Guideline for the pharmacological treatment of hypertension in adults

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Responsible technical officer: Taskeen Khan

WHO Steering Group members: Bernadette Cappello (MHP), Neerja Chowdhury (MSD), Gampo Dorji (SEARO), Jill Farrington (EURO), Taskeen Khan (NCD), Pedro Ordunez (PAHO/AMRO), Steven Shongwe (AFRO), Slim Slama (EMRO), Cherian Varghese (NCD), Marco Vitoria (HHS), Temo Waqanivalu (NCD).

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Shrish Acharya (WPRO), Akram Al-Makki (AMRO), Hind Mamoun Beheiry (EMRO), Beatriz Champagne (AMRO), Ugyen Choden (SEARO), Kenneth Connell (AMRO), Marie Therese Cooney (EURO), Donald DiPette (AMRO), Nnenna Ezeigwe (AFRO), Tom Gaziano (AMRO), Agaba Gidio (AFRO), Vilma Irazola (AMRO), Patricio Lopez Jaramillo (AMRO), Unab Khan (EMRO), Vindya Kumarapeli (SEARO), Andrew Moran (AMRO), Margaret Mswema Silwimba (AFRO), Brian Rayner (AFRO), K. Srinath Reddy (SEARO), Nizal Sarrafzadegan (EMRO), Apichard Sukonthasan (SEARO), Paul Whelton (AMRO), Jing Yu (WPRO).

Methodologist: M Hassan Murad (Professor of Medicine at the Mayo Clinic, Rochester, USA)

Systematic Review Team: Reem Mustapha, Abdallah Al Alayli, Romina Brignardello, Sara Jdiaa, Veena Manja (University of Kansas Medical Center, Kansas, USA)

External Review Group: WHO is grateful for the contributions of the following individuals who peer-reviewed the draft guideline:

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Acronyms and abbreviations

ACE1	angiotensin-converting enzyme 1
ACE2	angiotensin-converting enzyme 2
ACEi	angiotensin-converting enzyme inhibitor
ARB	angiotensin-II-receptor blocker
BB	beta-blocker
BP	blood pressure
CAD	coronary artery disease
CCB	calcium channel blocker
CKD	chronic kidney disease
CRE	WHO Office of Compliance, Risk Management and Ethics
CV	cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
DOI	declaration of interest
ECG	electrocardiogram
EML	Essential Medicines List
ERG	External Review Group
ESRD	end-stage renal disease
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCW	health care worker (nonphysician)
HIC	high-income country
HTN	hypertension
LIC	low-income country
LMIC	low- and middle-income country
LVH	left ventricular hypertrophy
MACE	major adverse cardiovascular event
MI	myocardial infarction
MIC	middle-income country
NCD	noncommunicable disease
PEN	WHO package of essential NCD interventions
PICO	population intervention comparator outcome
QALY	quality-adjusted life year
RAAS	renin-angiotensin-aldosterone system
SBP	systolic blood pressure

Executive summary

More people die each year from cardiovascular diseases than from any other cause. Over three quarters of heart disease and stroke-related deaths occur in low-income and middle-income countries. Hypertension – or elevated blood pressure – is a serious medical condition that significantly increases the risk of heart, brain, kidney and other diseases. Hypertension can be defined using specific systolic and diastolic blood pressure levels or reported use of antihypertensive medications. An estimated 1.4 billion people worldwide have high blood pressure, but just 14% have it under control. However, cost-effective treatment options do exist.

In this guideline, the World Health Organization (WHO) provides the most current and relevant evidence-based global public health guidance on the initiation of treatment with pharmacological agents for hypertension in adults. The recommendations target adult, non-pregnant patients who were appropriately diagnosed with hypertension and counselled about life-style modifications.

The guideline provides new recommendations on the threshold for the initiation of pharmacological treatment for hypertension, as well as recommendations on intervals for follow up, target blood pressure to be achieved for control, and the cadre of health care workers who may initiate treatment. The guideline provides the basis for deciding whether to initiate treatment with monotherapy, dual therapy or single-pill combinations, as well as guidance for countries selecting medicines and algorithms for hypertension control for their national guidelines for hypertension management.

The guideline was developed in accordance with the WHO Handbook for Guideline Development. In brief, the WHO Steering Group, in collaboration with the Guideline Development Group, developed key questions and rated outcomes to identify those critical for the development of the guideline. Conflicts of interest were handled in line with the current Compliance, Risk Management and Ethics (CRE) policy and all members of the GDG were asked to fill in the standard WHO Declaration of Interest (DOI) forms, which were reviewed. An overview of systematic reviews of the evidence was used to build summary of findings tables according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. The Guideline Development Group developed recommendations, considering the certainty of the evidence; the balance between desirable and undesirable effects; resource requirements and cost-effectiveness; health equity; acceptability, patient values and preferences, and feasibility.

Recommendations

1. RECOMMENDATION ON BLOOD PRESSURE THRESHOLD FOR INITIATION OF PHARMACOLOGICAL TREATMENT
WHO recommends initiation of pharmacological antihypertensive treatment of individuals with a confirmed diagnosis of hypertension and systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg.
Strong recommendation, moderate- to high-certainty evidence
WHO recommends pharmacological antihypertensive treatment of individuals with existing cardiovascular disease and systolic blood pressure of 130–139 mmHg.
Strong recommendation, moderate- to high-certainty evidence

WHO suggests pharmacological antihypertensive treatment of individuals without cardiovascular disease but with high cardiovascular risk, diabetes mellitus, or chronic kidney disease, and systolic blood pressure of 130–139 mmHg.

Conditional recommendation, moderate- to high-certainty evidence

2. RECOMMENDATION ON LABORATORY TESTING

When starting pharmacological therapy for hypertension, WHO suggests obtaining tests to screen for comorbidities and secondary hypertension, but only when testing does not delay or impede starting treatment.

Conditional recommendation, low-certainty evidence

3. RECOMMENDATION ON CARDIOVASCULAR DISEASE RISK ASSESSMENT

WHO suggests cardiovascular disease risk assessment at or after the initiation of pharmacological treatment for hypertension, but only where this is feasible and does not delay treatment.

Conditional recommendation, low-certainty evidence

4. RECOMMENDATION ON DRUG CLASSES TO BE USED AS FIRST-LINE AGENTS

For adults with hypertension requiring pharmacological treatment, WHO recommends the use of drugs from any of the following three classes of pharmacological antihypertensive medications as an initial treatment:

1. thiazide and thiazide-like agents
2. angiotensin-converting enzyme inhibitors (ACEis)/angiotensin-receptor blockers (ARBs)
3. long-acting dihydropyridine calcium channel blockers (CCBs).

Strong recommendation, high-certainty evidence

5. RECOMMENDATION ON COMBINATION THERAPY

For adults with hypertension requiring pharmacological treatment, WHO suggests combination therapy, preferably with a single-pill combination (to improve adherence and persistence), as an initial treatment. Antihypertensive medications used in combination therapy should be chosen from the following three drug classes: diuretics (thiazide or thiazide-like), angiotensin-converting enzyme inhibitors (ACEis)/angiotensin-receptor blockers (ARBs), and long-acting dihydropyridine calcium channel blockers (CCBs).

Conditional recommendation, moderate-certainty evidence

6. RECOMMENDATIONS ON TARGET BLOOD PRESSURE

WHO recommends a target blood pressure treatment goal of <140/90 mmHg in all patients with hypertension without comorbidities.

Strong recommendation, moderate-certainty evidence

WHO recommends a target systolic blood pressure treatment goal of <130 mmHg in patients with hypertension and known cardiovascular disease (CVD).
Strong recommendation, moderate-certainty evidence
WHO suggests a target systolic blood pressure treatment goal of <130 mmHg in high-risk patients with hypertension (those with high CVD risk, diabetes mellitus, chronic kidney disease).
Conditional recommendation, moderate-certainty evidence

7. RECOMMENDATIONS ON FREQUENCY OF ASSESSMENT
WHO suggests a monthly follow up after initiation or a change in antihypertensive medications until patients reach target.
Conditional recommendation, low-certainty evidence
WHO suggests a follow up every 3–6 months for patients whose blood pressure is under control.
Conditional recommendation, low-certainty evidence

8. RECOMMENDATION ON TREATMENT BY NONPHYSICIAN PROFESSIONALS
WHO suggests that pharmacological treatment of hypertension can be provided by nonphysician professionals such as pharmacists and nurses, as long as the following conditions are met: proper training, prescribing authority, specific management protocols and physician oversight.
Conditional recommendation, low-certainty evidence

1 Introduction

More people die each year from cardiovascular diseases than from any other cause. Over three quarters of heart disease and stroke-related deaths occur in low-income and middle-income countries *(1)*. Blood pressure is the force exerted by circulating blood against the walls of the body's arteries, the major blood vessels in the body. Blood pressure is written as two numbers. The first number (systolic) represents the pressure in blood vessels when the heart contracts or beats. The second number (diastolic) represents the pressure in the vessels when the heart rests between beats. Hypertension – or elevated blood pressure – is a serious medical condition that significantly increases the risk of diseases of the heart, brain, kidneys and other organs *(2)*. Hypertension can be defined using specific systolic and diastolic blood pressure levels or reported use of antihypertensive medications. An estimated 1.4 billion people worldwide have high blood pressure, but just 14% have it under control *(2)*. However, cost-effective treatment options do exist.

A World Health Organization (WHO) guideline dealing specifically with raised blood pressure was last published more than 20 years ago – in 1999 – and is now outdated. In 2007, a comprehensive guideline on cardiovascular risk included some recommendations on hypertension but this also needs revision and updating in the light of new evidence and practice *(3)*. Guidance is particularly needed on some controversial issues, such as when to start treatment and whether laboratory testing and cardiovascular risk assessment are needed prior to starting treatment. In the past decade, WHO has included diagnosis and management of hypertension in a total cardiovascular risk approach as part of the WHO package of essential noncommunicable disease (NCD) Interventions (WHO PEN) 2007, 2010 and 2013. However, this approach has not included the most recent advances in pharmacological treatment.

The WHO Essential Medicines List (EML) identifies all classes of antihypertensive drugs – angiotensin-converting enzyme inhibitors (ACEi), calcium channel blockers (CCB), angiotensin receptor blockers (ARB) and thiazide diuretics – as essential. In June 2019, the EML included single-pill combination medications for hypertension. This further supports the evaluation of all classes of antihypertensive drugs as well as single-pill combinations in this current guideline.

Scope and objectives of the hypertension guideline

The 2021 WHO hypertension guideline aims to provide the most current and relevant evidence-based global public health guidance on the initiation of treatment (with pharmacological agents) for hypertension in adults. The recommendations target the general adult, non-pregnant, hypertensive population.

Although several countries and professional societies have guidelines on the topic of hypertension, these are specific to the population of that particular country or the specific setting or constituency of the professional society. Recent shifts in hypertension management, such as moving away from using beta-blockers as a first-line agent or the increased research and adoption of combination therapies and single-pill combinations, are all additional reasons for new guidance. The *Guideline for the pharmacological treatment of hypertension in adults* will be the first global guideline in the past two decades on the topic and will have specific relevance to low- and middle-income countries (LMICs).

The guideline provides new recommendations on the threshold for the initiation of pharmacological treatment for hypertension, recommendations on intervals for follow up, target blood pressure to be achieved for control, and the cadre of health care workers who may initiate treatment. It provides the basis for deciding whether to initiate treatment with monotherapy, dual therapy, or single-pill combination, as well as guidance for countries on selecting medicines for hypertension control in their national guidelines for hypertension management.

This guideline will replace the guidance in the modules *Evidence-based protocols* and *Risk-based CVD management* of the HEARTS technical package, as well as the guidance in the WHO PEN package regarding the threshold for initiation of treatment, and for the preferred pharmacological treatment for hypertension.

The guideline does not address measurement of blood pressure or diagnosis of hypertension. It addresses pharmacotherapy in individuals with a "confirmed" diagnosis of hypertension, such as hypertension diagnosed when blood pressure is found to be elevated on two different days.

Although this guideline does not address modifiable risk factors for hypertension such as unhealthy diet, physical inactivity, consumption of tobacco and alcohol, and being overweight or obese, a comprehensive treatment plan for hypertension must include addressing these risk factors through life-style modifications and other interventions *(2)*.

Nonpharmacological approaches to treatment or prevention of hypertension include:

- reducing salt intake (to less than 5g daily)
- eating more fruit and vegetables
- being physically active on a regular basis
- avoiding use of tobacco
- reducing alcohol consumption
- limiting the intake of foods high in saturated fats
- eliminating/reducing trans fats in diet *(2)*.

The guideline does not address hypertensive crisis as it is focused on chronic blood pressure management in regular care settings.

The objectives of the hypertension guideline are to:

- provide a blood pressure threshold for the initiation of treatment for hypertension;
- determine if laboratory tests or cardiovascular risk assessment are required prior to initiation of treatment for hypertension;
- determine the pharmacological agents with which to initiate treatment;
- determine the need to initiate treatment with monotherapy, dual therapy, or single-pill combinations;
- provide targets for blood pressure control in hypertension;
- provide intervals for follow up for patients with hypertension; and
- determine how nonphysician health care workers can participate in the management of hypertension.

Target audience

Primary audience

Clinicians/health care providers at all levels of health care.

Secondary audience

National NCD/CVD programme managers, health care academics, policy-makers setting practice recommendations, students, and hypertension medicine manufacturers.

