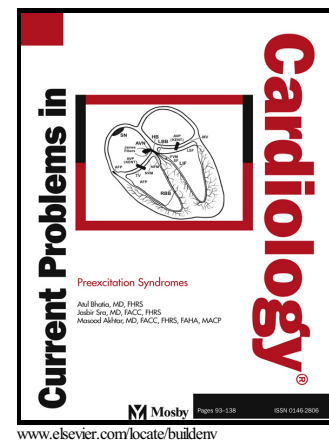# Author's Accepted Manuscript

Clinical Perspective on Antihypertensive Drug Treatment in Adults with Grade 1 Hypertension and Low to Moderate Cardiovascular Risk. An International Expert Consultation

A. Morales-Salinas, A. Coca, M.H. Olsen, R. Sánchez, W.K. Sebba Barroso, R. Kones, V. Bertomeu-Martínez, J. Sobrino, L. Alcocer, D.J. Piñeiro, F. Lanas, C.A Machado, F. Aguirre Palacios, J. Ortellado, G. Pérez, R. Sabio, O. Landrove, D. Rodriguez, A. Dueñas Herrera, A. Rodríguez Portelles, J. Parra-Carrillo, D. Piskorz, A. Bryce-Moncloa, G. Waisman, Y. Yano, H. Ventura, M. Orias, P. Dorairaj, J. Sundström, J. Wang, L.M. Burrell, A.E. Schutte, P. López-Jaramillo, E. Barbosa, J. Redon, M.A. Weber, C.J. Lavie, A. Ramírez, P. Ordunez, S. Yusuf, A. Zanchetti

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Clinical Perspective on Antihypertensive Drug Treatment in Adults with Grade 1 Hypertension and Low to Moderate Cardiovascular Risk. An International Expert Consultation.

Authors: Morales-Salinas A[1+], Coca A[2], Olsen MH[3], Sánchez R[4], Sebba Barroso WK[5], Kones R[6], Bertomeu-Martínez V[7], Sobrino J[8], Alcocer L[9], Piñeiro DJ[10], Lanas F[11], Machado CA[12], Aguirre Palacios F[13], Ortellado J[14], Pérez G[15], Sabio R[16], Landrove O[17], Rodriguez D[18], Dueñas Herrera A[19], Rodríguez Portelles A[18], Parra-Carrillo J[20], Piskorz D[21], Bryce-Moncloa A[22], Waisman G[23], Yano Y[24], Ventura H[25], Orias M[26], Dorairaj P[27], Sundström J[28], Wang J[29], Burrell LM[30], Schutte AE[31], López-Jaramillo P[32], Barbosa E[33], Redon J[34], Weber MA[35], Lavie CJ[25], Ramírez A[4,36], Ordunez P[37], Yusuf S[38], Zanchetti A[39].

Affiliations:[1]Cardiocentro "Ernesto Che Guevara", Santa Clara, Cuba. +Coordinator of the Consultation. [2]Unidad de Hipertension y Riesgo Vascular, Hospital Clínic (IDIBAPS), Universidad de Barcelona, España. [3]Department of Internal Medicine, Holbaek Hospital, and Centre for Individualized Medicine in Arterial Diseases (CIMA), Odense University Hospital, University of Southern Denmark, Denmark. [4]Hipertension Arterial y Unidad Metabólica, Hospital Universitario, Fundación Favaloro, Argentina. [5]Hypertension League - Federal University of Goias-Brasil. [6]Cardiometabolic Research Institute, Houston, USA. [7]Hospital Universitario de San Juan, Alicante-Valencia, España. [8]Fundació Hospital de l'EsperitSant, Barcelona, España. [9]Instituto Mexicano de Salud Cardiovascular, Mexico. [10]Universidad de Buenos Aires, Buenos Aires, Argentina. [11]Universidad de la Frontera, Chile. [12]Ministerio de Salud / Muncipal Health Office Campos do Jordão, Brasil. [13]Clínica Kennedy, Guayaquil, Ecuador. [14]Ministerio de Salud, Paraguay.[15]Clínica Olivos, Buenos Aires, Argentina. [16]Hospital de Alta Complejidad, Santa Cruz, Argentina. [17]Ministerio de Salud Pública, Cuba. [18]Universidad Médica de Holguin, Cuba. [19]Instituto de Cardiologia y

Cirugia Cardiovascular, Habana, Cuba. [20]Universidad de Guadalajara, México. [21]Instituto de Cardiología, Sanatorio Británico, Rosario, Argentina.[22]CARDIOGOLF Lima, Perú. [23]Hospital Italiano de Buenos Aires, Argentina. [24]The University of Mississippi Medical Center, USA. [25]Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-the University of Queensland School of Medicine, USA. [26]Sanatorio Allende y Universidad Nacional de Cordoba, Argentina. [27]Department of Research and Policy, Public Health Foundation of India and Centre for Chronic Disease Control, Haryana, India. [28]Department of Medical Sciences, Uppsala University, and Uppsala Clinical Research Center, Uppsala, Sweden. [29]The Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China. [30]Department of Medicine. The University of Melbourne, Austin Health. Victoria, Australia. [31]South African Medical Research Council Unit on Hypertension and Cardiovascular Disease, Hypertension in Africa Research Team,North-West University, South Africa. [32]Research Institute, Fundación Oftalmológica de Santander and Medical School, Universidad de Santander, Colombia Colombia and Universidad Tecnologica Equinoccial, Facultad de Medicina Eugenio Espejo, Ecuador. [33]H.Moinhos de Vento Porto Alegre, Brasil. [34]Universidad de Valencia, España. [35]Division of Cardiovascular Medicine, State University of New York, Downstate College of Medicine, New York. [36]Instituto de Medicina Traslacional, Trasplante y Bioingenieria. Universidad Favaloro-CONICET, Argentina. [37]Pan American Health Organization. Washington, U.S.A. [38]Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, Canada. [39]Istituto Auxologico Italiano, Centro Interuniversitario di Fisiologia Clinica e Ipertensione, University of Milan, Italia.

