Guideline for the pharmacological treatment of hypertension in adults

WEB ANNEX B

Evidence-to-decision frameworks

World Health Organization

Guideline for the pharmacological treatment of hypertension in adults. Web Annex B. Evidence-to-decision frameworks

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Contents

Acronyms and abbreviations

ACE1	angiotensin-converting enzyme 1
ACE2	angiotensin-converting enzyme 2
ACEi	angiotensin-converting enzyme inhibitor
AE	adverse events
ARB	angiotensin-II-receptor blocker
BB	beta-blocker
BP	blood pressure
CAD	coronary artery disease
CCB	calcium channel blocker
CKD	chronic kidney disease
CV	cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
ECG	electrocardiogram
GDG	Guideline Development Group
eGFR	estimated glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCW	health care worker (nonphysician)
HF	heart failure
HIC	high-income country
HTN	hypertension
ICER	incremental cost-effectiveness ratio
LIC	low-income country
LVH	left ventricular hypertrophy
MACE	major adverse cardiovascular event
MI	myocardial infarction
MIC	middle-income country
NCD	noncommunicable disease
PICO	population intervention comparator outcome
QALY	quality-adjusted life year
RAAS	renin-angiotensin-aldosterone system
RCT	randomized-controlled trial
RR	relative risk
SBP	systolic blood pressure
SES	socioeconomic status

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

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE/PANEL INPUT
VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	Important uncertainty or variability ☐ / Possibly important uncertainty or variability ☒ / Probably no important uncertainty or variability ☐ / No important uncertainty or variability ☐ / No known undesirable outcomes ☐ **Detailed judgements**	**RESEARCH EVIDENCE** **Societal/clinical/public health:** HTN treatment is generally highly valued from a public health and clinical perspectives (largest disease burden among NCD risks worldwide; population and long-term clinical outcome perspectives).[1 2] **Patient perspective**: When given for primary prevention, antihypertensive therapy represents a lifelong daily medication regimen for an asymptomatic condition; treatment may be perceived as low value from the asymptomatic patient perspective unless the person is convinced of a trade-off between immediate inconvenience/side-effects and potential long-term health gains.[3 4] **PANEL INPUT** **Age dependence**: young and asymptomatic people may not appreciate the benefit. There are differences in values based on race, gender, baseline BP, socioeconomic status, education, dependence. Those with home monitoring capacity may have a different view.
BENEFITS AND HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	No included studies ☐ / Very low ☐ / Low ☐ / Moderate ☒ / High ☐ **Detailed judgements**	**RESEARCH EVIDENCE** On average, benefits are 5–10/1000 CV events/death and harms (side-effects) are 20–30/1000. Harms are mostly not serious and have variable severity, could be a surrogate outcome such as rise in creatinine that may not be clinically relevant. On the other hand, benefits were major events (reduction in mortality, cardiovascular mortality, stroke, MI and heart failure events.). The benefits clearly outweigh harms. SBP threshold of 140 or above has the clearest benefit/risk balance, as opposed to a lower threshold of 130 in those with comorbidities. The certainty is high to moderate overall, varies according to the BP level. **PANEL INPUT** When CKD patients are recruited they already have been treated; thus it is difficult to assess their baseline BP, may not be unethical to study in RCT. Progression is slow and requires longer follow up for kidney disease outcomes. CV benefit is likely underestimated. Evidence from patients with CAD or DM can be extrapolated to CKD.
	How substantial are the desirable anticipated effects?	Don't know ☐ / Trivial ☐ / Small ☐ / Moderate ☐ / Large ☒ / Varies ☐ **Detailed judgements**	
	How substantial are the undesirable anticipated effects?	Don't know ☐ / Trivial ☐ / Small ☒ / Moderate ☐ / Large ☐ / Varies ☐ **Detailed judgements**	