2 Method for developing the guideline

2.1 Guideline contributors

In order to develop the hypertension guideline, WHO established three groups:

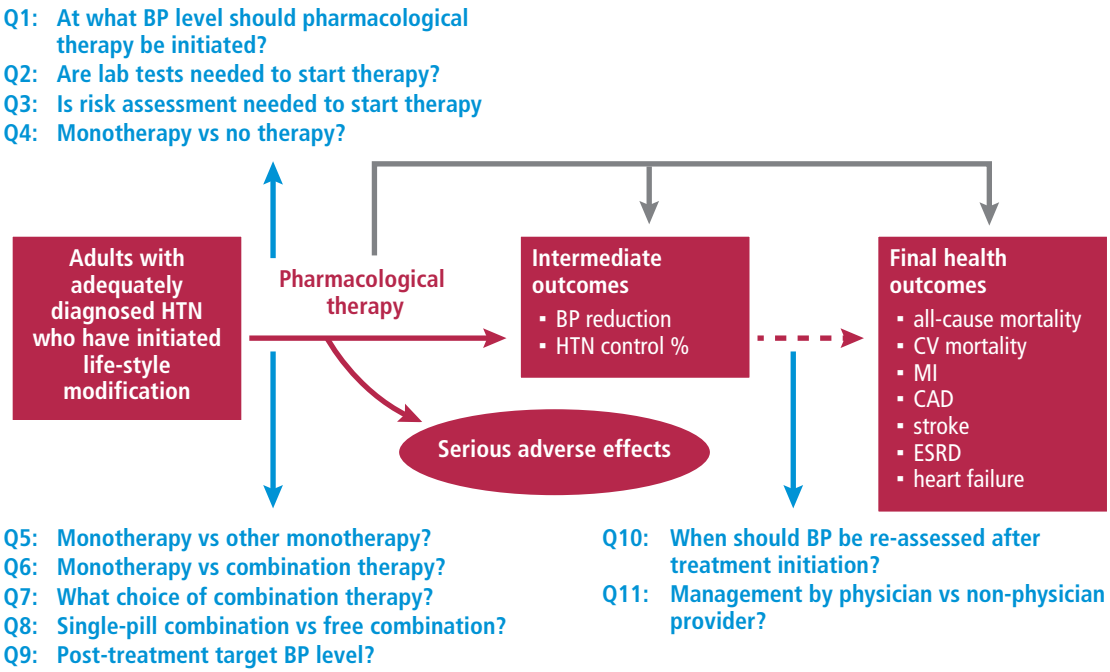
1. An internal WHO Steering Group to coordinate the guideline development process.
2. A Guideline Development Group (GDG), composed of hypertension (HTN) physicians, nephrologists, cardiologists, pharmacists, nurses, researchers, academics, policy-makers and representatives of patient groups, to review the evidence and develop recommendations. WHO selected the members of the GDG based on relevant expertise but it also considered appropriate representation by region and sex.
3. An External Review Group (ERG), composed of technical experts, representatives of HTN patient groups and ministries of health from low-resource countries, to provide peer review of the guideline and ensure recommendations are aligned with current global needs.

Annex 1 lists the contributors in each group. Annex 2 describes the process for declaring and managing conflicts of interest.

2.2 Analytical framework and PICOs

An initial GDG meeting was held in Geneva in July 2019 to determine the scope and PICO (population, intervention, comparison, outcome) questions of the guideline. The GDG first developed an analytical framework (Fig. 1) that demonstrates the impact of interventions on intermediate and final outcomes and displays the order of the key questions to better visualize and place them along the patient-flow pathway. Following this, and a preliminary scoping review and discussion between the steering group and methodologist, PICO questions were developed. These were considered, deliberated on, further refined and voted on during the meeting.

Fig. 1 Analytic framework for antihypertensive medication treatment



2.3 Outcome importance rating

Members of the WHO Steering Group, in consultation with the GDG and methodologist, developed a list of treatment outcomes most relevant to the care of individuals with HTN. The GDG then rated each outcome on a scale from 1 to 9 and indicated whether it considered each outcome critical (rated 7–9), important (rated 4–6) or not important (rated 1–3) for decision-making. The mean scores are provided in Annex 3.

2.4 Reviews of evidence

The WHO Steering Group, with the participation of the GDG, determined the scope of the guideline and identified eleven questions in the format of population, intervention, comparison, and outcomes (PICO) to guide the search for systematic reviews (Annex 4). Eleven overviews of reviews informed the guideline development process. A systematic search was carried out in PubMed, Embase, The Cochrane Library, and Epistemonikos to identify existing systematic reviews that answered the PICO questions published in 2015 or after. Suitable systematic reviews were then evaluated based on the following criteria:

- their methodology as appraised by the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) tool;
- how directly they matched the PICO questions;
- whether they reported sufficient information to allow for an assessment of the certainty of the evidence (e.g. tables with characteristics of included studies, risk of bias assessments at the study level, results of meta analyses in forest plots);
- whether they reported evidence in subgroups of interest (e.g. patients with diabetes mellitus (DM), cardiovascular disease (CVD), chronic kidney disease (CKD) etc); and
- the date of the most recent review to ensure the most updated evidence was used.

The Systematic Review Team prioritized the most useful reviews for each question, comparison, outcome and subpopulation within questions, and included as many reviews as necessary to address each question comprehensively. (Web Annex A provides details of the search terms and strategy used.) No reviews were updated.

Two questions (PICO 2 and 10, see Annex 4) were not addressed in an existing systematic review, and evidence from primary studies was therefore used. In this case, the Systematic Review Team reviewed the list of studies used in existing guidelines, queried the GDG and content experts, and searched for primary studies.

A total of 159 systematic reviews and 17 additional primary studies were included. Most of these were traditional systematic reviews in which the authors conducted pairwise meta-analysis, whereas nine analysed individual patient data. The Systematic Review Team also identified several published network meta-analyses. (See Web Annex A for full details.)

Most of the included reviews were found to be of high certainty when assessed using the AMSTAR tool. Details of the selection process, and the reviews and studies included for each PICO question, are presented in Web Annex A.

Another overview of reviews was conducted to identify systematic reviews to inform other decision criteria in the evidence-to-decision framework, including people's values, resources, acceptability, feasibility and equity, presented in Web Annex A. This review was enriched by primary studies identified by GDG members. This review focused on evidence informing HTN management in low- and middle-income settings.

2.5 Certainty of evidence and strength of recommendations

The GDG rated the certainty of evidence and developed the recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (4). When making recommendations, GRADE defines the certainty of a body of evidence as "the extent of our confidence that the estimates of an effect are adequate to support a particular decision or recommendation" *(5)*.

Members of the GDG, with the help of the methodologist, developed evidence profiles to summarize relative and absolute estimates of effects, and an assessment of the certainty of the evidence. One evidence profile for each comparison within a PICO question was constructed, using the online Guideline Development Tool GRADEpro (https://gradepro.org). When there were systematic reviews addressing the relative effects in specific subpopulations, separate evidence profiles were constructed for each subpopulation.

According to the GRADE approach, the certainty of the evidence can be high, moderate, low, or very low. Bodies of evidence from randomized controlled trials – which comprised almost the totality of those included in this guideline – start the assessment as high-certainty evidence but can be down-rated due to considerations of risk of bias, inconsistency, imprecision, indirectness, and publication bias. Table 1 presents an explanation of the different levels of certainty of the evidence *(5)*.

Table 1 Certainty of evidence and its implications

Certainty level	Definition
High	We are very confident that the true effect lies close to that of the estimate of effect.
Moderate	We are moderately confident in the effect estimate. (The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.)
Low	Our confidence in the effect estimate is limited. (The true effect may be substantially different from the estimate of the effect.)
Very low	We have very little confidence in the effect estimate. (The true effect is likely to be substantially different from the estimate of effect.)

The strength of the recommendations reflects the degree of confidence of the GDG that the desirable effects (e.g. beneficial health outcomes) of the recommendations outweigh the undesirable effects (e.g. adverse effects). The strength of recommendations in this guideline was graded into two categories:

A strong recommendation is one for which the GDG was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects.

A weak or conditional recommendation is one for which the GDG concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects, but was not confident about these trade-offs.

2.6 Deciding upon recommendations

The GDG met virtually for four sessions in February 2021. Systematic reviews and GRADE tables were presented at the meeting. Formulation of recommendations and their strength were facilitated by the chair and supported by the methodologist, with the aim of achieving unanimous consensus. While the plan was to use a simple majority vote, full consensus was reached on all recommendations.

The GDG used evidence-to-decision tables to guide the process of developing recommendations. These tables addressed the certainty of evidence, the balance between desirable and undesirable effects, values, resource use and cost-effectiveness, equity, acceptability and feasibility. These tables are available in Web Annex B, and the full evidence profiles in Web Annex A. The WHO Steering Group noted remarks made by members of the Expert Review Group and considered incorporating these into the final guideline. Some evidence-to-decision frameworks were consolidated to provide recommendations that are more practical and implementable from an end-user perspective; hence, the 11 questions led to eight recommendations.

2.7 Funding

The development of this guideline was financially supported by the US Centers for Disease Control and Prevention and the World Health Organization.

3 Recommendations

3.1 Blood pressure threshold for initiation of pharmacological treatment

1. RECOMMENDATION ON BLOOD PRESSURE THRESHOLD FOR INITIATION OF PHARMACOLOGICAL TREATMENT
WHO recommends initiation of pharmacological antihypertensive treatment of individuals with a confirmed diagnosis of hypertension and systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg.
Strong recommendation, moderate- to high-certainty evidence
WHO recommends pharmacological antihypertensive treatment of individuals with existing cardiovascular disease and systolic blood pressure of 130–139 mmHg.
Strong recommendation, moderate- to high-certainty evidence
WHO suggests pharmacological antihypertensive treatment of individuals without cardiovascular disease but with high cardiovascular risk, diabetes mellitus, or chronic kidney disease, and systolic blood pressure of 130–139 mmHg.
Strong recommendation, moderate- to high-certainty evidence
Implementation remarks: ▪ Initiation of pharmacological hypertension (HTN) treatment should start no later than four weeks following diagnosis of HTN. If blood pressure level is high (e.g. systolic ≥160 mmHg or diastolic ≥100 mmHg) or there is accompanying evidence of end organ damage, initiation of treatment should be started without delay.

Evidence and rationale

The GDG reviewed evidence from 14 relevant systematic reviews that summarized data from a large number of randomized trials involving over 120 000 adult participants (Web Annex A). Evidence summaries are presented for the general population and for higher-risk populations (with diabetes (DM), coronary artery disease (CAD), prior stroke) and were presented for various systolic blood pressure (SBP) thresholds (Web Annex A).

The anticipated benefits of a lower blood pressure (BP) target (140 SBP in the general population and 130 SBP in a high-risk population) were reduction in mortality, cardiovascular mortality, stroke, myocardial infarction (MI) and heart failure events. The anticipated harms were mostly not serious side-effects, and some were a surrogate outcome, such as rise in creatinine that may not be clinically relevant. On average, treatment was associated with a reduction in deaths and cardiovascular events that ranged from 5 to 10/1000 and harms that ranged from 20 to 30/1000. The benefits were a reduction in severe events with significant morbidity and mortality whereas the harms were mostly not clinically significant.

In summary, the anticipated benefits were large and clearly outweighed the harms. The overall certainty varied from moderate to high, depending on the BP level and agent used.

Evidence-to-decision considerations

The value of antihypertensive therapy is well accepted by most patients, health care providers, health systems, professional societies and government agencies. From a patient's perspective, preventing cardiovascular events is highly valued. However, some individuals who are eligible for antihypertensive treatment may not present to care, may be lost to follow up, or are prescribed a treatment but fail to take/adhere to the treatment. Treatment may be perceived as low value from the perspective of an asymptomatic patient unless the person is convinced of a trade-off between immediate inconvenience/side-effects and potential long-term health gains *(6)*. The patient perception of an unfavourable cost-benefit may be further exacerbated by the requirement for out-of-pocket payment for appointments or medications. Therefore, the GDG considered that although there is important variability in stakeholder values, overall initiation of hypertension (HTN) medications is likely to be feasible and acceptable overall. Given that the barriers to accessing HTN care in low-income settings include low patient health literacy, lack of financial protections, and limited resources *(7)*, the GDG felt that health inequalities would probably be reduced by HTN treatment.

In terms of costs and resource requirements, the GDG acknowledged variability, based on the structure of a country's public health system and its economic status. Other costs, including human resources and medications, were considered moderate, given the benefits. Multiple sources of cost effectiveness are available from various countries, such as Argentina, Nigeria, the USA and UK *(8, 9, 10, 11, 12, 13)*, and for lower thresholds and higher-risk individuals *(14, 15, 16)*. Most cost-effectiveness estimates were clustered below USD 1000 per averted disability-adjusted life year (DALY) – well below the average 2017 GDP per capita for lower-middle income countries of USD 2188 (17), suggesting they could be very cost-effective for this group of countries. HTN treatment (treating all with BP ≥140/90 mmHg) has been shown to be cost-effective and a "best buy" intervention by the Kostova study *(8)*. Treating high-risk/CVD patients with baseline 130–139 mmHg has been shown to be cost effective, but not cost saving (SPRINT cost-effective analyses) *(15)*; value depends on maintaining the intervention effect for more than five years.

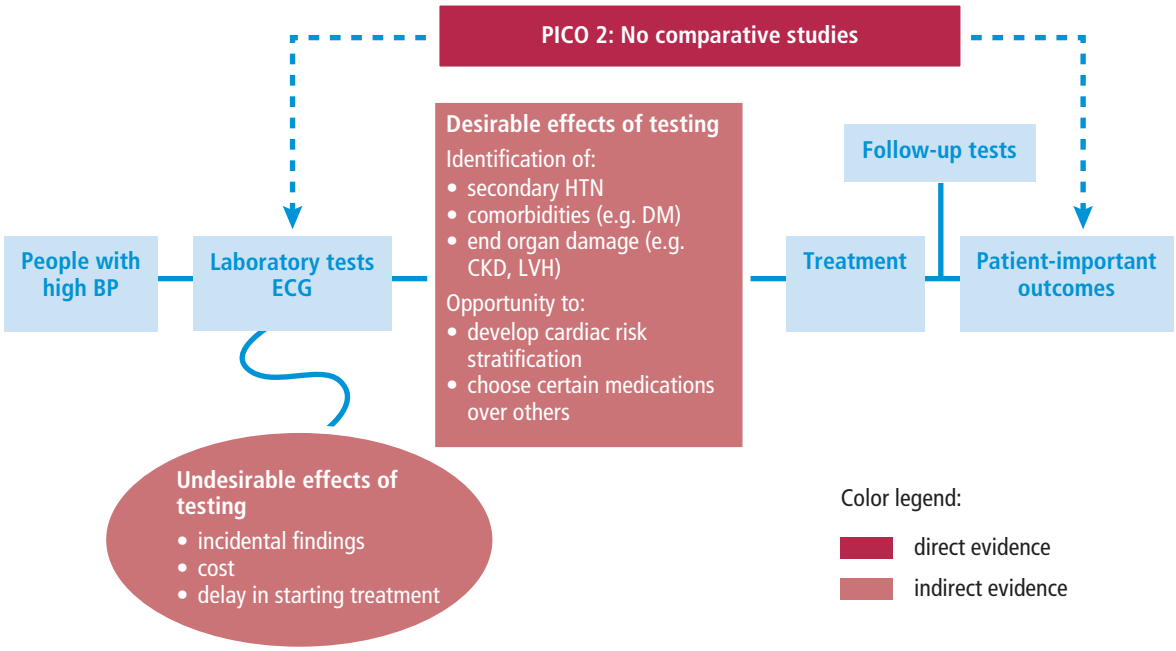
3.2 Laboratory testing before and during pharmacological treatment

2. RECOMMENDATION ON LABORATORY TESTING
When starting pharmacological therapy for hypertension, WHO suggests obtaining tests to screen for comorbidities and secondary hypertension, but only when testing does not delay or impede starting treatment.
Conditional recommendation, low-certainty evidence
Implementation remarks: ▪ Suggested tests include serum electrolytes and creatinine, lipid panel, HbA1C or fasting glucose, urine dipstick, and electrocardiogram (ECG). ▪ In low-resourced areas or non-clinical settings, where testing may not be possible because of additional costs, and lack of access to laboratories and ECG, treatment should not be delayed, and testing can be done subsequently. ▪ Some medicines, such as long-acting dihydropyridine calcium-channel blockers (CCBs) are more suitable for initiation without testing, compared to diuretics or angiotensin-converting enzyme inhibitors (ACEi)/angiotensin-II receptor blockers (ARBs).