Corresponding author: Dr. Alberto Morales Salinas. Address: Colon 473 e/ Estrada Palma y Misionero. Santa Clara. Villa Clara. Cuba. CP: 50100 E-mail: cardioams@yahoo.es

Abstract:

Hypertension is a leading risk factor for disease burden globally. An unresolved question is whether grade 1 hypertension (140-159/90-99 mmHg) with low (mortality <1% at 10 years) to moderate (mortality ≥1% and <5% at 10 years) absolute total cardiovascular risk (CVR) should be treated with anti-hypertensive agents.

A virtual international consultation process was undertaken to summarize the opinions of select experts. After holistic analysis of all epidemiological, clinical, psychosocial and public health elements, this consultation process reached the following consensus in hypertensive adults aged < 80 years: 1) The question of whether drug treatment in grade 1 should be preceded by a period of some weeks or months during which only lifestyle measures are recommended cannot be evidence based, but the consensus opinion is to have a period of lifestyle alone reserved only to patients with grade 1 "isolated" hypertension (grade 1 uncomplicated hypertension with low absolute total CVR, and without risk major factors and risk modifiers). 2) The initiation of anti-hypertensive drug therapy in grade 1 hypertension with moderate absolute total CVR should not be delayed. 3) Men ≥ 55 years

and women ≥ 60 years with uncomplicated grade 1 hypertension should automatically be classified within the moderate absolute total CVR category, even in the absence of other risk major factors and risk modifiers. 4) Statins should be considered along with blood-pressure lowering therapy, irrespective of cholesterol levels, in patients with grade 1 hypertensive with moderate CVR.

Key words: Drugs/Risk factors/Epidemiology/Blood pressure/Cardiovascular disease/ Guidelines/ Healthy lifestyle/Prevention/ Hypertension/Risk assessment/ Risk management/ Clinical trials/ Risk prediction/ Risk score/ Risk stratification / Treatment

Nonstandard abbreviations:

CVD	Cardiovascular diseases
CVR	Cardiovascular risk
SCORE	Systematic Coronary Risk Estimation
RCT	Randomized clinical trials
BP	Blood pressure
DM	Diabetes Mellitus, type 2
CKD	Chronic kidney disease
EUROASPIRE	European Action on Secondary and Primary Prevention through Intervention to Reduce Events
HOPE-3	Heart Outcomes Prevention Evaluation
NICE	National Institute for Health and Care Excellence
LDL	Low density lipoprotein cholesterol
MESA	Multi-Ethnic Study of Atherosclerosis
SPRINT	Systolic Blood Pressure Intervention Trial

I Introduction

Hypertension is a leading risk factor that contributes to the burden of global cardiovascular disease (CVD).[1,2] A related controversial but unresolved topic in CVD prevention is whether grade 1 hypertension (140-159/90-99 mmHg) with low to moderate absolute total cardiovascular risk (CVR) should be treated using anti-hypertensive drugs.[3,4,5,6,7,8] In this consensus, total CVR is defined as follows: *low* as CVD mortality <1% at 10 years and *moderate* as CVD mortality ≥1% and <5% at 10 years according to the SCORE (Systematic Coronary Risk Estimation).[9]

The elusiveness of the answers to the question posed are chiefly due to the lack of randomized clinical trials (RCT) that specifically evaluate treatment with anti-hypertensive drugs versus subgroups using placebo adjusted to the current definitions of grades of hypertension and absolute total CVR.[9,10,11] In addition, to be considered are i) recent results from meta-analyses,[12,13,14] ii) variability of clinical and psychosocial factors in subjects with grade 1 hypertension and low-moderate absolute total CVR, emphasizing the need for individualized pharmacological treatment[4] and iii) the gap between guideline recommendations and the actual treatment of hypertension in clinical practice.[15]

Although basing clinical guidelines exclusively upon RCT evidence might be considered ideal, truly direct evidence-based recommendations for every clinical situation are few, and that inconsistent (or even conflicting) data must often be interpreted and extrapolated.[16,17] Hence, on a practical basis, many trials have not adequately informed practice.[18] RCT limitations may include i) relatively small samples, ii) highly selected investigators, iii) highly selected participants, iv) use of multiple therapies prior to randomized treatments, v) inability to answer all possible questions generated during the course of medical practice,

vi) relatively short duration of controlled trials because of practical limitations—in most instances between 3 and 6 years, with an average time to an endpoint of only half of this, in order to achieve desired statistical results, vii) unwarranted extrapolation of results using one medication to the rest in its class, and viii) underrepresentation of the young, the elderly, and non-white populations.[9,16,17,18] Recommendations for life-long intervention are based on considerable extrapolation from data obtained over periods much shorter than the life expectancy of most patients. Support for the belief that the benefits measured during the first few years will continue over a much longer term comes from observational studies of a few decades' duration. As a corollary, there are no criteria for duration of specific treatments during different periods in life.[9] **Thus, it is necessary to create a holistic analysis of all epidemiological, clinical, psychosocial and public health elements in order to make informed and relevant decisions.**

The **aim** of this report is to present the results of an international consultation process carried out with select experts to explore current opinions, in order to pave the way to develop clinical future guideline recommendations about the following question.