	Do the desirable effects outweigh the undesirable effects?	No ☐ Probably No ☐ Don't know ☐ Probably Yes ☐ Yes ☒ Varies ☐ **Detailed judgements**	The risk of adverse events is twice that of placebo in treated CVD patients[5]. However, clinical significance of composite adverse events risk is not well established as the composite includes both mild and severe AEs. Evidence on harms is also mixed because of different amounts of BP lowering in trials and use of different classes and molecules of anti-HTN agents. The treatment trials have enrolled individuals with higher CV risk, thus, the results may be indirect when applied to lower risk, wider population.
RESOURCE USE	**How large are the resource requirements?**	Large costs ☐ Moderate costs ☐ Small ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Detailed judgements**	**RESEARCH EVIDENCE** Cost data is available from various countries such as the United States[6 7 8], China[9], and India[10]. **PANEL INPUT** Resources vary based on the public health system structure and the country economic status. Refugees have limited resources and depend on donated medications and samples. Even in the US, un- or under-insured people may choose food over BP meds. May choose to treat other conditions over HTN. Cost in low-income countries is sometimes higher than other countries. Prevention of CV events may lead to health savings. Cost of screening is to be considered when discussing thresholds of starting treatment. Resource allocation is large for population-based systematic HTN screening of the whole adult population to detect 140–159 SBP; but note that population screening is needed to identify higher BP groups (SBP ≥160 mmHg) anyway. Opportunistic screening in health facilities is more resource efficient and the logical first step for jurisdictions starting with low awareness of HTN and low HTN control rates. Identifying most existing CVD patients with SBP 130–139 should be relatively easy since they are usually known to the health system, but treatment of this relatively small group alone would mean much smaller population health impact. **Medications**: few lower income countries currently most likely do not allocate sufficient funds toward treating all of their hypertensive patients, but this information is not readily available. **Human resources**: Team based care involving task-sharing can make HTN treatment more affordable from a human resources perspective.

	How large is the incremental cost relative to the net benefit?	Very large ICER ☐ Large ICER ☐ Moderate ICER ☐ Small ICER ☒ Savings ☐ Varies ☐ **Detailed judgements**	**RESEARCH EVIDENCE** Multiple sources of cost effectiveness are available from various countries such as the US, UK, Nigeria and Argentina[11 12 13 14 15 16] and for lower thresholds and higher risk individuals. [17 18 19] Most cost-effectiveness estimates were clustered below USD 1000 per averted DALY – well below the average 2017 GDP per capita for lower-middle income countries of USD 2188,[20] suggesting they could be very cost-effective for lower-middle income countries. Per Kostova study[11], WHO, and Disease Control Priorities 3 study, HTN treatment (treating all with BP ≥140/90 mmHg) is cost-effective and a "best buy" intervention. Treating high risk/CVD patients with baseline 130–139 mmHg shown to be cost-effective, but not cost saving (SPRINT[18]); value depends on maintaining the intervention effect >5 years. **PANEL INPUT** Cost relative to benefit is likely small to moderate. Generic drugs will clearly lower the cost.
EQUITY	**What would be the impact on health inequities?**	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies ☐ **Detailed judgements**	**RESEARCH EVIDENCE** Barriers in access to HTN care in low-income settings include low patient health literacy, lack of financial protections, and limited resources.[21] Out-of-pocket payments for chronic, lifelong medicines and consultations can be impoverishing. **PANEL INPUT** Treating group with SBP 130–139 mmHg has potential to draw resources away from finding unaware population with HTN or from controlling BP in people with baseline ≥140/90 mmHg.
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	**RESEARCH EVIDENCE** **Patients**: patients don't perceive risk of HTN and may find it hard to accept daily medication regimen, especially when minor side-effects persist (e.g. mild but bothersome pedal oedema with Ca++ blocker).[22] **Clinicians**: trials evidence very solid and holds up to very conservative analyses. **Governments**: familiar, simple, easy to implement, though there is a cost, especially medications, screening.