Evidence and rationale

Comparative studies that evaluate various testing strategies prior to the initiation of antihypertensive treatment were not identified, despite a search of the literature. Therefore, indirect evidence was sought to evaluate this question. An analytic framework was developed to conceptualize the rationale for obtaining diagnostic testing, such as laboratory tests and electrocardiogram (ECG), in this context (see Fig. 2). This framework identified the four most important reasons for obtaining testing, which are to diagnose secondary HTN, identify comorbidities (e.g. DM), identify end organ damage (e.g. chronic kidney disease (CKD) or left ventricular hypertrophy (LVH)), and for cardiac risk stratification.

Fig. 2 Framework for analysis



In terms of secondary HTN, various studies suggest a prevalence of 5–10% among patients with a diagnosis of HTN and a higher prevalence of 10–30% among patients with particularly high BP (e.g. over 175/115 mmHg) or BP that is resistant to treatment *(18, 19, 20)*. Morbidities and end organ damage that could be identified by testing patients with HTN are also common. One estimation indicates that 23%, 24% and 39% of patients with a diagnosis of HTN have one, two, three or more comorbidities respectively. Common comorbidities among patients with HTN that can be discovered via laboratory testing are hyperlipidaemia and diabetes, which have a prevalence of 56% and 27% respectively *(21)*. Testing at the point of starting HTN medications or for subsequent monitoring can also identify patients who develop certain adverse events after treatment (e.g. hyperkalaemia and acute kidney injury), thus providing a rationale for testing. Testing also had the additional advantage of identifying compelling indications for choosing certain medications over others. For example, identifying diabetes would favour the use of ACEis/ARBs, and identifying hyponatraemia would lead to not starting diuretics. Overall, the desirable effects of testing were judged to be at least moderate.

The framework also identified the most undesirable effects of obtaining testing, which were delay of starting treatment, cost and incidental findings. Delay of treatment was judged to be the most important concern since it can lead to losing the patient for follow up and the potential for adverse cardiovascular (CV) outcomes. Incidental findings on testing were thought to be less important. The undesirable effects of testing were judged to have smaller magnitude. On balance, desirable effects are likely to outweigh undesirable effects. The certainty of evidence across outcome was judged to be very low due to serious concerns about the indirectness of evidence.

Evidence-to-decision considerations

There is uncertainty about patients' values and preferences regarding the issue of testing before starting treatment for HTN. The cost of tests such as electrolytes, creatinine, lipid panel, glucose, HbA1C, urine dipstick, and ECG relative to overall costs of treatment and complications of HTN are small *(22)*. However, in less well-resourced settings, this cost can have a large impact. Furthermore, if additional tests like ECG or 24-hour ambulatory BP monitoring were added, the cost can become a barrier *(23)*. It is unknown whether testing would lead to cost saving or be cost-effective. Testing was judged to be acceptable to most stakeholders, particularly patients and health care providers, and to a lesser extent to those governing health systems. Requiring testing before starting HTN medications can exacerbate health inequities and may not be feasible in low-resource settings.

3.3 Cardiovascular disease risk assessment as guide to initiation of antihypertensive medications

3. RECOMMENDATION ON CARDIOVASCULAR DISEASE RISK ASSESSMENT
WHO suggests cardiovascular risk assessment at or after the initiation of pharmacological treatment for hypertension, but only where this is feasible and does not delay treatment.
Conditional recommendation, low-certainty evidence
Implementation remarks: ▪ Most patients with SBP ≥140 or DBP ≥90 mmHg are high risk and indicated for pharmacological treatment; they do not require cardiovascular (CVD) risk assessment prior to initiating treatment. CVD risk assessment is most important for guiding decisions about initiating pharmacological treatment for hypertension (HTN) in those with lower SBP (130–139 mmHg). It is critical in those with HTN that other risk factors must be identified and treated appropriately to lower total cardiovascular risk. ▪ Many CVD risk-assessment systems are available. In the absence of a calibrated equation for the local population, the choice should depend on resources available, acceptability and feasibility of application. ▪ Whenever risk assessment may threaten timely initiation of HTN treatment and/or patient follow up, it should be postponed and included in the follow-up strategy, rather than taken as a first step to indicate treatment.

Evidence and rationale

The most direct evidence is derived from an individual patient data meta-analysis by Karmali that compared the number of major adverse cardiovascular events (MACE) at five years when using a CVD risk assessment strategy (based on age, sex, body mass index, blood pressure, previous antihypertensive treatment, smoking, diabetes mellitus (DM), and history of CVD) vs BP levels alone for determining which patients receive treatment *(24)*. This analysis suggested that risk assessment can potentially prevent 310 MACE events in 1000 people over five years, which the GDG considered to be a moderate-to-large benefit. However, this evidence was indirect for many reasons, including the effect being dependent on the BP at presentation (graphs diverge at higher level of BP, compared with starting medications without risk assessment) and the fact that these trials did not actually randomize patients to the two strategies sought in PICO question 3 (see Annex 4). Furthermore this evidence should not suggest that people with intermediate risk would not have important treatment benefit.

There was no evidence of the undesirable anticipated effects of starting treatment based on cardiovascular risk assessment. However, delay in initiating care for HTN management and loss to follow up are important considerations, especially in low-resource settings.

The GDG deduced that benefits of risk assessment may not all be attributable to risk assessment per se, but rather to the various treatments provided for risk factors identified during risk assessment. The certainty of evidence across outcome was judged to be very low due to serious concerns about the indirectness of evidence. Overall, the desirable effects of risk assessment at or after initiating HTN medications outweighed the plausible undesirable effects, particularly when risk assessment was deemed not to delay the initiation of treatment.

Evidence-to-decision considerations

There is important uncertainty over the value stakeholders place on conducting a CVD risk assessment prior to starting pharmacological treatment, and it was noted that patient perspectives may vary, depending on the setting. In low-resource settings, patients may focus more on immediate treatment without having to bear additional costs for screening for other risk factors and treating them. Studies have also shown that in high-income countries (HICs) such as the United States, people of a lower socioeconomic status have lower control of blood pressure and higher CVD risk over the years *(25)*. Thus, in low-resource settings, adding one more step before initiating treatment may increase inequities, as those patients who have limited access to health care services may suffer delays in treatment or even end up not receiving HTN treatment at all.

In terms of costs, there is no direct evidence of whether treatment of HTN with or without risk stratification is more cost effective. The cost of implementation of CVD risk assessment should also account for capacity building of health care providers and the time taken to do so for each patient.

Cost of testing and delay in initiating care can be significant following a CVD risk stratification strategy in low-resource settings. Modelling by Gaziano et al. showed significant cost reduction using CVD risk-stratification before initiation of treatment in low-resource settings. However, screening costs, including the cost of obtaining risk-factor information, productivity costs due to work loss, care costs and travel time were not included in the analysis *(26)*.

A meta-analysis showed that proportional relative risk reduction in major CVD events from BP lowering did not differ substantially with the presence or absence of previous CVD events, coronary heart disease, or cerebrovascular disease. Hence, the absolute benefit of blood pressure lowering would be greatest in those with the highest absolute risk of CVD *(27)*.

3.4 Drug classes to be used as first-line agents

To develop a recommendation that is practical and implementable by end-users, the evidence-to-decision frameworks of PICO questions 4 and 5 (see Annex 4) were used to develop one recommendation.

4. RECOMMENDATION ON DRUG CLASSES TO BE USED AS FIRST-LINE AGENTS
For adults with hypertension requiring pharmacological treatment, WHO recommends the use of drugs from any of the following three classes of pharmacological antihypertensive medications as an initial treatment: **1. thiazide and thiazide-like agents** **2. angiotensin-converting enzyme inhibitors (ACEis)/angiotensin-receptor blockers (ARBs)** **3. long-acting dihydropyridine calcium channel blockers (CCBs).**
Strong recommendation, high-certainty evidence
Implementation remarks: ▪ Long-acting antihypertensives are preferred. ▪ Examples of indications to consider specific agents include diuretics or CCBs in patients over 65 years or those of African descent, beta-blockers in ischaemic heart disease, ACEis/ARBs in patients with severe proteinuria, diabetes mellitus, heart failure or kidney disease.

Evidence and rationale

Data from 32 systematic reviews were used to derive evidence on benefits and harms of various medication classes (19 for comparisons against placebo and 13 for head-to-head comparisons). These reviews summarized the results of a many large randomized trials (Web Annex A). The anticipated benefits were considered to be large. Mortality and major adverse cardiac events (MACE) reduction per 1000 treated people for the various classes were 3 and 14 (low-dose thiazide), 12 and 39 (high-dose thiazide), 23 and 48 (ACEi), 8 and 23 (CCB), 2 and 8 (beta-blockers) and 14 and no data for MACE (ARBs) respectively. The anticipated adverse events were judged to be moderate. Compared to placebo, 60 and 100 additional adverse events per 1000 treated people were observed for thiazides and beta-blockers respectively. Withdrawal from ACEi treatment and cough per 1000 treated people were 12 and 26 respectively. A systematic review of studies of pharmacotherapy for HTN in sub-Saharan Africa showed a rate of side-effects of CCB of 6% (headache), 2% (dizziness) 2% (ankle oedema) *(28)*.

In terms of the head-to-head comparisons among various classes, there was a smaller body of evidence, with less data available on hard endpoints and patient-important outcomes. Comparisons showed overall minimal differences in SBP or DBP. For example, ACEis/ARBs vs CCBs differed by less than 2 mmHg, and so did comparisons between ACEis/ARBs vs thiazide or ACEis vs ARB. There were more stroke events with beta-blockers than CCBs or ACEis/ARBs.

The anticipated benefits clearly outweighed the potential harms for three classes of medications: thiazide and thiazide-like agents, ACEis/ARBs, and long-acting dihydropyridine CCBs. The adverse events of these three classes were infrequent, usually mild, and can be managed or another agent can be substituted. The amount of BP reduction appeared to be a more major determinant of reduction in CV events than the choice between these three classes of antihypertensive medications, as was shown in several landmark trials (ALLHAT, VALUE, CAMELOT trials) *(29, 30, 31)*. This balance of benefits and harms was not as clear for beta-blockers as a first choice for HTN management.

In terms of potential subgroups of patients that may benefit more from specific medication classes, ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) suggested greater BP reduction in individuals of African descent with chlorthalidone than lisinopril, and that stroke was significantly less likely with the diuretic than with the lisinopril in this group of patients than in those of Caucasian ethnicity *(32)*. Other studies suggested benefit of diuretics or CCBs in patients over 65 years of age or of African descent, beta-blockers in patients with HTN who are post-myocardial infarction, ACEis/ARBs in diabetes mellitus, heart failure or kidney disease *(33, 34)*. Diuretics were likely to be the most efficacious medications, and CCBs the least efficacious medications for the prevention of heart failure.

The overall certainty of evidence varied from high to moderate for these three classes of medications when compared against placebo. It was noted that diuretic trials were older and practice patterns may have changed over time, and that the severity and stage spectrum of diabetes mellitus and chronic kidney disease varied in the available trials. In addition, evidence supporting the efficacy of antihypertensive drug therapy is derived from trials conducted in adults at high risk for CVD/atherosclerotic CVD. Since CVD risk increases with higher levels of BP, and given that risk factors for CVD tend to track together, the assumption of greater benefits using CVD risk could be attributed to this.

Evidence-to-decision considerations

The value of antihypertensive therapy is well accepted by most patients, health care providers, health systems, professional societies and government agencies. From a patient's perspective, preventing cardiovascular events is highly valued. However, some individuals who are eligible for antihypertensive treatment may evade efforts aimed at treatment or are prescribed a treatment but fail to take/adhere to the treatment. The asymptomatic nature of the disease and concern about adverse events are the likely driver for this perspective. Interviews of patients in England suggested greater acceptance of antihypertensive drug therapy with higher socioeconomic status.

In one study, as many as 35% of the Caucasians and 20% of the South Asians in the two lowest socioeconomic categories told their interviewer that they would not accept antihypertensive drug therapy *(35)*. Shahaj et al. *(6)* synthesized six qualitative and 29 quantitative reviews and identified a range of individual and social factors that affect treatment adherence, including familial (lack of support, need for separate meals), and environmental (sense of security, local amenities, healthy food availability). A review by Fragasso et al *(36)*. suggested that quality of life on antihypertensive therapy is an important issue because clinicians are asked to initiate drug therapy in mostly asymptomatic patients who are never happy to become, instead, symptomatic because of side-effects. Therefore, the GDG considered that there is important variability in stakeholder values, but overall initiation of HTN medications is likely to be feasible and acceptable overall. Considering the ample literature on disparities in adherence to BP medication regimes and cardiovascular outcomes based on race or socioeconomic status, treatment was judged to reduce health inequities.

In terms of costs and resource requirements, thiazide-like agents, ACEis/ARBs and long-acting dihydropyridine CCBs are available as generic drugs, are simple to manufacture, and should be available at low cost globally. Other costs related to workforce requirements, provision of infrastructure, laboratory testing, lost work time etc. are real but modest. Numerous modelling studies demonstrate cost effectiveness of antihypertensive therapy, which is especially beneficial in LMICs where large numbers of adults have untreated HTN, as long as medications are available at low cost. Models were available from many countries, including Bangladesh, Ghana and Nigeria *(37, 38, 39, 40)*.