II Question guiding the consultation process

Should grade 1 hypertension with low to moderate absolute total CVR be treated with anti-hypertensive medication?

III Methods

The initial version of this manuscript was elaborated (by AMS) based on the latest guidelines and documents published by the major international hypertension societies, as well as several papers of interest for this consultation matter.[19,20,21,22,23,24,25,26,27,28,29,30,31,32] This version was sent to 55 select experts, some declined to participate. Finally in ensuing

phases, a thorough virtual discussion took place among 40 international experts from June 16, 2016 to Febraury 14, 2017. The review was periodically updated according to the suggestions of the experts during the different stages of evaluation, until a consensus emerged.

Several experts were authors and reviewers of the latest Guidelines of the European Society of Hypertension (AC, JR, MHO and AZ),[19] the Latin-American Society of Hypertension (PLJ, RS, ABM, JPC, FL, AR and AZ),[30] International/American Society of Hypertension (AR, MW, JW, AS)[21] and Joint European Task Force of Cardiovascular Prevention (JR)[9]. Besides, some expert were authors of recently statements from World Heart Federation (SY and DP)[27], World Hypertension League (MO)[29], Lancet Commission on Hypertension (MOH, PLJ, AES and JW)[24], Blood Pressure Lowering Treatment Trialists' Collaboration (JS)[31] and Working Group on the Summit on Combination Therapy for CVD (SY)[32] among others.

The authors, contemplate that this document could evolve as new information emerges.

IV What was recommended by the European Guidelines?

The 2013 European Guidelines recommend that the initiation of pharmacological treatment should be considered in grade 1 hypertension patients at low to moderate absolute total CVR, when blood pressure (BP) remains in this range during repeated visits, including after a reasonable trial of lifestyle modification, or is elevated by ambulatory BP criteria (Class IIa, Level B).[19] The same recommendation is considered as Class IIb, Level B by the 2016 European Guidelines on CVD Prevention.[9]

The 2013 European Guidelines suggest beginning the initial control of hypertension with lifestyle changes over a few weeks alone in the following categories:[19]

1.   Grade 1 hypertension (140-159/90-99 mmHg) and low absolute total CVR or no additional risk factors (lifestyle changes alone could be tried for a period of between 3-6 months).

2.   Grade 1 hypertension and moderate absolute total CVR (with 1 or 2 additional risk factors).

3.   Grade 1 hypertension with moderate-high absolute total CVR (with ≥ 3 risk factors). Lowering BP with drugs should not be delayed when the patients have diabetes mellitus (DM), evidence of target organ damage, chronic kidney disease (CKD) grade ≥ 3, symptomatic CVD or grade 3 hypertension (systolic BP ≥180 mmHg and/or diastolic BP ≥ 110 mmHg).[19]

European Guidelines on CVD prevention state that lifestyle measures (weight control, increased physical activity, alcohol moderation, sodium restriction in those with high consumption, and increased consumption of fruits and vegetables) **are recommended in all patients with hypertension** (Class I, Level A).[9]

The relationship between BP and CVD morbidity and mortality is modified by the presence of other risk factors.[19,31] The 2013 European Hypertension Guidelines recommend that decisions on treatment strategies depend on the initial level of absolute total CVR (Class I, Level B).[19] It also advises that in asymptomatic subjects with hypertension but without evidence for CVD, CKD and DM, total CVR stratification using the SCORE model is recommended as a minimal requirement (Class I, Level B).[18] In comparison, 2016 European Guidelines on CVD prevention considered systematic total CVR assessment in individuals with hypertension as Class I, Level C.[9]

V Elements Favoring Prompt Use of Anti-Hypertensive Medications in Grade 1 Hypertension with Low-Moderate Absolute Total CVR.

Our consultation process has identified several elements **that favor early antihypertensive pharmacological treatment.** Those factors can be divided into four categories (Table 1):

A. Relating to lifestyle and behavior.

1.   **Avoid potential missed opportunities in primary prevention of CVD,** because it is well known that after the diagnosis of hypertension a proportion of patients do not attend their next scheduled appointment; thus, their BP remains uncontrolled.

2.   Lifestyle modifications can be equivalent to drug monotherapy, but their major drawback is the **low level of adherence over time**.[19,33] In clinical practice, **the adherence to lifestyle changes is lower than the adherence to pharmacological treatment**. Based on data in secondary prevention, the EUROASPIRE III (European Action on Secondary and Primary Prevention through Intervention to Reduce Events) study reported that body weight and physical activity targets were achieved in 18% and 34% of patients, respectively, during the period from 2006-2013.[19,34] The degree of physical activity is often self-reported, and is higher compared with data using objective assessment methods.[35] In addition, one year after myocardial infarction, approximately 50% of hypertensive patients remained adherent to pharmacological treatment.[19] EUROASPIRE IV identified some improvements in the utilization of the pharmacological recommendations (aspirin, statins and beta-blockers) but adherence to lifestyle changes was still very low (nearly half of the participants who smoked at the time of their initial coronary event were persistent smokers and only 40% achieved a physical activity level of the recommended intensity for at least 20 minutes one or more times a week).[9,36]

In general, there is a favorable global trend in control of dyslipidemia and hypertension, largely attributed to improvements in pharmacological treatment. However, during the same time frame, there has been an increase in the prevalence of obesity and DM, two risk factors associated with an unhealthy lifestyle.[9,37] Evidence suggests that the increase in obesity and DM are offsetting gains in morbidity and mortality due to improvements in other risk factors.

