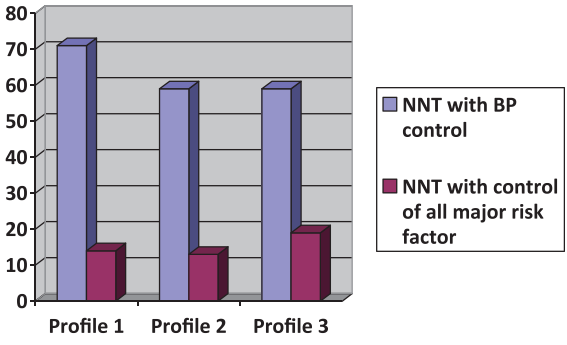
the BP level at which drug treatment should be initiated because 90% of patients were already taking antihypertensive treatment at baseline, and (2) SPRINT was adjusted to secondary prevention and patients in high or very high CVR categories without CV diseases (mean of Framingham 10-year CV disease risk score was 20.1%).[12] The ACC/AHA guidelines acknowledged that most of the participants in SPRINT had a much higher level of CVR than 6%-7% 10-year ASCVD risk based on the ACC/AHA Pooled Cohort Equations.[9]

Post hoc analysis of the Home Blood Pressure Measurement With Olmesartan Naive Patients to Establish Standard Target Blood Pressure study (HONEST study) showed that strict blood pressure targets may not be necessary for low-risk patients.[13] Participants in the HONEST study ($n = 21,591$) were stratified according to risk level as follows: SPRINT population ($n = 5823$)-patients ($\geq$50 years of age) without diabetes mellitus or prior stroke, with SPRINT-defined CV risk and systolic blood pressure (SBP) of $\geq$130 mm Hg; SPRINT-excluded high-risk population ($n = 5481$) patients with diabetes mellitus or prior stroke and non-SPRINT low-risk population—all other patients in the HONEST study ($n = 10,287$).[14]

The meta-analysis of Thomopoulos et al[15] demonstrated that in untreated patients with baseline systolic BP $<$ 140 mm Hg the initiation of drug treatment the benefit was limited to stroke in subjects with either high CVR or CV diseases. The CV mortality of the control group in this meta-analysis was 4.5% over 10 years.[15] Furthermore, the use of "mean" baseline values to define mild hypertension cannot exclude that a minority of patients with higher BP were included.[1]

However, despite some questioning of the evidence used in the ACC/AHA guidelines to set the treatment target at $<$130/80 mmHg,[16] the authors of these guidelines have remained confident in the validity of their recommendation (Fig).[17]

The ACC/AHA BP treatment goal, which was reduced from 140/90 mmHg to 130/80 mmHg, could indeed reduce CV event rates, although it may be important to consider the cost-effectiveness of the treatment and the feasibility of achieving BP control. The shift of the BP threshold to $\leq$130/80 mmHg level will significantly increase the number of patients diagnosed with hypertension, the number of patients treated with drugs and inevitably the number of patients with uncontrolled hypertension.[18] At the same time, it should be emphasized that starting statin drug therapy for patients at 130/80 mmHg or higher is recommended by the ACC/AHA Guidelines for patients at high CVR (ASCVD score $>$10%, whereas for people without a history of CV disease and with an ASCVD



NNT: number need to treat

Figure. Theoretical reduction of NNT if we compare the option of only hypertension control (Table 7) against the option of control of all major risk factors (Table 8). NNT, number need to treat.

score <10% (who are the focus of this Consensus II document on "mild solitary hypertension") the ACC/AHA recommendation is to start drug therapy at the higher threshold of >140/90 mmHg. Like ESH/ESC, ACC/AHA lifestyle modifications started earlier in life (healthy diet, regular exercise, good sleep habits, and other health promoting practices; such as the cessation of smoking) can facilitate primary CV prevention at earlier stages of the continuum of CVR. These measures should be strongly endorsed worldwide.[19-24]

Main barriers for the management of patients with mild hypertension and low CVR

The management of patients with mild hypertension and low CVR remains a relevant but controversial topic because:

1. No randomized clinical outcomes trials have been performed in patients with mild hypertension (140-159 and/or 90-99 mmHg) and low CVR (cardiovascular mortality <1% at 10 years).[1] All recommendations in this subgroup represent extrapolations from indirect evidence rather than translation from high quality direct evidence. As a result, it is necessary to analyze data from moderate and lesser quality levels of evidence.[1]
2. The phenomena of different interpretations of evidence among observers or guideline writing committee members, possibly due to differing preconceptions and experience.[25]