3.5 Combination therapy

To develop a recommendation that is practical and implementable by end-users, the evidence-to-decision frameworks of PICO questions 6, 7 and 8 (see Annex 4) were used to develop one recommendation.

5. RECOMMENDATION ON COMBINATION THERAPY
For adults with hypertension requiring pharmacological treatment, WHO suggests combination therapy, preferably with a single-pill combination (to improve adherence and persistence), as an initial treatment. Antihypertensive medications used in combination therapy should be chosen from the following three drug classes: diuretics (thiazide or thiazide-like), angiotensin-converting enzyme inhibitors (ACEis)/angiotensin-receptor blockers (ARBs), and long-acting dihydropyridine calcium channel blockers (CCBs).
Conditional recommendation, moderate-certainty evidence
Implementation remarks: ▪ Combination medication therapy may be especially valuable when the baseline BP is ≥20/10 mmHg higher than the target blood pressure. ▪ Single-pill combination therapy improves medication-taking adherence and persistence and BP control.

Evidence and rationale

The GDG developed three PICO questions to address: monotherapy vs combination therapy as a first-line treatment for HTN, a comparison of the various combination therapies, and a comparison of single-pill combinations vs multiple-pill combinations. These three questions were addressed separately in the evidence profiles and evidence-to-decision framework, but eventually led to one recommendation. The evidence base consisted of six, seven and eight systematic reviews respectively (Web Annex A).

Evidence summaries demonstrate several comparisons of combination therapy to monotherapy. Data on mortality, MACE and other hard endpoints were imprecise. Combination therapy lowered SBP more than monotherapy did (e.g. standard dose CCB combined with ARB vs high dose CCB; or ACE and ARB combination vs either drug class alone) and had fewer adverse events (standard dose CCB combined with ARB vs high dose CCB). Data on cardiovascular outcomes are limited from randomized trials. A large nonrandomized study from Italy (125 635 patients, age 40–85 years) evaluated those who started antihypertensive treatment with one drug vs a two-drug single-pill or free combination. Propensity score adjusted analysis suggests that an initial two-drug single-pill or free combination was associated with significant reductions in the risk of death (20%, 11–28%) and hospitalization for cardiovascular events (16%, 10–21%) compared with initial monotherapy *(41)*. Combination antihypertensive therapy may be associated with fewer side-effects due to use of lower doses of each drug.

A comparison of the various combination therapies suggested overall effectiveness of combination therapies that contained the three drug classes of diuretic, ACE/ARB and CCB. Other desirable effects of a combination therapy are improved treatment adherence and persistence. However, many of these studies used a single-pill combination, thereby confounding the question of monotherapy vs combination therapy. A meta-analysis compared adherence and persistence between groups of patients taking antihypertensives as single-pill combinations vs free-equivalent components based on 12 retrospective database studies. Adherence, measured as the mean difference in medication possession ratio, was 8–14% higher with a single-pill combination. Persistence was also twice as likely *(42)*. A second systematic review demonstrated that simplifying dosing regimens results in significant improvements in medication adherence, ranging from 6% to 20% *(43)*.

The desirable effects of greater adherence/persistence, improved BP control, and potentially improved clinical outcomes of combinations of the three classes of antihypertensive therapy compared outweigh the undesirable effects such as side-effects, particularly when provided as a single-pill combination. The overall certainty in evidence was low across the outcomes of interest, noting that evidence was limited in terms of hard endpoints.

Evidence-to-decision considerations

In terms of stakeholder values and preferences about monotherapy vs combination therapy or the various combination therapies, data were minimal. No important variability in values was expected with regard to the critical outcomes. A systematic review demonstrated that simplifying dosing regimens results in significant improvements in medication adherence, ranging from 6% to 20% *(43)*. Considering the comparative ease of using a single-pill combination over multiple-pill combinations, and the anticipated impact on adherence and persistence, the GDG judged that from a patient perspective the single-pill option will be favoured by most.

Combination therapy is accompanied initially by a moderate increase in resource requirements, such as procurement, supply chain, and direct medication costs. Some combinations may be expensive, or not allow for exact dosing of both agents. However, the net benefit of improved BP control and reduction of major events associated with the hypertensive process compared to the increase in cost is large. BP control is also likely to be achieved sooner with combination therapy. Many modelling studies that evaluated combination vs monotherapy used a fixed dose (thereby not truly addressing the question). One model from Japan used data from randomized trials and compared low-dose combination therapy of controlled-release nifedipine (20 mg/day) plus candesartan (8 mg/day) vs titrated monotherapy of

candesartan. In the combination therapy group, higher efficacy and lower incremental treatment cost (dominance) were observed when compared to the monotherapy group *(44)*. A retrospective cohort study that used the 2008–2012 BlueCross BlueShield of Texas claims suggests that mean annual drug utilization costs were highest for a single-pill combination strategy. However, disease-related inpatient services utilization costs were lower compared with the up-titration strategy, which may offset initial costs *(45)*. In one model from China, olmesartan/amlodipine as a single pill was dominant, compared with olmesartan and amlodipine free combination and valsartan/amlodipine single-pill combination *(46)*. In a second study, there was a reduction in the cost of therapy of 33%, with a saving of USD 19 per patient/month after switching from free combination to the single-pill combination *(47)*.

Since single-pill combination therapy increases medication adherence and persistence, which could improve HTN control rates and decrease major clinical events, the impact on health equities is expected to be favourable. In terms of acceptability, combination therapy, including in a single-pill form, can initially be met with scepticism among stakeholders, including health care providers. However, this initial scepticism may improve once BP control improves. Despite effective, safe, affordable, and available pharmacological antihypertensive agents, the control rates of HTN are dismal worldwide, and over the last 5 to 10 years have been decreasing in some HICs, and in LMICS, in tandem with increasing major cardiovascular events. Over 30% of the world population has HTN and only 13.8% of cases are considered controlled (48). One major reason for this poor level of control (one in seven) is that most patients only receive monotherapy, whereas empirical evidence demonstrates that most patients require two drugs or more to achieve optimal and sustained control *(44, 46, 49, 50, 51, 52)*. The rationale for recommending a combination therapy, particularly in a single-pill approach, is based on the following considerations:

- most individuals with HTN will eventually require two or more antihypertensive agents to achieve BP control;
- the combination of two agents from complementary classes yields greater BP-reduction efficacy (at the least additive of the two chosen agents);
- lower doses of each agent are needed, which results in a reduction of side-effects and the fact that use of complementary classes of antihypertensive agents may mitigate the side-effects of each agent;
- adherence and persistence are increased; and
- simplified logistics can lead to fewer stock-outs and a reduced pharmacy inventory *(53, 54)*.

In terms of feasibility, a study from India compared prices of antihypertensive single-pill combinations and equivalent single-agent pills in the private health care sector. The results suggested that manufacturers have priced the combination higher than the price of its components. These data demonstrate that the price of combination pills could be lowered to match the combined price of the component, and that manufacturing costs and market forces do not present a barrier to the implementation of antihypertensive combination pills *(55)*. Thus, the intervention is likely feasible to implement. The GDG acknowledged some challenges to single-pill combinations, such as limited flexibility in modifying the doses of individual components, and difficulty in attributing side-effects to one of its components *(56)*.

Although randomized trials addressing this issue are not abundant, and those available are not sufficiently large or conducted for a long enough period to clearly address differences in major clinical events, the initial combination treatment approach has been in place for over 15 years in large health systems, such as the Kaiser Permanente system in the United States *(57)* and is a major component of the WHO Global HEARTS Programme and the PAHO HEARTS in the Americas Initiative *(53)*. Recently, combination antihypertensive medications in a single pill have been added to the WHO Essential Medicines List *(49)*. This approach has demonstrated general acceptance by government, public, and private stakeholders and is demonstrating success in increasing HTN control rates worldwide.

3.6 Target blood pressure

6. RECOMMENDATION ON TARGET BLOOD PRESSURES
WHO recommends a target blood pressure treatment goal of <140/90 mmHg in all patients with hypertension without comorbidities.
Strong recommendation, moderate-certainty evidence
WHO recommends a target systolic blood pressure treatment goal of <130 mmHg in patients with hypertension and known cardiovascular disease (CVD).
Strong recommendation, moderate-certainty evidence
WHO suggests a target systolic blood pressure treatment goal of <130 mmHg in high-risk patients with hypertension (those with high CVD risk, diabetes mellitus, chronic kidney disease).
Conditional recommendation, moderate-certainty evidence

Evidence and rationale

The evidence base consisted of five systematic reviews as well as a review of the SPRINT trial *(58)*. Evidence profiles were constructed for various BP treatment targets, based on age and comorbidities (Web Annex A).

The desirable effects of lower target BP (per 1000 treated patients) were: a reduction in mortality of 27 (for SBP <120 vs <130–139) and of 7 (for SBP 140/90 vs 150–160); a reduction in cardiovascular mortality of 40 (for SBP <120 vs <130–139) and 6 (for SBP 140/90 vs 150–160); and a reduction in stroke of 17 (for SBP <130 vs <140). The undesirable effects (increase in serious adverse events per 1000 treated patients) were 20 (for SBP <130 vs <140) and 1 (for SBP <120 vs <130–139).

Summary results from a systematic review focusing on adults 65 years and older by Murad et al *(59)*. suggests that treatment to a lower BP target in individuals 65 years or older leads to a significant reduction in all-cause and CVD mortality, chronic kidney disease, myocardial infarction, or stroke outcomes. Similar conclusions were provided by another systematic review by Reboussin et al *(60)*. Neither of these meta-analyses was able to account for the high risk of patients enrolled in the available trials – at least in SPRINT and ACCORD *(11, 61)*. Therefore, the GDG cautions against applying this evidence to lower-risk patients with raised BP or HTN – specifically, those not meeting trial eligibility criteria for SPRINT, ACCORD or SPS3 *(62)*. Network meta-analyses found a similar direction of effect but more optimistic effect sizes regarding intensive treatment benefit *(63, 64)*.

In patients with comorbidity (CAD, DM, CKD) there is consistent benefit with lower targets (variable thresholds); however, data in these subgroups were imprecise and the evidence was less certain. Adverse events such as dizziness in intensive control group and ischaemia in patients with coronary artery disease can shift the balance of benefits and harms in those aged 65 years or older. Concern about lower adherence due to the need for extra patient and provider effort to reach lower targets should also be balanced against intensive control. The overall certainty of the evidence was judged to be moderate, with large benefits and moderate harms. The GDG made a judgement that the desirable effects outweigh the undesirable effects at a treatment goal of <140/90 mmHg in all patients with HTN without comorbidities and of <130 mmHg in high-risk patients with HTN – those with high CVD risk, diabetes, chronic kidney disease.

Evidence-to-decision considerations

From a patient perspective, HTN is often a silent disease and patients may not take antihypertensive medications as directed because the positive effects of these medications are not as obvious as potential side-effects *(61)*. Society and patients want to avoid premature mortality or disability. Serious adverse events are also feared, but their duration and severity are often not well characterized in trials. Lower targets are likely acceptable to other stakeholders, such as governments and providers, though there are usually several competing priorities and interests – especially the more acute demands of, and a higher priority placed on, acute conditions and health emergencies. Many well-known barriers to access to HTN care in low-income settings exist *(6)*. Investment in the primary health care platform required for effective HTN management is often a challenge. Countries with low rates of HTN control using more conservative BP thresholds may feel burdened by any request to set more ambitious BP treatment goals, even if only in selected high-risk patients.

Intensive treatment for selected patients adds complexity for health workers; emphasis on team-based care in low-resource settings means that simple, protocolized care is needed. Intensive treatment for some patients complicates treatment protocols and may lead to decisional overload, especially for health workers with more limited training and/or autonomy.

On the other hand, strict BP targets in the general population with HTN are likely to be less acceptable to stakeholders. Most available evidence is derived from high-risk patients receiving intensive treatment and not the general population living with HTN. Treating BP will reduce health inequity because preventing CV events reduces mortality across the population. Uncontrolled HTN might be over-represented in vulnerable populations. Therefore, improvement of HTN treatment and control through better treatment and a lower BP target could reduce long-standing inequality.

Regarding costs, intensive BP treatment in the SPRINT trial meant one additional medication, one additional office visit, and one additional laboratory test evaluation on average, and additional titration visits per participant over 3.25 years, compared with standard treatment. In the United States, this translates to about USD 13 000 more per patient over their remaining lifetime *(14, 15)*. Health care costs are much less in countries other than the United States. Treating to lower BP targets will have diminishing returns in progressively lower-risk patients as the magnitude of benefit becomes smaller. A cost-effectiveness study of screening and optimal management of HTN, diabetes mellitus and chronic kidney disease in an Australian setting found that an intensive management of previously uncontrolled HTN compared with usual care resulted in an incremental cost-effectiveness ratio of AUD 2588. The study does not specify the target BP for the comparisons *(65)*. A SPRINT trial health economic analysis provided similar inferences *(48, 50)*.

3.7 Frequency of re-assessment

7. RECOMMENDATION ON FREQUENCY OF ASSESSMENT
WHO suggests a monthly follow up after initiation or a change in antihypertensive medications until patients reach target.
Conditional recommendation, low-certainty evidence
WHO suggests a follow up every 3–6 months for patients whose blood pressure is under control.
Conditional recommendation, low-certainty evidence

There was a minimal number of comparative studies that evaluated different follow-up lengths after initiation of HTN medications. One randomized controlled trial compared a follow-up interval of three months to an interval of six months in family practice clinics in Canada. Participants (age 30–74 years) had essential HTN that was controlled for at least three months before entry into the study. Mean BP, control of HTN, patient satisfaction and adherence to treatment were similar between the two groups *(66)*. A retrospective population-based cohort study of family-practice clinics in the UK *(67)* studied 88 756 adults with HTN (1986–2010). This study showed that in patients newly diagnosed with HTN, those with >1.4 months prior to initiation of treatment had a hazard ratio of 1.12 (1.05–1.20) for a major adverse cardiovascular event (MACE) compared to those who started treatment at <1.4 months. For patients who were initiated on treatment, those who waited >2.7 months before re-evaluation had a hazard ratio of 1.18 (1.11–1.25) for MACE compared to those reassessed at <2.7 months. In addition, when reviewing protocols of large HTN trials that demonstrated important improvement in cardiovascular events with BP control, such as ACCORD and SPRINT, the initial length of time to follow up was one month *(68, 69)*. This evidence indirectly suggests the appropriateness of this initial follow up in settings that conferred important benefit.