3.   Adherence to **lifestyle changes might not be affordable, feasible, or effective over prolonged time periods,** and does not significantly improve after the diagnosis of hypertension.[38,39,40]

4.   N**on-pharmacological therapy is generally** insuficient **to achieve BP targets.**[41]

B.   Relating to Total CVR

5.   **CVR models have limitations.**[42,43,44] Among others, the specificity ranges of the risk models is between 84.5 to 99.3%, but the positive predictive value ranges from 9.5 to 17.1% and the sensitivity ranges from 3.6 % to 53.4%. [42,43,44] Moreover, the differences between observed and expected risk levels could be significant within some risk percentiles,[45] especially when unvalidated local risk estimation systems are used.[46,47,48] For example, the differences on the expected average risk for a sample of Koreans subjects using the Framingham score (7.65%) and the "local" Korea score (1.67%) is substantial.[48] Recalibration of the Framingham score for the Spanish population showed that the levels of absolute total CVR should be different in Spain.[47] The predictive value of the risk models is affected by the presence of factors that are usually not included in the CVR models, such as low physical activity, obesity, being of low socioeconomic status and other psychological factors, pre-DM, a family history of premature CVD, or increased

triglycerides, fibrinogen, apolipoprotein B, lipoprotein(a) levels and high-sensitivity C-reactive protein.[9]

In addition, it is important to point out that there are no validated tables for most low and middle income countries, where over three quarters of deaths from CVD occur. When non-recalibrated models are applied, there has been low concordance among scores, which generates uncertainty about their utility for clinical intervention.[49] Some of the qualitative risk predictive models recommended for management of hypertension are not based on cohort studies; therefore, their predictive capacity may be limited. This is the case regarding the scores promoted by the World Health Organization/Pan-American Health Organization,[50] European Hypertension Guidelines[19] and Latin American Hypertension Guidelines[30]. The continuous relationship between the main risk factors and CVD favors the use of quantitative risk predictive models such as Framingham and SCORE.[51]

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 cardiovascular mortality (SCORE[9]) or morbidity and mortality of coronary heart disease (Framingham[10] or Pooled Cohort Equations[28]). Recently, an attempt has been made to calculate the relationship of major cardiovascular events to cardiovascular death from the data in control groups of BP-lowering RCTs.[52] The ratio was shown to decrease with the increase in cardiovascular death rate, in such a way that cardiovascular mortality should be multiplied by about 4 in individuals with cardiovascular mortality below 5% in 10 years, by about 3 when cardiovascular mortality is between 5 and 10% and by about 2 when cardiovascular mortality is above 10% to predict the rate of major cardiovascular events.[52]

These data indicate that mortality rates may be an unprecise indicator of morbidity, particularly in younger hypertensive patients with low CVR.[52,53,54,55,56]

5.1 Risk modifiers

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.[9] There is concordance among the statements of the American College of Cardiology, American Heart Association[28] and European Society of Cardiology[9] concerning the utility of the following risk modifiers: a) family history of premature CVD, b) coronary calcium score ≥300 Agatston units or ≥75th percentile for age, c) atherosclerotic plaques determined by carotid artery scanning, d) ankle–brachial blood pressure index <0.9 and e) high-sensitivity C-reactive protein ≥2 mg/L.[9,28] However, there is no agreement concerning other important risk modifiers such as: psychosocial risk factors[9], heart rate (>90 beats/min is often a practical surrogate for adrenergic neurohumoral activation and increased CVR)[9,57,58,59], ergo-anthropometric risk[60,61,62,63], relative total CVR (see section 12.2)[64,65], arterial stiffness[9,19,66,67,68], hypertension subtype[69,70], ambulatory BP[9,71,72], obstructive sleep apnoea syndrome[9], among others.

5.2 Definition of grade 1 "isolated" hypertension

For proper CVR stratification it may be useful to define grade 1 "isolated" hypertension as patients with grade 1 uncomplicated hypertension, low (absolute and relative) total CVR and without other risk major factors and risk modifiers.