There is no consensus in the guidelines concerning the best method to classify the risk of patient cohorts included in the available studies. In addition, CVR models have limitations,[26-28] and confusion may exist concerning: (1) the utility of CV mortality as a marker of CVR at individual and population levels, and (2) in the appropriate definition of mild untreated hypertension with low risk.[29] There are many CVR models, but there are no validated tables for most low and middle income countries, where over three-quarters of CV deaths occur.[1] It is well known that locally validated CVR estimation systems should be used at individual levels, much as the Framingham risk functions appeared to apply well to white and African American population samples[27] or Pooled cohort equations in the general United States population[4], the Framingham-REGICOR score in Catalonia (a Southern Europe region with relatively low acute myocardial infarction incidence), Spain,[29-32] or the FRESCO function validated on representative population sample in Spain.[33] The specificity ranges of the risk models is between 84.5% and 99.3%, but the positive predictive value ranges from 9.5% to 17.1% and the sensitivity ranges from 3.6 % to 53.4%.[1] Another unresolved controversy related to CVR models is the target of prediction, an occasionally imprecisely-defined but important variable. This is the case, for example, with total CV mortality in SCORE[4,8] or morbidity and mortality of coronary heart disease in Framingham,[26] Pooled Cohort Equations[9] or Framingham-REGICOR.[33] Comments were made about other limitations of the CVR scores in the First Consultation.[1] Estimation of CV mortality risk with SCORE is a feasible method for an approximate estimate of CVR in research such as clinical trials, cohort studies or meta-analysis.[1,3,29] However, to generate more accurate CVD risk prediction that includes non-fatal CV events—an important point to prevent overlooking those events in younger population—we suggest re-calibration of existing risk models or developing new models.[26,34] There is paucity of large-scale studies that have provided head-to-head comparisons of standard risk prediction algorithms.

3. The mandatory estimation of CVR in younger hypertensive individuals ages ≤50 years[4] (mainly in <40 years) is not feasible in most of the scoring systems in use (estimation of relative CVR in patients <40 years old is not possible in SCORE, and, although it can be manually calculated, ACC/AHA Pooled Cohort Equations, ACC/AHA, Framingham-REGICOR, and FRESCO do not inform the relative CVR or CVR age).[4,8,9,28,30-33]

4. The presence of risk modifiers may move an individual's estimated absolute total CVR upward; absence of these modifiers should lead to lowering an individual's estimated risk. There is concordance among the statements of the ACC/AHA and ESC/ESH CV prevention guidelines concerning the utility of the (1) coronary calcium score ≥300 Agatston units or ≥75th percentile for age, (2) atherosclerotic plaques determined by carotid artery scanning, (3) ankle−brachial blood pressure index <0.9, and (4) high-sensitivity C-reactive protein ≥2 mg/L.[1] However, some of these assessment methods are not available in low-middle income countries or in the primary care setting. Unfortunately, there is a lack of evidence supporting simple re-stratification strategies (they do not need additional detailed screening tests) in mild hypertension with low CVR, such as CV relative risk (the traditional definition uses a ratio of the absolute risk of the individual under consideration and the average absolute risk of a baseline population, either a low-risk group or an average risk group),[1] CV age (the risk age of a person with several CVR factors is the age of a person of the same gender with the same level of risk but with ideal levels of risk factors) or an ideal CV health score.[35,36]

   Potential advantages of using CV relative risk are that it can be used in any population independently of the baseline CVR (avoiding the need of recalibration) and reduces or eliminates influence of age on the total CVR.[1] A 3-fold increase in relative risk above the lowest risk level is designated moderately high risk; a 4-fold or greater increase is called high risk.[37]

   Metrics of the American Heart Association definition of ideal CV health focus on 4 behavioral lifestyle factors (smoking, body weight, physical activity, and diet) and 3 established risk factors (blood cholesterol, blood glucose, and BP).[36,37] The report by Yang et al examines associations between the numbers of ideal CV health metrics and mortality over 14.5 years.[38] Compared with individuals with 0 or 1 metrics at ideal levels, those with metrics 6 or more at ideal levels had 51%, 76%, and 70% lower adjusted hazards ratios for all-cause, CV diseases, and ischemic heart disease mortality, respectively.[36,37]
5. Age is the most influential CVR factor at individual and population level. (1) Among such people without existing disease, the most discriminatory screening factor is age, since over 90% of deaths from ischemic heart disease or stroke, occur in people aged 55 and over.[1,39] (2) Two-thirds of total CVD events of primary prevention occur in subjects with low to moderate absolute CVR, and this

proportion could be higher in women (three-quarters),[40] and (3) men ≥55 years and women ≥60 years with mild hypertension often have at least moderate CVR (Table 5A) even in the absence of other identifiable major CVR factors[1] in high CVR regions[35,36] or subgroups[9] (these age thresholds should be increased to ≥60 years in men, and to ≥65 years in women from low CVR regions or subgroups including Caucasians[38] (Table 5B); countries at low CVR[4,8,36]—Table 5C—and region of Catalonia[31,32] (Table 5D). Two different SCORE charts have been developed to estimate risk in both high- and low-risk European populations (Table 5C),[4,8,35] while in the