The anticipated desirable consequences of shorter follow up are better BP control and monitoring of side-effects, and perhaps improved adherence. Longer follow-up times are expected to lead to loss to follow up. A systematic review of the impact of interventions to improve medication adherence in adults prescribed antihypertensive medications suggested a decrease in adherence with an increase in time between intervention and follow up *(70)*. The undesirable consequences of shorter follow up are the burden on patients and the health system. Certainty relating to these effects is very low.

The GDG found no evidence related to the question of the optimal follow-up time after the point that the treated HTN patient achieves stable blood pressure control.

Evidence-to-decision considerations

Data on what patients consider significant in terms of the length of follow up after initiation of HTN medications are lacking. Many patients, particularly those aged 65 years or older, or who live alone, are likely to be reassured by more frequent monitoring of BP, which can identify early signs of clinical deterioration and provide a sense of security *(71)*. However, younger asymptomatic patients may have the opposite perspective and find that frequent monitoring interferes with work and family responsibilities. Telemonitoring may reduce the need for follow up, especially for patients living in areas remote from health care facilities. However, despite existing evidence on the effectiveness of telemonitoring for patients with HTN, there is no empirical evidence of its long-term outcomes or generalizability to patients with various backgrounds and educational levels *(72)*.

Data on costs, resources and cost-effectiveness were unavailable. Frequent follow up is anticipated to be associated with additional resource requirements, which may be offset by improved adherence, BP control and improved outcomes that are important to patients. Burden on the health system may be reduced by involving nonphysician providers in follow up.

The WHO GDG considered a one-month follow up after initiation of medications for HTN to be a reasonable approach, whereas intervals of 3 to 6 months can be applied when patients' BP is close to the target and stable. Due to the lack of comparative data, these recommended intervals should be viewed as suggestions and may be modified, based on feasibility and other contextual factors. Such intervals were judged to be feasible and acceptable to key stakeholders. The impact of such follow-up lengths on health equity is unclear.

3.8 Administration of treatment by nonphysician professionals

8. RECOMMENDATION ON TREATMENT BY NONPHYSICIAN PROFESSIONALS
WHO suggests that pharmacological treatment of hypertension can be provided by nonphysician professionals such as pharmacists and nurses, as long as the following conditions are met: proper training, prescribing authority, specific management protocols and physician oversight.
Conditional recommendation, low-certainty evidence
Implementation remarks: ▪ Community health care workers (HCWs) may assist in tasks such as education, delivery of medications, blood pressure (BP) measurement and monitoring through an established collaborative care model. The scope of hypertension care practised by community HCWs depends on local regulations and currently varies by country. ▪ Telemonitoring and community or home-based self-care are encouraged to enhance the control of BP as a part of an integrated management system, when deemed appropriate by the treating medical team and found feasible and affordable by patients. ▪ Physician oversight can be done through innovative methods such as telemonitoring or similar to ensure access to treatment is not delayed.

Evidence and rationale

PICO question 11 (see Annex 4) addressed BP management by nonphysician health care workers (HCWs) as well as self-management by patients. The evidence base for this question consisted of 11 systematic reviews (Web Annex A). The available evidence focused on evaluating care models in which BP control was managed by pharmacists, nurses, dietitians, and community HCWs. The outcome assessed in these studies were BP level and control. There was no data on cardiovascular events. Although the certainty of evidence was in general low, the magnitude of effect showed better control in 91–264 more patients per 1000 (pharmacist studies) and an SBP/DBP reduction of 1–8 mmHg (nurse/HCW/dietitian studies). No study showed that nonphysician management was inferior to physician management.

A systematic review by Greer et al., showed that pharmacist-managed care led to better BP control (relative risk 1.44 or 170 more controlled per 1000) with no obviously reported difference in adherence, clinical events or quality of life *(73)*. A systematic review by Anand has shown that in LICs and MICs, task sharing with pharmacists led to reductions of 8 mmHg SBP and 3.74 mmHg DBP. Similar results were yielded by task sharing with nurses (5.34 mmHg lower), dieticians (4.67 mmHg lower), and community HCWs (3.67 mmHg lower) *(74)*. Data on undesirable effects (harms) were unavailable, which may be due to publication bias, or reflect minimal harms.

In terms of self-management, a systematic review by Tucker *(75)* shows that self-monitoring by patients led to a 3.24 mmHg lower level SBP and 1.5 DBP, both statistically significant, and better BP control, as long as self-monitoring was remotely managed by a HCW. However, the study limitation was the inability to adequately blind participants to the intervention. There was minimal evidence about self-titration on BP medications.

The GDG also concluded that since the evidence was from HICs, it may be less applicable to other settings and that training of nonphysician HCWs varies considerably between countries. Overall the certainty of evidence was low, with large anticipated desirable effects and a small magnitude of undesirable effects.

Evidence-to-decision considerations

There is significant variability in patient and provider perspectives. Overall, society and patients want to reduce the risk of premature mortality or morbidity. Most of the available quantitative data were focused on remote monitoring and not specifically on whether patients preferred BP being managed by physicians vs other providers, which was the primary question. Limited information provided mixed results, with some patients appreciating some applications of self-care while others were concerned that being managed by others could harm the patient–doctor relationship, but these comments were related to use of home-monitoring devices. In some studies in which BP was managed by nonphysicians, there was good patient satisfaction and high retention, suggesting at least willingness, if not a preference, to have BP managed by nonphysicians *(76, 77)*.Conversely, in-depth interviews with a sample of patients in the UK explored nurse and pharmacist prescribing and demonstrated that patients had concerns about clinical governance, privacy and whether sufficient space was available to provide the service in community pharmacies. Participants had less concern about nursing management *(78)*. Another study from Scotland explored patients' perspectives on pharmacist prescribing and reported high patient satisfaction, but 65% stated that they would prefer to consult a doctor *(79)*. Presumably, health inequities are reduced, since task shifting in the public sector increases access to those using public health vs private health. Increasing access in underserved areas can improve inequities.

Regarding costs, Jacob et al. *(80)* synthesized data from 31 studies (24 from the US) and suggested that studies that use community team approaches project a cost around USD 200/person/year to implement, but with cost-savings for prevention of CVD outcomes such that net costs had a median cost of USD 65/person/year, with 10 studies indicating negative or cost-savings overall. Most cost/quality-adjusted life year (QALY) estimates were between USD 3888 and USD 24 000/QALY, with pharmacist-led programmes being more cost-effective than nurse-led ones. Only two were >USD 50 000/QALY out of 28 studies.

Most of the remaining cost data presented were related to self-monitoring and not to the question of physician-led vs nonphysician-led care. However, if it is assumed that nonphysician salaries are lower, then potentially costs will be lower, but that assumes that only limited effort by physicians is involved in any oversight of nonphysicians. Kulchaitanaroai et al. found similar results with a physician–pharmacist collaborative system *(81)*.

The two available analyses, by Jacob et al. and Kulchaitanaroai et al., focused on team-based interventions as opposed to specifically physician vs other provider, and it is not clear if incremental cost-effectiveness ratios fit countries in all economic categories, nor whether the countries' willingness- to-pay thresholds were analysed. All values appear to be below USD 50 000/QALY. For the US, the results were highly cost-effective, with most estimates well under USD 50 000/QALY but it remains unclear exactly how these may be translated to countries in lower economic categories. Even at USD 10 000/QALY, however, this would be acceptable for most MICs, though perhaps not for all LICs. However, if the costs were the same or lower in programmes led by nurses or pharmacists compared to those led by physicians then cost-saving was likely.

The GDG proposed four conditions that must be met for nonphysician-prescribing of antihypertensives. These focused on the prescribers having proper training, prescribing authority in their locale, working within specific management protocols and having physician oversight. Community HCWs were suggested as personnel who could assist with tasks such as education, delivery of medications, BP measurement and monitoring through an established collaborative care model.

Telemonitoring supervised by HCWs, and community- or home-based self-care, were considered as tools to enhance BP control as part of an integrated management system.

4 Special settings

4.1 Hypertension in disaster, humanitarian and emergency settings

Hypertension (HTN) is seen in a range of humanitarian crises and disaster settings (natural or humanmade). This includes, but is not limited to, the wars in Syria and Iraq, the impact of the Great East Japan Earthquake and Hurricane Katrina, and the living conditions of Palestinian refugees. The burden of HTN on those populations can be considerable *(82)*. There are very little data on HTN control, access to care and treatment, and patient understanding of HTN from Africa and Asia (except Japan), despite protracted refugee situations on these continents. Violent and protracted conflicts are disastrous to civilian populations and their health care systems, and result in interruptions to treatment and care *(83, 84)*. Armed conflicts are associated with increased short-term and long-term cardiac morbidity and mortality and increases in blood pressure (BP) *(85)*. Following exposure to conflict, research in military populations shows that post-traumatic stress disorder and severe injury are independent risk factors for the development of HTN *(86)*. The rates of treatment ranged from 53.4% to 98.1% of patients with HTN in this population *(87, 88)*.

There are currently no data regarding target BP or the best antihypertensive agent to treat disaster-related HTN. Opinion-based recommendation is that the target BP control level should be less than 140 mmHg for SBP and less than 90 mmHg for DBP. According to Kario et al, long-acting CCBs are preferred because they are metabolically neutral, and best at reducing BP variability, which is an independent predictor of clinical outcomes, especially stroke. In addition, the BP-lowering effect of long-acting CCBs is dose-dependent, and the degree of BP reduction that can be anticipated from these agents is known *(89)*. Despite the challenges of working in humanitarian settings, several agencies have produced guidelines for the identification and management of HTN. The WHO's Interagency Emergency Health Kit has included a supplementary module with antihypertensive medications since 2017, but it is unclear how widely these are being used *(90, 91)*. According to a personal communication from a physician who treated HTN in Syrian refugees, the treatment was variable, and dependent on whatever drug samples were available in the clinic. They had limited choices, including atenolol, lisinopril, and verapamil. Treatment was tailored to the patient's history. For example, patients with a history of coronary artery disease received atenolol and lisinopril, patients with diabetes received lisinopril, and patients with migraine received verapamil.

Assessment of HTN and appropriate resourcing to treat it should be a priority for agencies providing emergency and longer-term care for patients after or during humanitarian crises to prevent significant mortality and morbidity. Further studies are needed to accurately estimate prevalence of HTN in crisis-affected populations throughout the world and to evaluate the best treatment approach for this population.

Humanitarian crises and disaster settings (natural or humanmade) can affect health care and services in many different ways. A list of potential barriers that can affect the management of individuals with hypertension is as follows:

- significant decline of living standards
- loss/destruction of health care facilities
- flight of medical personnel causing shortage of medical care providers
- severe shortage of medicines
- lack or absence of essential supplies, equipment and materials
- compromise of the provision of primary and secondary health care
- interruption of water, food and electricity
- lack of morbidity and mortality data due to destruction of information systems and data collection
- high psychological stress burden on both general population and health care personnel.

4.2 COVID-19 and hypertension

Almost all available evidence suggests that hypertension increases the risk of severe COVID-19, defined as admission to intensive care, clinically defined severity or a combination of these; or mortality. It was sometimes unclear, however, whether this risk was independent of other risk factors *(92)*. Initial reports have identified higher rates of HTN among severely ill, hospitalized COVID-19 patients, with overall HTN rates of 50–56% *(93, 94)*. It had been unclear if this relationship was causal or confounded by age and other comorbidities associated with HTN, including obesity, diabetes and chronic kidney disease. Concerns regarding use of angiotensin-converting enzyme inhibitors (ACEis) in these patients were raised due to identification of angiotensin-converting enzyme 2 (ACE2), the monocarboxypeptidase that inactivates angiotensin II and thereby counters the activation of the classic renin–angiotensin–aldosterone system (RAAS), as the functional receptor for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *(95, 96)*. The WHO conducted a rapid review of evidence related to the use ACEis or ARBs in COVID patients which identified 11 observational studies. No studies were found that were designed to directly assess whether ACEis or ARBs increase the risk of acquiring COVID-19. After adjustment for confounders, history of ACEi or ARB use was not found to be associated with increased severity of COVID-19 illness. There were no studies that addressed the potential benefits and harms of initiating ACEis or ARBs as treatment for patients with COVID-19 *(97)*. Accordingly, discontinuation of ACEis or ARBs may yield worse outcomes than continuation of their use in patients with a diagnosis of COVID-19. In contrast to the uncertainty about the potential benefit of initiating RAAS blocker use in patients with COVID-19, there is a clear potential for harm in withdrawing these agents in high-risk COVID-19 patients with established myocardial injury, HTN or heart failure *(96)*. Most of the world's professional societies either recommend or strongly encourage continuing ACEis/ARBs in COVID-19-infected patients *(98)*. Further research that will address key unanswered questions about the role of the RAAS in the pathogenesis and possible treatment of COVID-19 and other coronavirus-based diseases is urgently needed. Prospective studies – in particular, ongoing randomized, placebo-controlled trials such as the Ramipril for the Treatment of COVID-19 (RAMIC) trial (ClinicalTrials.gov number, NCT04366050) may provide clearer insight regarding the effect of ACEis or ARBs in patients with COVID-19.

4.3 Pregnancy and hypertension

Hypertension, including chronic HTN, gestational HTN, pre-eclampsia, and eclampsia, is a very common medical condition in pregnancy *(99)*. Due to the adverse consequences of increased morbidity and mortality to both the women and fetus, HTN in pregnancy must be diagnosed, treated (when appropriate), and followed up diligently. It is important to note that up to 10% of pregnancy-related deaths are attributed to HTN, and its presence in pregnancy leads to long-term adverse cardiovascular consequences. Unfortunately, hypertensive disorders of pregnancy are markedly increasing *(100, 101)*. For instance, in the United States between 1998 and 2006, hypertensive disorders in pregnancy increased from 6.7% to 8.3%, chronic HTN in pregnancy increased from 1.1% to 1.7%, and pre-eclampsia/eclampsia from 0.9% to 1.2%. The potential serious consequences of HTN and pregnancy and the contraindication in pregnancy of some of the commonly prescribed pharmacological antihypertensive medications discussed below should be discussed with women who are or could become pregnant.

The normal haemodynamic state of pregnancy is one of systemic vasodilation accompanied by an increase in cardiac output and decrease in total peripheral resistance. This results in a normal decrease in BP in the second trimester. HTN in pregnancy is generally diagnosed when BP is ≥140 mmHg and/or ≥90 mmHg on at least two occasions, at least six hours apart. Chronic HTN is defined as a diagnosis of HTN before 20 weeks gestation, while gestational HTN is defined as a diagnosis of HTN at 20 weeks or later. Pre-eclampsia and eclampsia are pregnancy-specific medical conditions requiring immediate and specific medical management.