6.   **Delaying pharmacological therapy increases total CVR**, and ensuing risk is often not entirely reversible by treatment.[19]

7.   **BP levels in mid-life are directly related to later CVR.**[73]

8.   After publication of the European Hypertension Guidelines[19], an **enlarged meta-analysis of patients with grade 1 hypertension** reported that BP lowering induced a significant reduction in the risk of stroke, major CVD events and all-cause mortality[12]. Limitations of that meta analysis   include a considerable proportion of individuals using background anti-hypertensive treatment at baseline, a high prevalence of participants with DM, and a high overall CVD-mortality risk of 6.2% over 10 years (above the upper < 5% cutoff for moderate total CVR according to the SCORE model).[4,6]   (new paragraph here)

Another recent meta-analysis has identified RCTs in which mean untreated baseline BP was within the grade 1 hypertension range, and found that in grade 1 hypertension with low to moderate absolute total CVR approximately 21 strokes, 34 major CVD events and 19 deaths could be prevented for every 1000 patients treated for 5 years (number needed to treat for 5 years to prevent one stroke=47, one major CVD event= 34, and one death= 19).[13] The results of this meta-analysis provides a higher level of evidence for recommendations in grade 1 hypertension with moderate CVR.[13] In this meta-analysis the CVD mortality rate of the control group was 4.5% over 10 years,[13] that is within the moderate CVR range, but above the low-risk range (<1%). Furthermore, the use of "mean" baseline values to define grade 1 hypertension cannot exclude that a minority of patients with higher BP were included, although the number of these patients is likely to be small because the average BPs were near the middle value of the range.[13]

9.   **The HOPE-3 (Heart Outcomes Prevention Evaluation) RCT** showed that participants with at least moderate absolute total CVR (men ≥ 55 and women ≥ 65 years of age with ≥1 CVR factors but without evidence for prior CV disease), who were in the subgroup for the upper third of systolic BP (>143.5 mm Hg) and received active treatment

(hydrochlorothiazide 12.5 mg and candesartan 16 mg), had significantly lower rates of major cardiovascular outcomes than those in the placebo group.[74] The combination of these anti-hypertensive therapies with rosuvastatin (10 mg per day) was associated with the greatest reduction in CVR (40%) compared with dual placebo.[75] The benefits associated with this combination were observed in all low density lipoprotein cholesterol (LDL) tertiles – i) LDL ≤ 112.3 mg/dl (mean=89.1), ii) LDL 112.4-141.7 mg/dl (mean=126.8) and iii) LDL >141.7 mg/dl (mean=166.7)-.[75] Therefore, a comprehensive, holistic approach should be emphasized to reduce CVR to the maximum possible. **The addition of statin drugs to blood-pressure lowering therapy provides greater benefit in patients with grade 1 hypertensive with moderate CVR.**[75,76,77,78,79] One must stress that both the American College of Cardiology/American Heart Association and NICE (National Institute for Health and Care Excellence) guidelines now focus on an individual's risk of vascular events rather than on their LDL cholesterol concentrations alone.[11,76] HOPE-3 also supports the use of low dose of combination BP lowering therapy in grade 1 hypertenson with moderate absolute CVR.[74]

10.   **Two-thirds of total CVD events occur in subjects with low to moderate absolute CVR**, and this proportion could be higher in women (three-quarters). In contrast, **1/3 of total CVD events occur in subjects with low absolute CVR, with considerable gender differences** as well (1/4 and 1/2 in men and women, respectively).[45,46]

11.   Although clinicians often require decision thresholds to trigger interventions, in a sense this is artificial, since **overall risk is actually a continuum**, **and there is no particular point above which, for example, a drug is automatically indicated, nor below which lifestyle advice may not usefully be offered.**[9,19,80,81]

12.   A**ge clearly has the most profound influence on the calculation of the absolute total CVR.**[9,19]

12.1   All standard absolute total CVR calculators show that older individuals without risk factors are still at moderate-high risk. On the other hand, calculators show people <50 years as having low CVR, regardless of underlying CVR factors. However, some younger individuals are at very high relative CVR compared with individuals of a similar age and may have high lifetime CVR; they are more likely to develop CVD early, and may prematurely suffer fatal or non-fatal CVD events.[9,19] For these reasons, efforts to improve CVR stratification in youger hypertensive is an important challenge in preventive medicine.

12.2 Age as a marker of population and individual CVR

In this context, an age of 55 years seems to be a practical and meaningful dividing line because:

a)   **The lifetime risk of hypertension is approximately 90% for men and women who were nonhypertensive at 55 or 65 years old and survived to age 80 to 85.**[41]

b)   **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.**[80]

c)   **Men ≥ 55 years (women ≥ 60 years) with uncomplicated grade 1 hypertension often have moderate total CVR even in the absence of other CVR factors (Figures 1 and 2).**

Figure 1. Absolute total CVR (13.5%) at 10 years and vascular age (61 years), grade 1 hypertensive, male, 55 years old, non-smoker, no DM and lipid levels are close to the means in the United States of America population.[82] (Using the Framingham online