FEASIBILITY	**Is the option feasible to implement?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	**RESEARCH EVIDENCE** The many barriers in access to HTN care in low-income settings include overburdened health-care providers; the lack of an organizational structure to accommodate nonphysicians as part of a primary care team; the lack of confidence and/ or policy towards the nonphysician providers' ability to manage uncomplicated and stable patients; and the lack of infrastructure for data collection and longitudinal monitoring of clinical information on an ongoing basis.[21 23] **PANEL INPUT** It varies based on health system structure and commitment of the country/health system. However, likely feasible in most countries.

Recommendation 1: blood pressure threshold for initiation of pharmacological treatments

Recommendation 1a	**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.**
Recommendation 1b	**WHO recommends pharmacological antihypertensive treatment of individuals with existing cardiovascular disease and systolic blood pressure of 130–139 mmHg.**
Recommendation 1c	**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.**

Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	**We recommend the option**
	☐	☐	☐	☐	☒

Justification	Benefits clearly outweigh the non-serious harms with at least moderate certainty.
Subgroup considerations	• Existing CVD • Diabetes • CKD
Implementation considerations	Initiation of HTN treatment should occur within four weeks of diagnosis of HTN. If BP level is high or accompanying evidence of end organ damage, initiation of treatment should be faster. Treating HTN require a functional primary care system with ability to track BP over time, adequate staffing and equipment, and steady supply of affordable, quality-assured and affordable medications, and an information system for tracking patients' health information over time. Identify existing CVD and treat with BP lowering medication if SBP 130–139 mmHg; adding this indication will require re-training of health workers and a health information system that tracks history of CVD over time.

Monitoring and evaluation considerations	Screening intervals for HTN vary by country, usually variance between every 1–5 years. Some guidelines recommend more frequent screening for patients with borderline raised BP on initial screen (130–139/ 80–89). Note that the most recent US guideline (ACC/AHA 2017) defines diagnosis of HTN starting at ≥130/90 mmHg, but this is an outlier among national/international guidelines. Monitor BP over time; capture adverse events (AEs) related to medication treatment. For AEs register acute outcomes and record long term consequence.
Research priorities	• More evidence needed regarding treatment of subgroups in 130–139 mmHG SBP range: diabetes, CKD, heart failure, older age • Better outcomes data: need more trials that include heart failure, cognitive impairment among outcomes; need better standardization of outcomes in trials • Clarify clinical significance of adverse events registered in clinical trials. • Quantify difference in estimates between blinded, placebo-controlled trials and unblinded active control trial using standard framework • Period analysis of trials – to capture effects of changes over time in background epidemiology of CVD, non-BP treatments, competing risks, etc • More evidence needed in LICs, MICs and other non-North American/European populations.

PICO question 2: Is any laboratory testing necessary prior to initiation or during titration of pharmacological treatments?

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE/PANEL INPUT
VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	Important uncertainty or variability: [X] Possibly important uncertainty or variability: [ ] Probably no important uncertainty or variability: [ ] No important uncertainty or variability: [ ] No known undesirable outcomes: [ ] **Detailed judgements**	There is no research evidence about how people value performing tests prior to starting pharmacological treatment although intuitively people generally like to have tests performed
BENEFITS AND HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	No included studies: [ ] Very low: [X] Low: [ ] Moderate: [ ] High: [ ] **Detailed judgements**	**RESEARCH EVIDENCE** The systematic review did not identify direct evidence to support this question. Indirect evidence demonstrates that 10-30% patients with HTN may have secondary HTN, comorbidities or develop adverse events after treatment (e.g. hyperkalaemia and AKI), thus providing a rationale for testing (i.e. desirable effects). The undesirable effects would be incidental findings on testing (likely not important) but importantly can include delay of treatment with potential for adverse CV outcomes. On balance, desirable effects likely outweigh undesirable effects. **PANEL INPUT** All guidelines mention that basic laboratory tests need to be performed at initial assessment. The rationale would be: 1. to identify secondary HTN 2. to identify comorbidities (e.g., DM, dyslipidaemia) 3. to identify end organ damage (e.g. CKD or LVH) 4. cardiac risk stratification 5. to pre-identify potential adverse events from treatments (e.g. uric acid, abnormal electrolytes) 6. compelling indications to pharmacological treatment It would be highly desirable to have this information as it has a major influence on further investigation for secondary causes, treatment of other CV risk factors, BP goal, and initiation and choice of antihypertensive drugs.
	How substantial are the desirable anticipated effects?	Don't know: [ ] Trivial: [ ] Small: [ ] Moderate: [X] Large: [ ] Varies: [ ] **Detailed judgements**	
	How substantial are the undesirable anticipated effects?	Don't know: [ ] Trivial: [ ] Small: [X] Moderate: [ ] Large: [ ] Varies: [ ] **Detailed judgements**	
	Do the desirable effects outweigh the undesirable effects?	No: [ ] Probably No: [ ] Don't know: [ ] Probably Yes: [X] Yes: [ ] Varies: [ ] **Detailed judgements**	