While BP treatment thresholds for HTN in pregnancy continue to change, it is generally recommended for both chronic and gestational HTN that pharmacologic treatment be initiated when the SBP is ≥160 mmHg and/or the DBP is ≥105 mmHg. In chronic HTN, frequently the woman has already been diagnosed with HTN prior to the pregnancy and thus may already be on chronic antihypertensive pharmacological therapy. In this case, the current regimen may be continued, with the caveat that the medication regimen may have to be changed to preferred medications, and certain antihypertensive medications that are contraindicated in pregnancy must be discontinued. The recommended treatment BP goal/target also has been subject to debate and is changing. For instance, achieving a lower BP target (DBP of 85 mmHg vs 100 mmHg) has recently been shown to decrease the maternal development of severe HTN while not increasing maternal or fetal risk. If target organ damage is present, initiating antihypertensive pharmacological treatment at a DBP of ≥90 mmHg should be considered.

As with most, if not all, other medical conditions requiring pharmacological treatment during pregnancy, the treatment considerations in HTN are no different from those of non-pregnant adults. Thus, since medications are not studied specifically for efficacy and safety in pregnancy, medication selection is usually based on long-term clinical use and experience. This usually means older medications that have had a substantial long-term track record of efficacy and safety are to be considered. For the pharmacological treatment of HTN in pregnancy, preferred medications include methyldopa, beta-blockers (particularly labetalol), CCBs (particularly nifedipine and, as an alternative, verapamil), and the direct-acting vasodilators (particularly hydralazine). There is evidence to suggest that among these agents, beta-blockers and CCBs appear to be more effective than methyldopa in decreasing the development of severe HTN later in the pregnancy. The use of thiazide diuretics has been debated, particularly if the individual is already chronically on a thiazide prior to the pregnancy. In this situation the thiazide diuretic may be continued during the pregnancy.

There are clear contraindications to the use of some antihypertensive medications during pregnancy. These include all the renin–angiotensin system inhibitors, such as the ACEis, the ARBs and, although not used any more, the direct-acting renin inhibitors, due to direct adverse effects on the fetus, and the mineralocorticoid receptor antagonist spironolactone due to fetal anti-androgen effects. The use of the beta-blocker atenolol is also contraindicated due to the observation of intrauterine fetal growth inhibition *(102)*.

In summary, HTN in pregnancy, manifested by the various hypertensive pregnancy disorders, is a very common medical condition. HTN pregnancy disorders have serious maternal and fetal consequences. There are currently several preferred oral antihypertensive pharmacological agents available to treat chronic HTN and gestational HTN during pregnancy. In addition, there are antihypertensive pharmacological agents that are contraindicated in pregnancy. There is evidence to support the pharmacological treatment of HTN in pregnancy at given BP thresholds without and with the presence of end organ damage to decrease the likelihood of the development of severe HTN later in the pregnancy. Even with the effective lowering of BP during the pregnancy and in the immediate post-partum period, the presence of hypertensive disorders of pregnancy significantly increases long-term CV risk, including future HTN, coronary disease, and stroke.

5 Publication, implementation, evaluation and research gaps

5.1 Publication

This guideline is available to download from the WHO website. Given that an overview of published systematic reviews was used for the development of the guideline, all reviews are already published and available online.

5.2 Implementation and dissemination

WHO regional and country offices, through their contacts with ministries of health, will encourage implementation at country level. WHO will provide technical assistance if substantial country adaptation is required. The HEARTS technical package, which is currently being implemented in 18 countries and has significant partner endorsement, membership and engagement, will be the platform used to implement and disseminate this guideline. The package will be revised to include the implementation tools from this guideline. Separate implementation aspects are being considered as implementation or derivative tools for nonphysician treatment and the treatment of hypertension in areas of humanitarian crises, following publication of the guideline. Implementation support will be extended to countries through all three levels of WHO.

5.3 Evaluation

WHO will monitor uptake and implementation of the guideline in national policies and programmes by reviewing the number of countries that have adapted or endorsed the guideline nationally.

5.4 Future updating of the guideline

The guideline is expected to be valid for a period of five years. This period reflects the fact that new research findings are likely to become available in the meantime but also represents a feasible time frame, considering the costs, time and other resources that are needed for the updating process. If the evidence base or user needs change before the five-year mark, consideration will be given to producing updates sooner.

5.5 Research gaps

Several research gaps were identified by the GDG according to the theme of the PICOs.

Thresholds to determine initiation of therapy and targets to achieve for control

- More evidence is required regarding treatment of those in the SBP 130–139 range who fall into one or more of the following subgroups: diabetes, chronic kidney disease, heart failure, 65 years or older.
- There is a need for better outcomes data from, for example, trials that include heart failure and cognitive impairment among outcomes.
- Clinical significance of adverse events registered in clinical trials needs greater clarity.
- There is a need to quantify the difference in estimates between blinded, placebo-controlled trials and unblinded, active control trials using a standard framework.

- There is a need for periodic analysis of trials in order to capture effects of changes over time in background epidemiology of CVD, non-BP treatments, competing risks, etc.
- More evidence is needed in LICs, MICs and other non-North American/European countries.
- An assessment of the feasibility, resource needs, and costs of intensive treatment in real clinical practice is needed. The resource commitment required for more intensive treatment in LMICs needs to be quantified.
- The opportunity cost of directing resources towards achieving SBP <130 in high-risk individuals needs to be established.
- Research is needed on the feasibility, acceptability, and efficacy of intensive treatment, especially in high-risk populations in LICs and MICs.

Laboratory tests to determine initiation of treatment

- A greater understanding of the essential tests to be performed in all patients to reduce costs and improve outcomes is required.

Role of cardiovascular risk in hypertension treatment

- An exploration is needed of key operational aspects of the implementation of a risk-based approach to CVD prevention and BP-lowering pharmacological treatment in primary health care settings.

Monotherapy versus combination therapy

- A comparison is required of long-term data about hard clinical endpoints between monotherapy and combination therapy.
- There is a need for research studies on real-world experiences, designed and statistically powered, to determine if there is a difference in clinical outcomes, such as reduction in MACE, mortality, and serious adverse events, between single-pill combinations vs multiple-pill combinations.
- Health economic analyses are needed to quantify cost-effectiveness and budget implications of implementing incremental initial combination therapy compared with initial monotherapy.

Frequency of re-assessment

- Criteria establishing the clinical definition of stable BP control will be needed to guide the selection of patients for less frequent follow-up visits.
- Research is needed for early and accurate identification of patients less likely to achieve BP control and less likely to follow up as requested by their health care provider.
- Better evidence is needed on the timing, frequency, and intensity of interventions that improve treatment adherence.

Team-based care for hypertension

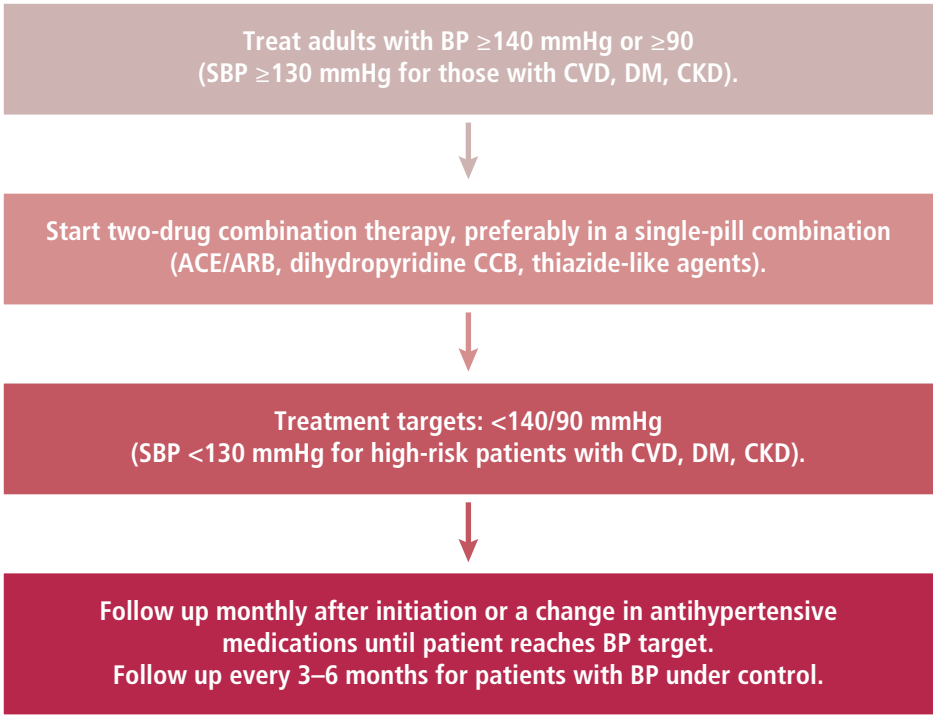
- Evidence is needed that remote monitoring and use of community HCWs/navigators can assist in the management of BP.
- Evidence of the feasibility, costs, and effectiveness of community/home-based monitoring of BP is needed.

6 Implementation tools

6.1 Guideline recommendations

Graphic summaries of the guideline recommendations are presented below in an algorithmic approach (Figs 3 and 4). This maps the recommendations to a patient-care pathway.

Fig. 3 An approach for starting treatment with a single-pill combination



Pharmacological treatment to be initiated under the following circumstances:

- A diagnosis of HTN has already been made.
- Initiation of pharmacological HTN treatment should start no later than four weeks after diagnosis of HTN.
- If BP level is high or there is accompanying evidence of end organ damage, initiation of treatment should be started without delay.
- Patient should be counselled about starting medication therapy.
- Basic laboratory testing (electrolytes, creatinine, lipogram, glucose, HbA1C, urine dipstick, and ECG) to occur as long as it does not delay treatment.
- A CV risk assessment can be conducted immediately (as long as it does not delay initiation of treatment) or at a later visit.
- Consider using diuretics or CCB in patients 65 years or older, or those of African or Afro-Caribbean descent, beta-blockers (BBs) post MI, ACEis/ARBs in those with DM, heart failure or CKD.

Fig. 4 An approach for starting treatment not using a single-pill combination (i.e. with monotherapy or free combination therapy)

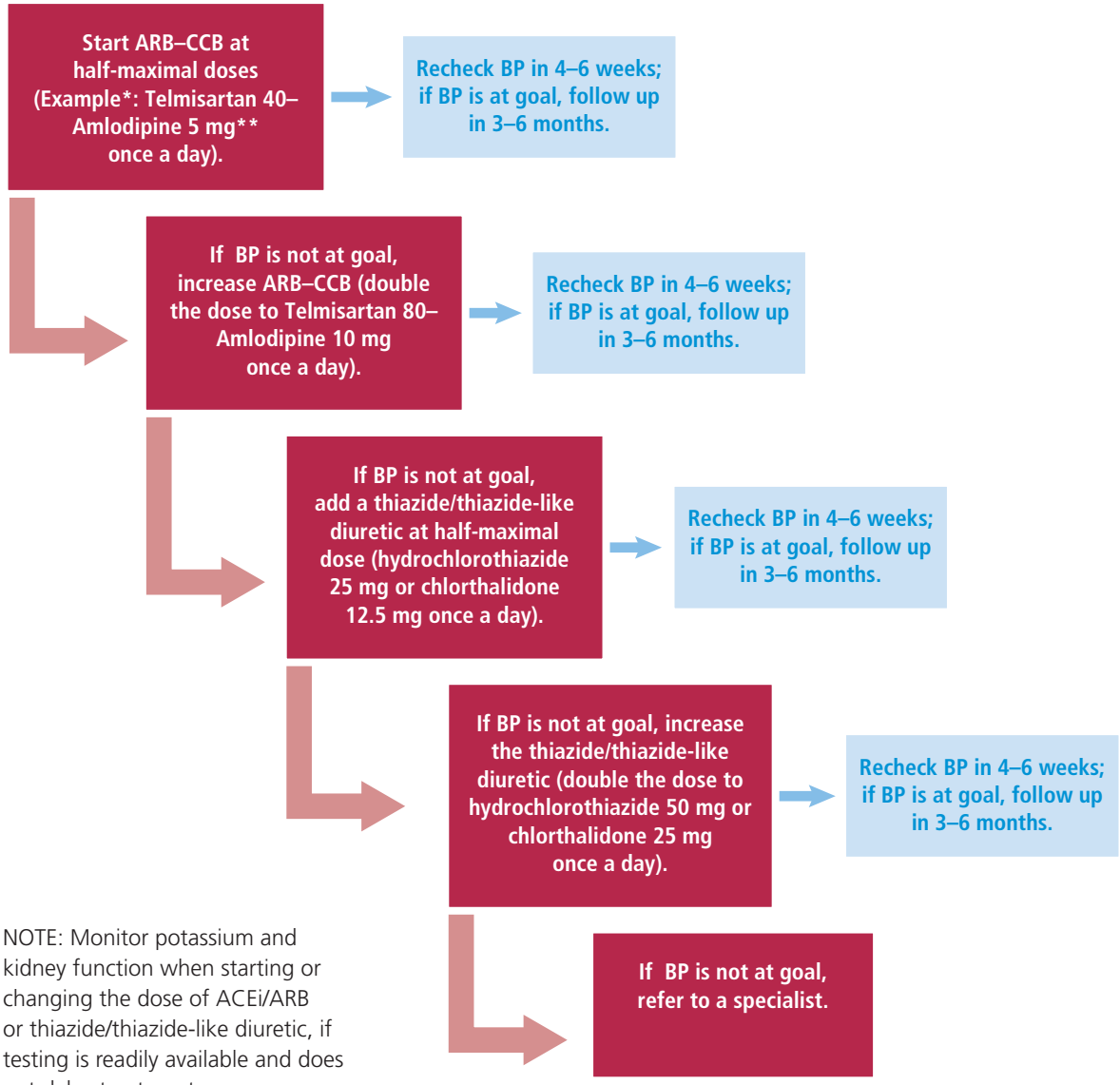
6.2 Drug- and dose-specific protocols

Two examples of suggested drug and dose-specific protocols are presented below (Figs 5 and 6). These should be viewed as examples and other approaches are possible.