Table 5A. Framingham risk score

Profile	10-year risk of cardiovascular diseases (myocardial infarction, coronary death, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease and heart failure)
Nonsmoker No diabetes Systolic blood pressure = 150 mmHg No treatment for hypertension Total cholesterol =197 mg/dl HDL = 50 mg/dl	
Male: 55 years old	14.1%
Female: 60 years old	10.7%

Notes: (a) Using lipid levels similar to the means in the United States of America population.[41]
(b) Framingham online calculator available at https://framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/.
(c) In Framingham score risk is categorized as **low** (<10%), **moderate** (10% to <19%) and **high** (≥20%).

Table 5B. ACC/AHA Pooled Cohort equation according to the race

Profile	10-year risk of first CHD death, non-fatal MI or fatal or nonfatal stroke	
	Race: African-American	Race: white
Nonsmoker No diabetes Systolic blood pressure = 150 mmHg Diastolic blood pressure = 95 mmHg No treatment for hypertension Total cholesterol =197 mg/dl HDL = 50 mg/dl LDL = 100 mg/dl		
Male: 55 years old	8.8%	7.2%
Female: 60 years old	8.3%	4.7%
Male: 60 years old	10.7%	11.1%
Female: 65 years old	11.4%	7.8%

Notes: (a) online ACC/AHA calculator available **at** http://www.cvriskcalculator.com/.
(b) 10-year risk for ACC/AHA Pooled Cohort equation, risk is categorized as low (<5%), borderline (5% to <7.5%), moderate (7.5% to <20%), and high (≥20%).[38]

Table 5C. SCORE equation according to the CVR region

Profile: Nonsmoker No diabetes Systolic blood pressure = 150 mmHg No treatment for hypertension Total cholesterol =197 mg/dl HDL = 50 mg/dl	10-year risk of cardiovascular death	
	Countries at high CVR	Countries at low CVR
Male: 55 years old	4%	2%
Female: 60 years old	3%	1%
Male: 60 years old	6%	3%
Female: 65 years old	5%	3%

Notes: (a) Online calculator available at http://www.heartscore.org/en_GB/access.
(b) SCORE (Systematic Coronary Risk Estimation). Low: cardiovascular mortality <1% at 10 years, moderate: cardiovascular mortality ≥1% and <5% at 10 years, high: cardiovascular mortality ≥5% and <10% at 10 years and very high: cardiovascular mortality ≥10%.[8]

Table 5D. Framingham-REGICOR in Spain (adapted to Catalonia)

Profile: Nonsmoker No diabetes Systolic blood pressure = 150 mmHg Diastolic blood pressure = 95 mmHg No treatment for hypertension Total cholesterol =197 mg/dl HDL = 50 mg/dl	10-year risk of coronary heart disease event (fatal and nonfatal myocardial infarction, silent myocardial infarction and angina pectoris)
Male: 55 years old	4%
Female: 60 years old	4%
Male: 60 years old	5%
Female: 65 years old	5%

Notes: (a) Using online calculator available at www.regicor.cat/aplicacions/regicor.
(b) 10-year risk for Framingham-REGICOR is categorized as low (<5%), moderate (5% to <10%), high (≥10 to <15%) and very high (≥15).[42]

ACC/AHA Pooled Cohort Equations race had great influence in the CVR (Table 5B).[9,40]

6. Most patients with mild hypertension should have out-of-office monitoring to confirm their diagnosis to exclude white coat effect, which is not usually possible in low-middle-income settings.[1,8,9] However, in Nigeria home blood pressure monitoring has been effective.[43]
7. The subgroup of patients with mild hypertension and low absolute CVR is not homogenous, emphasizing the need for individualized treatment (Table 6).
8. Substantive questions regarding clinical (the number of years lost due to disability or premature death, beneficial effects of

Table 6. General CVR at 10 years (Framingham Heart Study)