calculator available at https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php#)
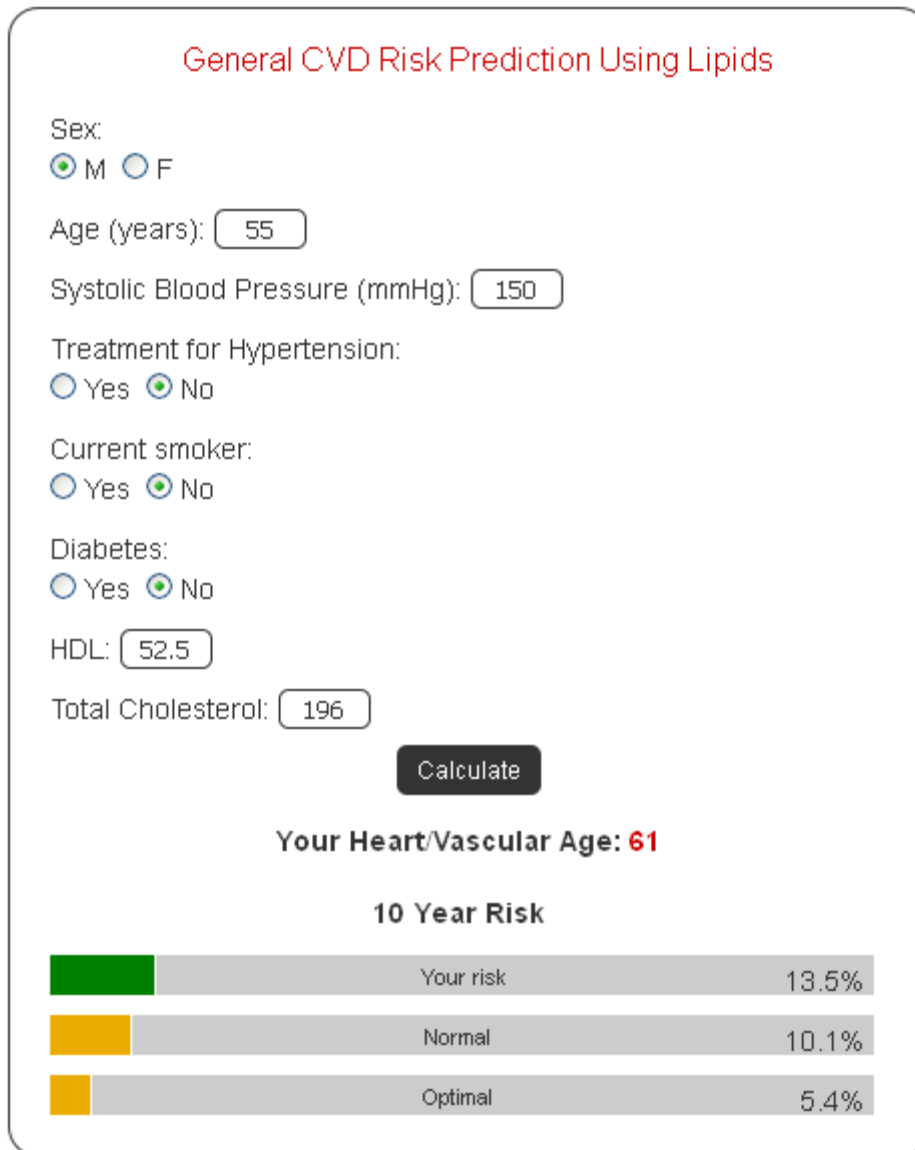

Figure 2. Absolute total CVR (10.3%) and vascular age (74 years) of grade 1 hypertensive, female, 60 years old, non-smoker, no DM and lipid levels are close to the means in the United States of America population.[82]

General CVD Risk Prediction Using Lipids

Sex:
○ M ● F

Age (years): [60]

Systolic Blood Pressure (mmHg): [150]

Treatment for Hypertension:
○ Yes ● No

Current smoker:
○ Yes ● No

Diabetes:
○ Yes ● No

HDL: [52.5]

Total Cholesterol: [196]

[Calculate]

Your Heart/Vascular Age: 74

10 Year Risk

	Your risk	10.3%
	Normal	6.4%
	Optimal	3.2%

12.3 Relative total CVR

One of the most important elements for stratification of grade 1 hypertensive subjects with low absolute total CVR is the relative total CVR (the traditional definition uses a ratio of the absolute risk of the individual under consideration and the the average absolute risk of a baseline population, either a low-risk group or an average risk group).[64,65] New variants of the relative CVR are a) vascular age or risk age[9,83,84], b) the age and gender total CVR

percentile[83] and **c) long-term (eg lifetime) risk approach[28]. There is no consensus about relative CVR thresholds of low, moderate, and high risk.**

The relative risk (using the traditional concept) and vascular age of the subjects represented in Figures 1 and 2 are 2.5 and 61 years, and 3.2 and 74 years in each case.

Estimation advantages of using relative total CVR are that it:[9,19,64,65,83]

a) Is independent of the predictive events ("hard" coronary disease, CVD-mortality, etc.),

b) Can be used in any population independently of the baseline CVR (avoiding the need of recalibration),

c) Reduces or eliminates influence of age on the total CVR.

This tool can be used to improve adherence, better communicate risk, and guide pharmacological anti-hypertensive treatment decisions. However, the guidelines do not recommend the use of any relative-CVR variants for treatment decisions.[9,11,19,28]

12.3.1 Alternatives to relative total CVR

Age- and gender-specific relative risk has been assessed from other parameters. Among them are **percentile tables of coronary calcium content according to age and gender**.[85,86] MESA (Multi-Ethnic Study of Atherosclerosis) study reported that the CVR at > 90 percentile of calcium score (according to age and gender), is double than the absolute calcium > 400 Agatston units (18.9 vs 9.94, respectively).[85]

13   Individuals with a **CVR factor at early ages tend to remain** in rank-proportional levels of risk.[86,87]

14   Simulation studies have suggested that total CVR-based blood pressure management strategies will be more cost-effective than hypertension control strategies based solely upon BP numbers,[9,28,42,89,90] but **direct evidence for the role of total CVR in treatment decisions is lacking[9,91] and the** best way to reduce total CVR is the control of

each risk factor.