Algorithm 1: Initiation of treatment with a single-pill combination

- Beginning treatment with two antihypertensive drugs from different classes is recommended when baseline BP is ≥20/10 mmHg above goal, and should be considered when baseline BP is ≥140/90 mmHg.
- Drugs affecting the renin–angiotensin system (ACEis, ARBs, and aliskiren) have been associated with serious fetal toxicity, including renal and cardiac abnormalities and death; they are contraindicated for use during pregnancy.

Fig. 5 Algorithm 1



NOTE: Monitor potassium and kidney function when starting or changing the dose of ACEi/ARB or thiazide/thiazide-like diuretic, if testing is readily available and does not delay treatment.

This protocol is contraindicated for women who are or could become pregnant. Neither an ACEI or ARB should be given to pregnant women.

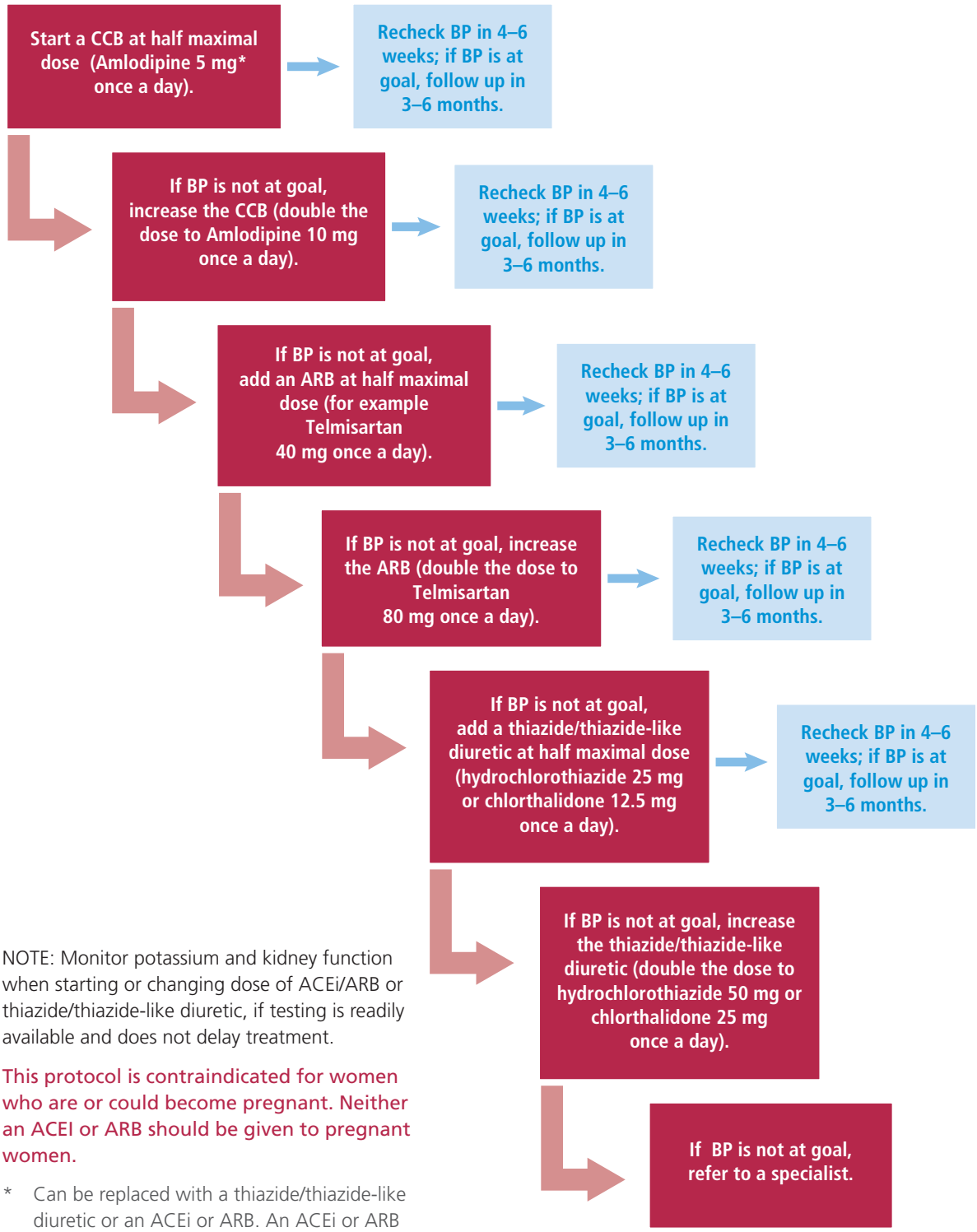
* The medications mentioned serve as examples and can be replaced with any two medications from any of the three drug classes (ACEis/ARBs, CCBs or thiazide/thiazide-like diuretics). Start two individual pills or, if available, both in a single-pill combination (fixed-dose combination).

** Can be replaced with other individual pills or, if available, other single-pill combinations (fixed-dose combinations).

Algorithm 2: Initiation of treatment not using a single-pill combination (i.e. with monotherapy or free combination therapy)

- A CCB, rather than a thiazide-type diuretic or ACEi/ARB, was selected as first-line medication if one agent is used, to avoid the need for electrolyte measurements or to alleviate concerns regarding potential change in GFR.
- Drugs affecting the renin-angiotensin system (ACEis, ARBs, and aliskiren) have been associated with serious fetal toxicity, including renal and cardiac abnormalities and death; they are contraindicated for use during pregnancy.

Fig. 6 Algorithm 2



NOTE: Monitor potassium and kidney function when starting or changing dose of ACEi/ARB or thiazide/thiazide-like diuretic, if testing is readily available and does not delay treatment.

This protocol is contraindicated for women who are or could become pregnant. Neither an ACEI or ARB should be given to pregnant women.

* Can be replaced with a thiazide/thiazide-like diuretic or an ACEi or ARB. An ACEi or ARB is preferred for patients with proteinuria.

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Annex 1: List of contributors

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WHO Steering Group

Name	Department/Office
Bernadette Cappello	Department of Essential Medicines and Products
Neerja Chowdhury	Department of Mental Health
Gampo Dorji	Regional Office of South East Asia (SEARO)
Jill Farrington	Regional Office of Europe (EURO)
Taskeen Khan	Department of Noncommunicable Diseases
Pedro Ordunez	Pan American Health Organization/Regional Office of the Americas (PAHO/AMRO)
Steven Shongwe	Regional Office for Africa (AFRO)
Slim Slama	Regional Office of the Eastern Mediterranean (EMRO)
Cherian Varghese	Department of Noncommunicable Diseases
Marco Vitoria	Department of HIV/AIDS
Temo Waqanivalu	Department of Noncommunicable Diseases

Guideline Development Group

Name	Affiliations	Expertise	Region
Shrish Acharya	Consultant Physician and Head of Internal Medicine, Colonial War Memorial Hospital, Fiji Chair, National Medicine and Therapeutics Committee, Ministry of Health, Fiji	Internal medicine Clinical practice guideline development	WPRO
Akram Al-Makki	Director of Graduate Medical Education, Medical Director of Acute (Inpatient) Dialysis Unit, Indiana University, IN, USA Health-Arnett, Affiliate Faculty of Pharmacy Practice, Purdue University, College of Pharmacy	HTN management in disaster and humanitarian settings, pharmacology of hypertensive medicines and HTN management, Nephrology	AMRO
Hind Mamoun Beheiry	Associate Professor of Physiology, Dean Faculty of Nursing Sciences, International University of Africa (IUA), Sudan	Nursing and HTN, guideline development, access to HTN care in low-resource settings, pathophysiology of HTN, HTN management and prevention at community level	EMRO

Beatriz Champagne	CLAS Coalición Latinoamérica Saludable/ Coalition for Americas' Health @CLASenLA	Advocacy, coalition building, policy change, patient perspectives, implementation research, behavioural sciences	AMRO
Ugyen Choden	Chief Analyst, Department of Financial Regulation and Supervision, Royal Monetary Authority, Bhutan	Patient perspective, drafting guidelines, policies and implementing policies	SEARO
Kenneth Connell	Deputy Dean of Internationalization & Recruitment and Lecturer in Clinical Pharmacology, The UWI, Cave Hill Campus Consultant Internist, Queen Elizabeth Hospital, Barbados Governor of the American College of Physicians Caribbean Chapter	Internal medicine, HTN & ethnicity, medical education	AMRO
Marie Therese Cooney	Clinical Professor, University College Dublin, Ireland Consultant Physician in Geriatric and General Medicine, St Vincent's University Hospital, Ireland	Cardiovascular risk estimation, cardiovascular disease prevention, frailty and multi-morbidity	EURO
Donald DiPette	Distinguished Health Sciences Professor, University of South Carolina and University of South Carolina School of Medicine, Columbia, SC, USA	Clinical pharmacology and pharmacology of HTN medications, HTN management, pathophysiology of HTN, health care and policy making including primary care	AMRO
Nnenna Ezeigwe	Consultant Public Health Physician; Director/ National Coordinator, Non-Communicable Diseases (NCDs), Federal Ministry of Health, Abuja, Nigeria	Public health, policy-making, programme implementation	AFRO
Tom Gaziano	Associate Professor, Harvard Medical School Center for Health Decision Science, Harvard TH Chan School of Public Health Clinical Director, iHeart Champion Program Director, Global Cardiovascular Health Policy and Prevention Unit Cardiovascular Medicine Division, Brigham & Women's Hospital	Implementation of HTN treatment guideline, cost-effectiveness, global health policy, epidemiology, screening strategies	AMRO
Agaba Gidio	Consultant Physician (endocrinologist)/Head Adult Diabetes Clinic Mulago National referral Hospital, Kampala Uganda	Endocrine HTN, HTN in patients with Diabetes	AFRO
Vilma Irazola	Director, Instituto de Efectividad Clinica y Sanitaria (IECS); Institute for Clinical Effectiveness and Health Policy (IECS) Deputy Director of the Master's Degree Program in Clinical Effectiveness, University of Buenos Aires Senior Researcher, National Scientific Council (CONICET), Argentina	Implementation science, NCDs epidemiology, prevention and management; cardiovascular health, global health, health policy	AMRO

Patricio Lopez Jaramillo	Director, Masira Research Institute, Universidad de Santander (UDES) Scientific Director, Centro Integral para la Prevencion de la Enfermedades Cardiometabolicas (CIPCA), Bucaramanga, Colombia	Endocrinology, clinical management of HTN, research	AMRO
Unab Khan	Diplomate, American Board of Family Medicine and Adolescent Medicine Associate Professor and Chair, Department of Family Medicine, Aga Khan University, Karachi, Pakistan	NCDs, educational programmes for primary care physicians, workplace/employee wellness and safety, program implementation research	EMRO
Vindya Kumarapeli	Consultant Community Physician, Director (Non-Communicable Diseases), Ministry of Health, Sri Lanka	Access to HTN care in low-resource settings, public health, policy-making, programme implementation, primary health care	SEARO
Andrew Moran	Director, Global Hypertension Control, Resolve to Save Lives, an initiative of Vital Strategies Associate Professor of Medicine, Columbia University Irving Medical Center, New York, NY, USA	HTN, primary care, health economic evaluation, HTN program evaluation	AMRO
Margaret Mswema Silwimba	Clinical Pharmacist and Head of Pharmaceutical services, Premium Department (UTH) Part-time Lecturer (Faculty of Pharmacy) Lusaka Apex Medical University, Zambia	HTN pharmaceuticals, pharmacy education	AFRO
Brian Rayner	Emeritus Professor and Senior Research Scholar, Division of Nephrology and Hypertension, Department of Medicine, University of Cape Town, Cape Town, South Africa	Guidelines, resistant HTN especially in individuals of African descent, genetics of HTN, diabetic kidney disease	AFRO
K Srinath Reddy	President, Public Health Foundation of India	Cardiology, prevention and control of NCDs, epidemiology, health systems and policy, universal health coverage, public health	SEARO
Nizal Sarrafzadegan	Distinguished Professor of Medicine and Cardiology, Director of Isfahan Cardiovascular Research Institute, a WHO Collaborating Centre in Iran Affiliate Professor, School of Population and Public Health, Faculty of Medicine, University of British Columbia, Vancouver, Canada	Cardiology, epidemiology, prevention and control of NCDs, public health, programme implementation and evaluation, global health	EMRO
Apichard Sukonthasan	Cardiac Specialist and Head of Medicine Department, Bangkok Hospital Chiang Mai	Guideline development, cardiovascular disease prevention, HTN management	SEARO

Paul Whelton	Show Chwan Chair in Global Public Health, Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, Tulane, USA	Epidemiology and prevention of cardiovascular and renal disease, research, guidelines development, global health, health policy	AMRO
Jing Yu	MD, PhD, Professor of Internal Medicine, Chief of Cardiology, Director, Center of Hypertension, Director, Department of Cardiology, Lanzhou University Second Hospital, China Chairman of Hypertension League in Gansu, Ningxia and Qinghai Region of China	Acute and chronic complications of HTN, access to HTN care in low-resource settings, pharmacology of hypertensive medicines, cardiovascular complications	WPRO

Consultant and Systematic Review Team

Methodologist: M Hassan Murad (Professor of Medicine at the Mayo Clinic, Rochester, USA)

Systematic Review Team: Reem Mustapha, Abdallah Al Alayli, Romina Brignardello, Sara Jdiaa, Veena Manja (University of Kansas Medical Center, Kansas, USA)

External Review Group

Name	Affiliation	Region
Mabel Aoun	Head of the Department of Nephrology, Saint-Georges Hospital Ajaltoun Assistant Professor, Medical School, Saint-Joseph University of Beirut, Lebanon	EMRO
Antoinette Péchère Bertschi	Head Hypertension Unit and Centre, Service of Nephrology and Hypertension, University Hospital of Geneva, Switzerland	EURO
Jennifer Cohn	Senior Vice President, Cardiovascular Health Assistant Professor, Division of Infectious Diseases, University of Pennsylvania, PA, USA	AMRO
Prabhdeep Kaur	Scientist E and Head of Division of Noncommunicable Diseases, ICMR-National Institute of Epidemiology, Chennai, India	SEARO
Daniel T Lackland	Professor of Epidemiology and Neurology Director, Division of Translational Neurosciences and Population Studies, Medical University of South Carolina, Charleston, SC, USA	AMRO
Venus Mushininga	Program Manager, Non Communicable Diseases, Ministry of Health and Child Care, Harare, Zimbabwe	AFRO
Marcelo Orias	Chief of Nephrology at Sanatorio Allende Professor in Internal Medicine at National University of Córdoba, Associate Professor of Internal Medicine, Yale University, CT, USA	AMRO

Xin Hua Zhang	Professor of Medicine Vice-Director of Beijing Hypertension League Institute, Beijing, China President, World Hypertension League, WHL Global Office Director, WHL Asia-Pacific Regional Office	WPRO

Overall coordination and writing of the guideline

The guideline process was coordinated by the WHO Department of Noncommunicable Diseases. The first draft was written by Taskeen Khan. Drafts were reviewed by the Guideline Development Group and External Review Group, and subsequently revised by Taskeen Khan.