Profile of the 3 patients at low absolute CVR (<10%) with systolic BP =150 mmHg.	CVR age	Absolute CVR	Normal CVR	Optimal CVR
30-year-old, male, no anti-hypertensive drugs, smoker, no diabetes and dyslipidemia (HDL 35 mg/dl and total cholesterol 250 mg/dl).	51	8%	1.7%	0.9%
40-year-old, male, nonsmoker, no diabetes and dyslipidemia (HDL 35 mg/dl and total cholesterol 250 mg/dl).	55	9.9%	3.9%	2.1%
50-year-old, male, nonsmoker, no diabetes, HDL 45 mg/dl and total cholesterol 160 mg/dl.	54	9.5%	7.7%	4.1%

Notes: (a) Framingham online calculator available at https://framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/.

antihypertensive drugs—number needed to treat (Table 7), treatment-related adverse events, etc.) and economic (at both individual, health system and national level) cost benefit ratio of the medicalization of this subgroup of hypertensive patients still persist.[1,8,9] Earlier treatment can prevent more severe hypertension and the development of CV target organ damage or CV diseases, which may not be completely reversible with later treatment.[7,44-47]

Table 7. NNT estimation if patients lower their systolic blood pressure (SBP) from 150 mmHg to 135 mmHg with antihypertensive drugs in the ensuing 12 months

	Event rate % at 10 years		ARR	NNT
Three patient profiles of low absolute CVR (<10%) with SBP =150 mmHg.	SBP of the control group (150 mmHg)	SBP of Treatment group (135 mmHg)		
1. 30-year old, male, no anti-hypertensive drugs, smoker, non-diabetes and dyslipidemia (HDL 35 mg/dl and total cholesterol 250 mg/dl).	8%	6.6%	1.4%	71
2. 40-year old, male, nonsmoker, no diabetes and dyslipidemia (HDL 35 mg/dl and total cholesterol 250 mg/dl).	9.9%	8.2%	1.7%	59
3. 50-year old, male, nonsmoker, no diabetes, HDL 45 mg/dl and total cholesterol 160 mg/dl.	9.5%	7.8%	1.7%	59

Note: NNT, number need to treat (at 10 years); ARR, absolute risk reduction %.

9. Adherence to medication is worse in low CVR patients than in secondary prevention, and appreciable residual risk is associated with non-adherence to treatments.[1]
10. Hypertension guidelines generally base their recommendations for low CVR patients on the moderate CVR category despite the differences between the levels of evidence regarding the management of hypertension for these 2 subgroups.[1,8,29]
11. The recommendations concerning treatment in patients with mild hypertension with low CVR that specify an initial period of weeks or months of only lifestyle measures before starting drug treatment are not based on high-moderate quality evidence.[1,26]

All patients with hypertension should have nonpharmacological intervention.[1,7,8] Healthy lifestyle should also be recommended for the entire population.[1,7,8,31] Lifestyle modifications can produce effect sizes that sometimes can be similar to the effects of drug monotherapy but their major drawback is the low level of adherence over time.[1] A proportion of low-income patients with hypertension do not even have the resources to follow healthy lifestyle changes.[1] The consumption of fruit and vegetables is inadequate worldwide, particularly in low-income countries or among less-affluent people in higher income countries, and can be attributed to both difficulty of access and unaffordability.[1,48] No resources are needed to stop smoking and reduce alcohol intake, or even to modestly increase physical activity, but success with these strategies is related to socio-economic status. Finally, there are no randomized clinical trials that at any level of hypertension and CVR have compared outcomes of lifestyle measures alone with the use of anti-hypertensive drug treatment.[1,29,49] Thus, these mandatory recommendation for initial lifestyle interventions can only justify a level of evidence of C.

12. Nevertheless, the combination of pharmacological and non-pharmacological treatment at the individual and population levels appear to be a valuable approach for reducing cardiovascular events (Table 8).[35,50]

It is important to note that the CVR models are primarily built on epidemiological data and not on intervention studies. Therefore, the extrapolation of these theoretical reductions of NNT to the "real world" will overestimate the true effectiveness of the intervention on CVR. Moreover, in the "real world" one must take into account the residual risk (absolute level of treatment failures), socio-economic status, adherence

Table 8. NNT estimation if patients controlled all their major risk factors with antihypertensive drug and lifestyle interventions in the next 12 months

Three patient profiles of low absolute CVR (<10%) with SBP = 150 mmHg.	Event rate % at 10 years		ARR	NNT
	Baseline CVR	CVR after 1-year treatment and optimization of risk factors		
1. 30-year old, male, no anti-hypertensive drugs, smoker, nondiabetes and dyslipidemia (HDL = 35 mg/dl and total cholesterol = 250 mg/dl).	8%	0.9%	7.1%	14
2. 40-year old, male, non-smoker, non-diabetes and dyslipidemia (HDL = 35 mg/dl and total cholesterol = 250 mg/dl).	9.9%	2.1%	7.8%	13
3. 50-year old, male, non-smoker, non-diabetes, HDL = 45 mg/dl and total cholesterol = 160 mg/dl.	9.5%	4.1%	5.4%	19