15 **Grade 1 hypertension with low absolute total CVR is not a benign condition.**[19] Even in children and adolescents this combination is associated with increased CVR, which is reversible with treatment.[92] Grade 1 hypertension is associated with impaired arterial distensibility that improves with pharmacological treatment.[93]

16 If the success of BP lowering is measured not only by the absolute reduction in outcome it achieves, but also by the absolute level of treatment failures (**residual risk**)[14], it is not surprising that **the greatest success of BP lowering may be actually achieved in low-moderate risk patients.** Targeting BP-lowering treatment to only those with the greatest CVR seems unwarranted because the reduction in the number of patients needing treatment to obtain a given benefit is counterbalanced by the dramatic increase in the number of patients in whom BP lowering fails to prevent fatal and nonfatal CVD events**.**[14]

17 **Gaps in knowledge exist about short- and long-term total CVR assessment and outcomes in all racial/ethnic groups**, across the age spectrum, and in women and men.[28]

18 **Many physicians, rarely or ever use total CVR models.** Yet, essentially all applicable guidelines recommend assessment of global CVR prior to pertinent medical decision making. Thus, in addition to gaps in knowledge there is a shortfall in CVR model utilization. One intriguing, but as-yet untested, solution is the routine inclusion of CVR in medical records.[94,95]

C. Relating to medical management

19 RCT demonstrate that **most hypertensive patients require 2 or more drugs to achieve BP control.**[19,41]

20 A large number of safe anti-hypertensive **medications are now available, and treatment can be personalized** in order to optimize both efficacy and tolerability[19].

21 **Use of traditional algorithms often fails to achieve the desired** hypertension **control**[18], particularly in those less than 75 years of age.[96,97]

22 **Strategies to utilize anti-hypertensive pharmacological treatments earlier** in the course of grade 1 hypertension and low-moderate absolute total CVR **could have an important impact on CVD prevention and counteract physician inertia.**[98] Physician inertia is considered to be one of the main causes of the low rate of BP control in modern anti-hypertensive practices, mainly in youger adults with grade 1 hypertension.[18,99,100] Often it is difficult to tease apart performance deficits due to insufficient treatment advancement and poor patient adherence.

23 **The intensity and quality of anti-hypertensive pharmacological treatment is one of the key elements in attaining significant improvements of** hypertension **control** as well as successful reductions in CVD mortality.[101,102]

24 Although **SPRINT** (Systolic Blood Pressure Intervention Trial)[103] does not provide direct information on the BP level at which drug treatment should be initiated (90% of SPRINT patients were already on antihypertensive treatment at baseline). The demonstration of cardiovascular benefits in the subgroup of uncomplicated hypertensive patients with moderate total CVR,[103] may be used as indirect support favouring treatment of grade 1 hypertension.

25 **High blood pressure is the leading risk factors for death in the world**[104]**; and anti-hypertensive pharmacological treatment** could be **the most effective of cardiovascular preventive interventions** (in primary and secondary prevention).[105,106] For example, in Canada, an increase in the use of pharmacological treatment from 35% to 80% was accompanied by significant improvements in hypertension control (13% to 68%).[102]

26   The initial evaluation of a patient with hypertension should detect causes of secondary hypertension, target organ damage and concomitant clinical conditions.[19] This requirement could pose a burden in communities and/or individuals with limited resources. **Key routine laboratory investigations such as blood chemistries (haemoglobin, haematocrit, fasting plasma glucose, cholesterol, uric acid, creatinine, potassium and sodium), urine testing (Class I and Level B) and electrocardiograms (Class I and Level B) in asymptomatic grade 1 hypertensive adults are not always available.[19]** Thus, it is often impossible to know whether individual patients in fact already have detectable cardiovascular target organ damage, or whether they have concomitant risk.

D. Relating to socio-economic and public health policies

27   A proportion of **low-income patients with hypertension do not even have the resources to try favorable lifestyle changes.[22]** The consumption of fruit and vegetables is inadequate worldwide, particularly in low-income countries or in less-affluent people in higher income countries, and may be attributed to both difficulty of access and unaffordability.[38]

28   Many **anti-hypertensive agents** are out of patent, generic, and are therefore affordable with acceptable **cost–benefit ratios in high income countries.[19]** Even generic drugs that are low cost in high income countries, may be relatively (compared to income) expensive in low-middle income countries unless subsidized or provided free by governments.[107]

29   **The availability and affordability of** healthy lifestyles **could be a more signficant obstacle than for pharmacological treatment in hypertensive patients,** but improvements are needed at all levels.**[38,108]**

30   The number needed to treat is a concise, epidemiologically useful presentation of the effect of an intervention in the short term , but **the economic and social analysis of pharmacological treatment in young adults requires a different assessment**, such as the life-years gained-to-years of potential life lost ratio.[109,110] In addition, the quantitation of compression of morbidity and improvement in quality of life remain inexact, leaving estimation of the component of disease-free life extension an art rather than science.[109,110]

31   **A population-based primary prevention strategy seeks to reduce the exposure to a highly prevalent risk factor for disease**.[111] The effect of current population strategies for BP reduction has done little to decrease population systolic BP mean and hypertension prevalence**.[111]** European Guidelines on CVD prevention state that scientific evidence of the impact of food and nutrition policy instruments on outcome measures such as food intake and cardiovascular health is lacking.[9] Cost-effectiveness studies of the impact of different policy options are also limited.[9]

Table 1. Main elements favoring early use of drugs in adults aged < 80 years with grade 1 hypertension and low to moderate CVR
Relating to lifestyle and behavior.
• Avoid missing opportunities in primary prevention of CVD. • Adherence to lifestyle changes is lower than to pharmacological treatment. • Lifestyle changes might not be affordable or effective over longer periods of time. • Non-pharmacological therapy is generally insufficient to reach BP targets.
Relating to Total CVR

- Predictions using CVR models have limitations.

