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

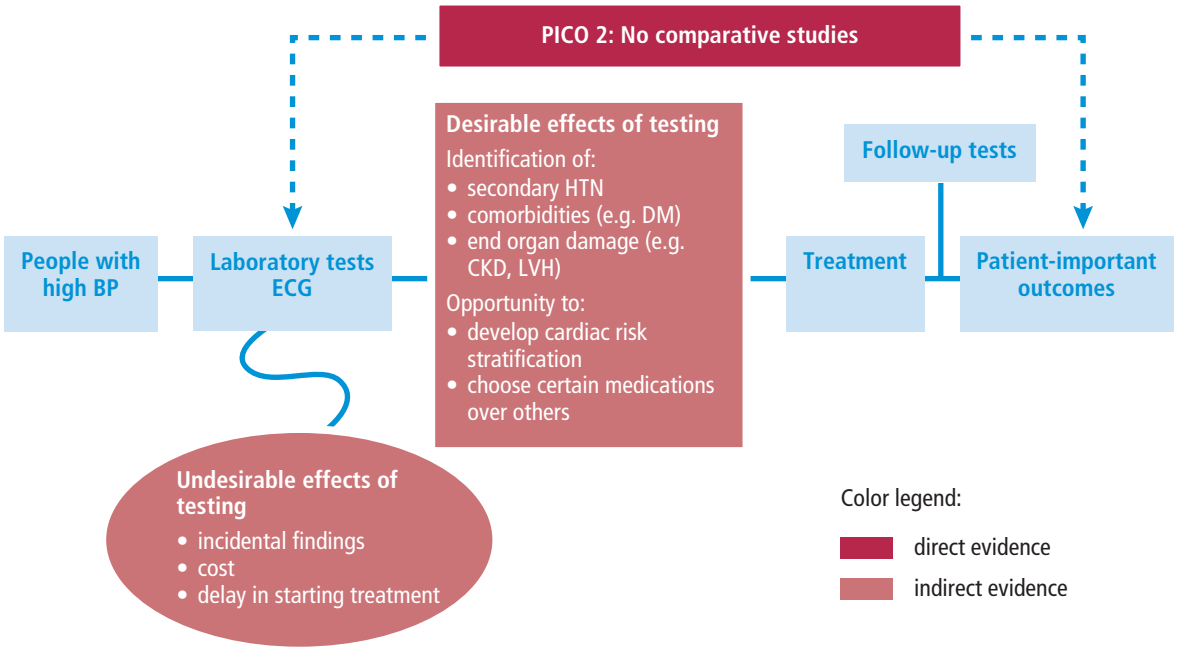
Implementation remarks:

- 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.