NNT, number need to treat (at 10 years); ARR, absolute risk reduction %.
If we compare tables 7 and 8, there is a reduction of NNT in all cases: Profile 1 from 71 to 14—representing an 80.3% reduction of NNT-, Profile 2 from 59 to 13 (78%), and Profile 3 from 59 to 19 (67.8%; Fig).

to treatment, and access to essential medicines and professional or skilled care.[1] The greatest success of BP lowering (fewest treatment failures) appears to be actually achieved in low CVR patients.[51]

13. The cardiovascular prevention strategies are focused on high risk patients as indicated by the "25 by 25" Global Action Plan of the United Nations Political Declaration on the Prevention and Control of Non-Communicable Diseases (cardiovascular diseases, cancer, diabetes type 2, or chronic respiratory diseases).[52]

Two-thirds of total CV events of primary prevention occur in subjects with low to moderate absolute CVR, and this proportion may approach three-quarters in women.[40] As a result, more ambitious strategies at individual and population levels are needed (Table 9A).[53]

Upgrading the recommendations

After the re-evaluation of the available evidence the Second Consensus puts forward the following update regarding the management of mild hypertension with low CVR in adults:

Table 9A. Recommendations for the management of recently diagnosed mild uncomplicated hypertension (140-149/90-99 mmHg) with low cardiovascular risk

Any model re-calibrated for the target population or developed with its own population data, or, in its absence, general-purpose models such as SCORE, can be used to estimate CV risk at the individual level. (Class II, Level C)
Guidelines should separate their recommendations for the low CVR category from the moderate CVR category. (Class I, Level C).[1]
The practical value of such traditional risk modifiers as: (1) coronary calcium score, (2) artery scanning, (3) ankle–brachial index, and (4) high-sensitivity C-reactive protein) and simple re-stratification strategies such as relative total CVR, CVR age and ideal cardiovascular health score need to be evaluated in well-designed observational studies (Class II and Level C).[1]
Age is the most influential CVR factor at both the individual and population levels. Men ≥ 55 years and women ≥ 60 years (men ≥ 60 years and women ≥ 65 years in low CVR regions or subgroups) with uncomplicated mild hypertension should automatically be classified at least within the moderate absolute total CVR category (even in the absence of other risk major factors). (Class II and Level C; Tables 5A-5D).[1] More than 95% of patients with mild hypertension have additional major risk factors: diabetes mellitus, dyslipidemias, or evidence of target organ damage of cardiovascular diseases.[52,53]
In mild hypertension with at least one additional major risk factor, drug treatment should be initiated simultaneously with lifestyle interventions (Class I and Level B; Table 9B).[52,53] Cardiovascular risk factors are multifactorial and interact over time to produce cardiovascular diseases. The Framingham Heart Study demonstrated that the relationship between BP category and CVR can vary according additional cardiovascular factors such as elevated total cholesterol, low high-density lipoprotein cholesterol, presence of diabetes mellitus, diseases adding to the inflammatory burden, and tobacco use. The CVR of mild hypertension with at least one major risk factor is higher than the CVR of moderate hypertension (160-179/100-109 mmHg) in patients without additional risk factors. More than 50% of patients with mild hypertension have at least one CVR factor (excluding diabetes mellitus and evidence of target organ damage of cardiovascular diseases).[54,55]
Mild hypertension at low absolute CVR without additional major risk factors ("solitary" hypertension) should be initially treated with lifestyle interventions alone while monitoring BP, CVR and key routine laboratory investigations (Class II and Level C; Table 9B).[1] Solitary hypertension represents fewer than 5% of all adults with mild (140-149/90-99 mmHg) hypertension.[54,55]
Patients with mild hypertension and low absolute CVR constitute a heterogeneous subgroup, emphasizing the need for individualized treatment. (Class I and Level C). Additional detailed screening tests are sometimes needed to exclude secondary hypertension and concomitant clinical conditions.[1] Secondary hypertension is most common among patients aged <40 years.[8] Even in children and adolescents, mild hypertension is associated with increased CVR, which is usually reversible with treatment.[56] Mild hypertension is associated with impaired arterial distensibility that improves with pharmacological treatment.[57]
Asymptomatic individuals without a personal history of hypertension and cardiovascular diseases with blood pressure between 130-139 mmHg/80-89 mmHg should adopt healthy lifestyles to prevent mild hypertension, cardiovascular target organ damage or cardiovascular diseases. (Class II and level C).[8,9] Lifestyle modifications (regular physical activity, salt and simple-sugar restriction, limitation of alcohol consumption, high consumption of vegetables and fruits, low-fat diet; and elimination of smoking) should be started early in life to prevent or delay the onset of