- Delaying pharmacological therapy increases total CVR.

- Two-thirds of CVD events occur in subjects with low to moderate absolute total CVR.

- Direct evidence for the role of total CVR in treatment decisions is lacking.

- Individuals with a CVR factor at early ages tend to remain at rank-proportional levels of risk.

- Grade 1 hypertension with low to moderate absolute total CVR is not a benign condition.

- Most physicians rarely or never use total CVR models.

- Assessment of relative CVR may be a key risk modifier in younger hypertensive adults, but there is currently no consensus on relative CVR thresholds.

Relating to medical management

- Most hypertensive patients require 2 or more drugs to achieve BP control.

- Treatment can be personalized, optimizing both efficacy and tolerability.

- Early treatment may minimize later treatment failures.

- Traditional algorithms often fail to achieve the desired hypertension control, particularly in those under 75 years of age.

- Strategies to utilize anti-hypertensive pharmacological treatments earlier in the course of grade 1 hypertension and low-moderate absolute total CVR could have an important impact on CVD prevention and counteract physician inertia.

- Extrapolating evidence from recent meta-analyses and clinical trials may favor

an aggressive stance.

- Anti-hypertensive pharmacological treatment could be the most productive of cardiovascular preventive interventions.

- Substantial barriers exist in the detection of secondary hypertension, target organ damage, and concomitant clinical conditions, mainly in communities and/or individuals with low resources.

Relating to socio-economic and public health policies

- The availability and affordability of healthy lifestyle could be a greater obstacle than for pharmacological treatment.

- The economic and social analyses of pharmacological treatment in young adults require calculation of the life-years gained-to-years of potential life lost ratio.

VI Final considerations

A. Individual[19] and population interventions[112,113] are not opposing, but synergistic strategies; hypertension management should always take into account the balance between clinical and the public health approaches, an issue particularly relevant for low-middle income countries.[24,26,27,114] The cost perspective is a critical component of this balance, because governments and individuals need to prioritize how their limited funds are best spent. [9,24,26,27]

B. This consultation, properly aligned with current global context of the **cardiovascular prevention comes at a unique time in hypertension management** philosophy and approach.[9,24,26,27,115,116,117,118] Indeed, several relevant partners led by the

World Health Organization launched an initiative to improve cardiovascular health named HEARTS.[24] The HEARTS technical package covers six elements: healthy lifestyle (counsel on CVR factors and self-care), evidence-based treatment protocols (simple and standardized protocols), access to essential medicines and technology (a core set of affordable medicines and basic technologies), risk-based management (total cardiovascular risk assessment, treatment and referral), team care and task-sharing (patient-centered care through a team approach and community participation), and systems for monitoring (patient and programme monitoring and evaluation).[24] This global initiative is promoting a set of needed major system changes within the delivery of health care to achieve improvements in hypertension control.[24] Therefore, this consultation, properly aligned with this new context of the approach to hypertension management, can pave the way to develop a more innovative clinical recommendations in the near future. Our attainable goal is a practical and standardized algorithm to raise the quality of medical care of patients with hypertension and hence, improve control and outcomes.[24,26,27]

VII Key conclusions

This consultation process reached the following consensus in hypertensive adults aged < 80 years (Table 2).

1.   The question of whether drug treatment in grade 1 should be preceded by a period of some weeks or months during which only lifestyle measures are recommended cannot be evidence based, but the consensus opinion is to have a period of lifestyle alone reserved only to patients with grade 1 "isolated" hypertension (grade 1 uncomplicated hypertension with low absolute total CVR, and without other risk major factors and risk modifiers).

2.   The initiation of anti-hypertensive drug therapy in grade 1 hypertension with moderate absolute total CVR should not be delayed.[13,74]

3.   Men ≥ 55 years and women ≥ 60 years with uncomplicated grade 1 hypertension should automatically be classified within the moderate absolute total CVR category, even in the absence of other risk major factors and risk modifiers.

4.   Statins should be considered along with blood-pressure lowering therapy, irrespective of cholesterol levels, in patients with grade 1 hypertensive with moderate CVR. [75,76,77,78]

Table 2. Management of recently diagnosed grade 1 hypertension with low to moderate absolute total CVR in adults aged < 80 years	
Office BP ≥ 140/90 mmHg (or the equivalent in ambulatory BP monitoring)+	
Not grade 1 "isolated" hypertension	Grade 1 "isolated" hypertension++
a) In patients with moderate absolute total CVR or in patients aged ≥ 55 in men (women ≥ 60 year), prescribe both non-pharmacological and pharmacological treatment. b) The decision should be individualized in other subgroups.	Promotion of positive lifestyle changes for 3-6 months while monitoring BP and total CVR.

+Before starting anti-hypertensive drug treatment, most patients should have out-of-office monitoring to confirm hypertension. ++ See sections 5.1 and 5.2.

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