Annex 2. Managing declarations of interest and conflicts of interest

The steering group followed the current Compliance, Risk Management and Ethics (CRE) policy.

All members of the Guideline Development Group (GDG) were asked to fill in the standard WHO Declaration of Interest (DOI) forms, which were reviewed. The WHO Secretariat reviewed the curriculum vitae of each potential participant and conducted internet searches (PubMed, Open Payments Data, Google Scholar) for information on potential financial and academic conflicts of interest related to the subject of the meeting. All DOIs are on file at the WHO Department of Noncommunicable Diseases.

The WHO Steering Group published the names and brief biographies of potential GDG members on the WHO website for more than two weeks, together with a description of the objective of the meeting, for public review and comment. There were no concerns raised about any members.

None of the declared interests was judged sufficient to affect any of the experts' objective judgement during the guidelines development process or on the recommendations, or therefore to preclude their full participation in the development of the guidelines.

During the course of the development of the guideline, one GDG member's status of conflict of interest changed as she accepted a temporary appointment as a staff member at WHO. She was removed from further GDG engagements immediately upon accepting appointment.

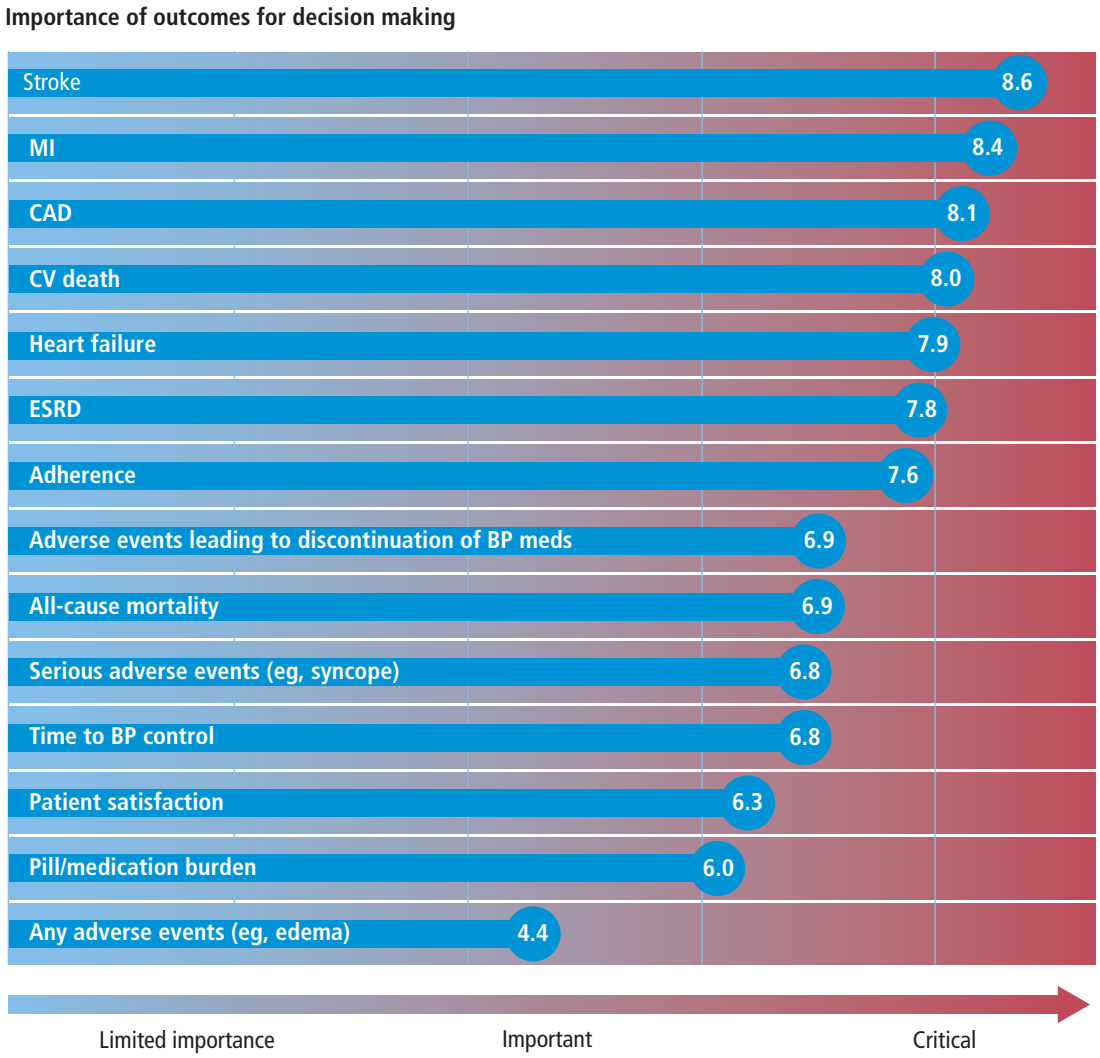
All members of the GDG and all meeting observers were required to sign a confidentiality agreement before participating in the meeting.

All members of the External Review Group (ERG) were asked to fill in the standard WHO DOI forms, which were reviewed. None of the declared interests was judged sufficient to affect any of the judgement during the review process, or therefore to preclude their participation as expert reviewers.

Annex 3: Treatment outcomes relevant to hypertension

Members of the WHO Steering Group, in consultation with the GDG and methodologist, developed a list of treatment outcomes most relevant to the care of individuals with hypertension. The GDG then rated each outcome on a scale from 1 to 9 and indicated whether it considered each outcome critical (rated 7–9), important (rated 4–6) or not important (rated 1–3) for decision-making (Fig. A3.1).

Fig. A3.1 Rating of outcomes



Annex 4: PICO questions

The eleven questions in population, intervention, comparison, and outcomes (PICO) format used to guide the systematic reviews. In addition, relevant subgroups (s) were identified.

1 At what level of blood pressure should pharmacological therapy be started to prevent cardiovascular events?

P	Adult men and women
I	Specific systolic and diastolic blood pressure thresholds:* systolic (mmHg): ≥120, ≥130, ≥140, ≥150 diastolic (mmHg): ≥80, ≥90
C	Placebo or systolic or diastolic blood pressure threshold that is higher than intervention thresholds
O	Death (all-cause mortality), cardiovascular death (death from MI, sudden cardiac death or stroke), stroke, myocardial infarction, end-stage renal disease, cognitive impairment/dementia, heart failure events and adverse events
s	Based on different effect modifiers such as: estimated cardiovascular risk; pre-existing CAD, stroke, diabetes, age, sex, chronic kidney disease and race/ethnicity

* Each BP threshold in the intervention category (I) will be compared with a higher threshold. For example, I (<140) will be compared to C (≥140)

2 Is any laboratory testing necessary prior to initiation or during titration of pharmacological treatments

P	Adult men and women requiring antihypertensive treatment
I	Initiation or titration of antihypertensives without lab tests
C	Initiation or titration of antihypertensives with lab tests
O	Death (all-cause mortality), cardiovascular death (death from MI, sudden cardiac death or stroke), stroke, myocardial infarction, end-stage renal disease and heart failure events, cognitive impairment/decline BP control Time to control BP Adherence Adverse effects Patient satisfaction
s	Individual drugs and doses Patients with no comorbidities Baseline blood pressure Type of lab test (ECG, blood, etc)

3 Should cardiovascular risk assessment be used to guide initiation of antihypertensive medications?

P	Adult men and women without pre-identified CVD
I	Initiating antihypertensives drug therapy based on a formal CVD risk estimation
C	Initiating antihypertensives drug therapy without formal CVD risk assessment (i.e. using only BP threshold)
O	Death (all-cause mortality), cardiovascular death (death from MI, sudden cardiac death or stroke), stroke, myocardial infarction, end-stage renal disease heart failure events, cognitive impairment/dementia, and adverse events Proportion of people prescribed with antihypertensives BP levels
s	BP levels

4 In adults with hypertension requiring pharmacological treatment, which drugs should be used as first-line agents?

P	Adult men and women with hypertension requiring pharmacological treatment
I	BB, CCB, diuretics, ACE, or ARB
C	Placebo
O	Death (all-cause mortality), cardiovascular death (death from MI, sudden cardiac death or stroke), stroke, cognitive impairment/dementia, myocardial infarction, end-stage renal disease and heart failure events Adverse effects such as bradycardia, acute kidney injury, angioedema, asthma, electrolyte abnormalities or hypotension BP reduction and control (if data on CVD events are absent)
s	Based on different effect modifiers such as: estimated cardiovascular risk; pre-existing CAD, stroke, diabetes, age, sex, chronic kidney disease and race/ethnicity, level of baseline BP

5 In adults with hypertension requiring pharmacological treatment, which drugs (BB, CCB, diuretics, ACE, or ARB vs BB, CCB, diuretics, ACE, or ARB in head-to-head studies) should be used as first-line agents?

P	Adult men and women with HTN requiring pharmacological treatment
I	BB, CCB, diuretics, ACE, or ARB
C	BB, CCB, diuretics, ACE, or ARB (head-to-head studies)
O	Death (all-cause mortality), cardiovascular death (death from MI, sudden cardiac death or stroke), stroke, cognitive impairment/dementia, myocardial infarction, end-stage renal disease and heart failure events Adverse effects such as bradycardia, acute kidney injury, angioedema, asthma, electrolyte abnormalities or hypotension Blood pressure reduction and control (if data on CVD events are absent)
s	Based on different effect modifiers such as: estimated cardiovascular risk; pre-existing CAD, stroke, diabetes, age, sex, chronic kidney disease and race/ethnicity, level of baseline blood pressure

6 In adults with hypertension requiring pharmacological treatment, which drugs (monotherapy using BB, CCB, diuretics, ACE or ARB vs combination therapy using BB, CCB, diuretics, ACE or ARB) should be used as first-line agents?

P	Adult men and women with HTN requiring pharmacological treatment
I	BB, CCB, diuretics, ACE, or ARB
C	Combination therapy
O	Death (all-cause mortality), cardiovascular death (death from MI, sudden cardiac death or stroke), stroke, cognitive impairment/dementia, myocardial infarction, end-stage renal disease and heart failure events Adverse effects such as bradycardia, acute kidney injury, angioedema, asthma, electrolyte abnormalities or hypotension BP reduction and control (if data on CVD events are absent)
s	Based on different effect modifiers such as: estimated cardiovascular risk; pre-existing CAD, stroke, diabetes, age, sex, chronic kidney disease and race/ethnicity, level of baseline BP

7 In adults with hypertension requiring pharmacological treatment, which combination therapy of two or more drugs (BB, CCB, diuretics, ACE, or ARB) vs different combination therapy of two or more drugs (BB, CCB, diuretics, ACE, or ARB) should be used as first-line agents?

P	Adult men and women with HTN requiring pharmacological treatment
I	Combination therapy of two or more drugs (BB, CCB, diuretics, ACE, or ARB)
C	Different combination therapy of two or more drugs (BB, CCB, diuretics, ACE, or ARB)
O	Death (all-cause mortality), cardiovascular death (death from MI, sudden cardiac death or stroke), stroke, cognitive impairment/dementia, myocardial infarction, end-stage renal disease and heart failure events Adverse effects such as bradycardia, acute kidney injury, angioedema, asthma, electrolyte abnormalities or hypotension BP reduction and control (if data on CVD events are absent)
s	Based on different effect modifiers such as: estimated cardiovascular risk; pre-existing CAD, stroke, diabetes, age, sex, chronic kidney disease and race/ethnicity, level of baseline BP

8 In adults with hypertension requiring pharmacological intervention, is use of a single-pill combination of antihypertensive drugs associated with improved outcomes?

P	Adult men and women with HTN requiring pharmacological intervention
I	CSingle-pill combination (FDC) of antihypertensive drugs – five classes (any two or more from the five)
C	Pharmacological interventions that do not involve use of single-pill combinations
O	Death (all-cause mortality), cardiovascular death (death from MI, sudden cardiac death or stroke), stroke, myocardial infarction, end-stage renal disease and heart failure events. Adverse effects Patient satisfaction Adherence BP level/change Number of antihypertensive medications
s	Based on different effect modifiers such as: estimated cardiovascular risk; pre-existing CAD, stroke, diabetes, age, sex, chronic kidney disease and race/ethnicity, level of baseline BP

9 What target blood pressure should pharmacological treatment aim to achieve?

P	Adult men and women
I	Specific systolic and diastolic blood pressure targets: systolic (mmHg): <120, <130, <140, <150 diastolic (mmHg): <70, <80, <90
C	Systolic or diastolic blood pressure targets that are higher than the intervention targets
O	Death (all-cause mortality), cardiovascular death (death from MI, sudden cardiac death or stroke), stroke, myocardial infarction, end-stage renal disease heart failure events, cognitive impairment/dementia, and adverse events
s	Based on different effect modifiers such as: estimated cardiovascular risk; pre-existing CAD, stroke, diabetes, age, sex, chronic kidney disease and race/ethnicity

10 In adults with hypertension given pharmacological treatment, when should blood pressure be reassessed?

P	Adult men and women with HTN receiving a pharmacological intervention
I	Specific interval
C	Alternative interval
O	Death (all-cause mortality), cardiovascular death (death from MI, sudden cardiac death or stroke), stroke, myocardial infarction, end stage renal disease and heart failure events Adverse effects BP control Adherence Patient satisfaction
s	Titration phase vs controlled HTN follow up, level of initial BP, other conditions, remote monitoring vs clinical visit

11 Can pharmacological management of hypertension be provided by nonphysician care providers?

P	Adult men and women
I	Pharmacological management by nonphysician care providers
C	Pharmacological management by medically qualified practitioners (doctors)
O	Death (all-cause mortality), cardiovascular death (death from MI, sudden cardiac death or stroke), stroke, myocardial infarction, end-stage renal disease and heart failure events BP control Adherence Serious adverse effects Patient satisfaction
s	Initiation vs follow up Self-care vs CHW vs nurse vs pharmacist vs physician assistant vs in or out of clinic Levels of care Rural vs urban settings Ethnicity

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