(*continued*)

hypertension and its complications. The initial clinical manifestations of cardiovascular diseases can be sudden death. Among young adults, those with BP between 130-139 mmHg/80-89 mmHg before age 40 years, had significantly higher risk for subsequent cardiovascular disease events compared with those with normal blood pressure before age 40 years.[6]

BP between 130-139 mmHg/80-89 mmHg is associated with an increased risk of cardiovascular disease.[58,59]

Table 9B. Treatment algorithm of recently diagnosed mild uncomplicated hypertension with low cardiovascular risk in adults

Office BP 140-159 and/or 90-99 mmHg (or the equivalent in ambulatory BP monitoring)	
Not solitary hypertension	**Solitary hypertension**
Drug treatment should be initiated simultaneously with lifestyle interventions in: • Patients aged ≥ 55 in men or women ≥ 60 year (men ≥ 60 years and women ≥ 65 years in low CVR regions or subgroups). • Patients with at least one additional major risk factor.	Promotion of positive lifestyle changes for 3-6 months while monitoring BP, total CVR and key routine laboratory investigations in: • Patients without additional major risk factors (solitary hypertension).

Notes: (a) Before starting anti-hypertensive drug treatment, most patients with blood pressure (BP) between 140-159 mmHg / 90-99 mmHg should have out-of-office monitoring to confirm hypertension, if logistically and economically feasible.[1]

(b) The definition of solitary hypertension is: uncomplicated hypertension, BP between 140-159 and/or 90-99 mmHg, low absolute total CVR without any other major CVR factors, age: male>55 years and female>65 years, postmenopausal status in women, smoking, dyslipidemia, diabetes mellitus, obesity and family history of premature CV disease).

Conclusions

1. In both the ESC/ESH and ACC/AHA guidelines the general management of mild hypertension (140-159 and/or 90-99 mmHg) with low absolute CVR are aligned with our First Consensus[1] and other regional guidelines (or roadmap to achieve 25% hypertension control).[22,60,61]
2. There are still gaps in evidence and a need for studies in younger hypertensive patients (ages ≤50 years), mainly in ages ≤40 years.
3. There are several challenges in the management of newly diagnosed mild hypertension with low absolute total CVR at individual and population levels.
4. The 8 recommendations of the Second Consensus could improve individualized patient management. The recommendations also call for well-designed trials of recently diagnosed mild hypertension with low absolute total CVR.

Acknowledgments

Dr. Alberto Morales completed the final version of this manuscript by May, 2019. He was an educator, researcher, clinician, friend, and family man. The coauthors, who already provided their comments, read and approved that final version have reviewed it again and changed the text to include information from recent publications, preparing it for submission.

REFERENCES

1. Morales-Salinas A, Coca MH, Olsen R, et al. Clinical perspective on antihypertensive drug treatment in adults with grade 1 hypertension and low to moderate cardiovascular risk. An international expert consultation. *Curr Probl Cardiol* 2017;42:198–225.
2. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *J Hypertens* 2020;38:982–1004.
3. Zambon A, Arfè A, Corrao G, et al. Relationships of different types of events to cardiovascular death in trials of antihypertensive treatment: an aid to the definition of total cardiovascular risk in hypertension. *J Hypertens* 2014;32:495–508.
4. Mancia G, Fagard R, Narkiewicz K, et al. 2013ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology Eur Heart J. 2013;34:2159-219.
5. Muntner P, Whelton PK. Using predicted cardiovascular disease risk in conjunction with blood pressure to guide antihypertensive medication treatment. *J Am Coll Cardiol* 2017;69:2446–56.
6. Yano Y, Reis JP, Colangelo LA, et al. Association of blood pressure classification in young adults using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life. *JAMA* 2018;320:1774–82.
7. Bavishi C, Goel S, Messerli FH. Isolated systolic hypertension: an update after SPRINT. *Am J Med* 2016;129:1251–8.
8. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). *Eur Heart J* 2018;39:3021–104.
9. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC /AHA /AAPA /ABC /ACPM/ AGS /APhA /ASH /ASPC /NMA /PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;71:1269–324.
10. Lonn EM, Bosch J, Lopez-Jaramillo P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med* 2016;374:2009–20.
11. Sundstrom J, Arima H, Jackson R, et al. Effects of blood pressure reduction in mild hypertension. A systematic review and meta-analysis. *Ann Intern Med* 2015;162:184–91.

12. Reboussin DM, Allen NB, Griswold ME, et al. Systematic review for the 2017 ACC /AHA /AAPA /ABC /ACPM /AGS /APhA /ASH/ ASPC /NMA /PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;71:e116–35.
13. SPRINT Study Research Group. A randomized trial of intensive versus standard blood pressure control. *N Engl J Med* 2015;373:2103–16.
14. Kario K, Iwashita M, Okuda Y, et al. HONEST investigators. Morning home blood pressure and cardiovascular events in Japanese hypertensive patients. *Hypertension* 2018;72:854–61.
15. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. effects at different baseline and achieved blood pressure levels−overview and meta-analyses of randomized trials. *J Hypertens* 2014;32:2296–304.
16. Kaul A. How strong is the evidence to support blood pressure treatment goal of 130/80 mm Hg? *Circulation* 2018;138:2594–6.
17. Reboussin DM, Carey RM, Whelton PK. Evidence supporting the blood pressure treatment goal of less than 130/80 mm Hg. Hypertension.2+;73:972-4.
18. Kario K. Differential approaches are much needed for "Real World" management of hypertension in the era of "hypertension paradox". *Curr Hypertens Rev* 2018;14:2–5.
19. Kario K, Wang JG. Could 130/80 mm Hg be adopted as the diagnostic, threshold and management goal of hypertension in consideration of the characteristics of Asian populations? *Hypertension* 2018;71:979–84.
20. Kario K. Global impact of 2017 American Heart Association/American College of Cardiology hypertension guidelines: a perspective from Japan. *Circulation* 2018;137:543–5.
21. Wang JG. Why is the Chinese hypertension guideline necessary? *J Geriatr Cardiol* 2019;16:1–3.
22. Joint Committee for Guideline Revision. 2018 Chinese Guidelines for Prevention and Treatment of Hypertension—a report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. *J Geriatr Cardiol* 2019;16:182–241.
23. Schutte AE, Botha S, Fourie CMT, et al. Recent advances in understanding hypertension development in sub-Saharan Africa. *J Human Hypertension* 2017;31:491–500.
24. Stefler D, Pikhart H, Jankovic N, et al. Healthy diet indicator and mortality in Eastern European populations: prospective evidence from the HAPIEE cohort. *Eur J Clin Nutr* 2014;68:1346–52.
25. Tsioufis C, Thomopoulos C, Kreutz R. Treatment thresholds and targets in hypertension. Different reading of the same evidence. *Hypertension* 2018;71:966–8.
26. Laukkanen JA, Kunutsor SK. Is 're-calibration' of standard cardiovascular disease risk algorithms the panacea to improved CVD risk prediction and prevention? *Eur Heart J* 2019;40:632–4.

27. Lisa Pennells L, Kaptoge S, Wood A, et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. *Eur Heart J* 2019;40:621–31.
28. D'Agostino RB, Michael J, Pencina MJ, et al. Cardiovascular disease risk assessment: insights from Framingham. *Global Heart* 2013;8:11–23.
29. Morales-Salinas A. Are there gaps in the evidence on the treatment of mild hypertension in patients with low cardiovascular risk? *Rev Esp Cardiol* 2019;72:885–6.
30. Baena-Díez JM, Grau M, Sánchez-Pérez R, et al. The REGICOR-calibrated function provides a better classification of high-risk patients on statin treatment in the Spanish population than the Framingham or SCORE classifications. *Rev Esp Cardiol* 2009;62:1134–40.
31. Baena-Díez JM, Subirana I, Ramos R, et al. Validity assessment of low-risk SCORE function and SCORE function calibrated to the Spanish population in the FRESCO Cohorts. *Rev Esp Cardiol* 2018;71:274–82.
32. Marrugat J, Solanas P, D'Agostino R, et al. Coronary risk estimation in Spain using a calibrated Framingham function. *Rev Esp Cardiol* 2003;56:253–61.
33. Marrugat J, Subirana I, Ramos R, and the FRESCO Investigators. Derivation and validation of a set of 10-year cardiovascular risk predictive functions in Spain: the FRESCO Study. *Prev Med* 2014;61:66–74.
34. Di Angelantonio E, Pennells L, Kaptoge S, et al. Equalisation of four cardiovascular risk algorithms after systematic re-calibration: individual-participant meta-analysis of 86 prospective studies. *Eur Heart J* 2019;40:621–63.
35. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and invited experts). *Eur Heart J* 2016;37:2315–81.
36. Lloyd−Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation* 2010;121:586–613.
37. Grundy SM, Pasternak R, Greenland P, et al. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 1999;100:1481–92.
38. Yang Q, Cogswell ME, Flanders WD, et al. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA* 2012;307:1273–83.
39. Dégano IR, Salomaa V, Veronesi G, et al. Acute Myocardial Infarction Trends in Europe (AMITIE) Study Investigators. Twenty-five-year trends in myocardial infarction attack and mortality rates, and case-fatality, in six European populations. *Heart* 2015;101:1413–21.
40. Lloyd-Jones DM. Improving the cardiovascular health of the US Population. *JAMA* 2012;307:1314–6.

41. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. *BMJ* 2002;324:1570–6.
42. Marrugat J, Vila J, Baena-Díez JM, et al. Relative validity of the 10-year cardiovascular risk estimate in a population cohort of the REGICOR Study. *Rev Esp Cardiol* 2011;64:385–94.
43. Augustine NO, Bolaji A, Adaku MN, et al. Characteristics of self-measured home blood pressure in a Nigerian urban community: the NIPREGH study. *Blood Pressure Monit* 2015;20:260–5.
44. Jr Goff DC, DM Lloyd-Jones, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:2935–59.
45. Carroll MD, Kit BK, Lacher DA, et al. Trends in lipids and lipoproteins in US adults, 1988-2010. *JAMA* 2012;308:1545–54.
46. de Simone G, Devereux RB, Izzo R, et al. Lack of reduction of left ventricular mass in treated hypertension: the Strong Heart Study. *J Am Heart Assoc* 2013;2:e000144.
47. Lonnebakken MT, Izzo R, Mancusi C, et al. Left ventricular hypertrophy regression during antihypertensive treatment in an outpatient clinic (the Campania Salute Network). *J Am Heart Assoc* 2017;6:e004152. pii:.
48. Miller V, Yusuf S, Chow CK, et al. Availability, affordability, and consumption of fruits and vegetables in 18 countries across income levels: findings from the Prospective Urban Rural Epidemiology study. *Lancet Glob Health* 2016;4:e695–703.
49. Whelton PK, He J, Appel LJ, et al. Primary prevention of hypertension clinical and public health advisory from the National High Blood Pressure Education Program. *JAMA* 2002;288:1882–8.
50. Vartiainen E. The North Karelia Project: Cardiovascular disease prevention in Finland. *Global Cardiol Sci Pract* 2018;2:13.
51. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 3. effects in patients at different levels of cardiovascular risk—overview and meta-analyses of randomized trials. *J Hypertens* 2014;32:2305–14.
52. World Health Organization. Draft comprehensive global monitoring framework and targets for the prevention and control of noncommunicable diseases. http://apps.who.int/gb/ebwha/pdf_files/WHA66/A66_8-en.pdf?ua=1. Consulted May 10th2020.
53. Morales Salinas A, Kones R. Barriers and context in reaching "25 by 25" targets of the United Nations Political Declaration on the Prevention and Control of Noncommunicable diseases: *proposal modifications to amplify and extend reach*. *J Prev Med* 2018;3(No.1):1.
54. Karmali KN, Lloyd-Jones DM. Global risk assessment to guide blood pressure management in cardiovascular disease prevention. *Hypertension* 2017;69:e2–9.
55. Lloyd-Jones DM, Evans JC, Larson MG, et al. Cross-classification of JNC VI blood pressure stages and risk groups in the Framingham Heart Study. *Arch Intern Med* 1999;159:2206–12.

56. Litwin M, Niemirska A, Śladowska-Kozlowska J, et al. Regression of target organ damage in children and adolescents with primary hypertension. *Pediatr Nephrol* 2010;25:2489–99.
57. Reneman RS, Meinders JM, Hoeks APG. Non-invasive ultrasound in arterial wall dynamics in humans: what have we learned and what remains to be solved. *Eur Heart J* 2005;26:960–6.
58. Ueda H, Miyawaki M, Hiraoka H. High−normal blood pressure is associated with new-onset electrocardiographic left ventricular hypertrophy. *J Human Hypertension* 2015;29:9–13.
59. Vasan RS, Larson MG, Leip EP, et al. Impact of high normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291–7.
60. Dzudie A, Rayner B, Ojji D, et al. Roadmap to achieve 25% hypertension control in Africa by 2025. *Glob Heart* 2018;13:45–59.
61. Task Force of the Latin American Society of Hypertension. Guidelines on the management of arterial hypertension and related comorbidities in Latin America. *J Hypertension* 2017;35:1529–45.