			However, the question is whether treatment can be initiated before having these tests available. There is almost no data to clarify the position. In the Creole study, only 1% of subjects were excluded from the study based on laboratory values – mainly low eGFR or hypokalaemia (personal communication from lead investigator). When testing for aldosterone/rennin activity, treatment may affects test results. An incidental finding of hyponatraemia would lead to not starting diuretics. However, these issues are uncommon. Level of BP matters although without a consistent direction. Some GDG members argued that a very high level should prompt treatment before labs; whereas others thought that a high BP can signal secondary HTN and may signal towards getting the labs.
RESOURCE USE	**How large are the resource requirements?**	Large costs ☐ Moderate costs ☐ Small ☒ Moderate savings ☐ Large savings ☐ Varies ☐ **Detailed judgements**	**RESEARCH EVIDENCE** The basic cost would be for electrolytes, creatinine, lipogram, glucose, HBA1C, dipsticks urine, and ECG. Cost to the individual are small in comparison to lifelong treatment. For health systems laboratory tests will have substantial impact on the health system due to the high levels of HTN in most communities. This may impact under-resourced communities. However, relative to overall costs of treatment and complications this is relatively small.[6] [24]
	How large is the incremental cost relative to the net benefit?	Very large ICER ☐ Large ICER ☐ Moderate ICER ☐ Small ICER ☒ Savings ☐ Varies ☐ **Detailed judgements**	**RESEARCH EVIDENCE** Unlikely to be cost saving. The incremental costs would be small in relation to overall cost of management of HT and its complications. It is unknown whether this would lead to cost saving. It depends on the type of test. Basic tests are less costly. However, if additional tests like echocardiogram, 24 ABPM monitoring were added this will have substantial impact.[24]
EQUITY	**What would be the impact on health inequities?**	Increased ☐ Probably increased ☒ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies ☐ **Detailed judgements**	**PANEL INPUT** Lab tests are easier to get in well-resourced settings, but in low-resourced settings mandating them before starting treatment can impede treatment and cause disparities.

ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	No clear data to suggest lack of acceptability.
FEASIBILITY	**Is the option feasible to implement?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	**PANEL INPUT** This depends on available resources but is likely more feasible in well-resourced settings. It is also more likely to be feasible in a clinical setting as opposed to HTN being managed in a public health setting or non-clinical environment. It can vary based on the health system infrastructure and payment system. The move towards point of care diagnostics can make this more feasible.

Recommendation 2: laboratory testing

Recommendation 2	**When starting pharmacologic 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.**				
Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	**We suggest using the option**	**We recommend the option**
	☐	☐	☐	☒	☐
Justification	Performing tests will assist in evaluating the following, which is an essential clinical component of the assessment and management of HTN: 1. Identifying secondary HTN 2. Identifying comorbidities (e.g., DM, dyslipidaemia) 3. Identifying end organ damage (e.g. CKD or LVH) 4. Cardiac risk stratification 5. Pre-identifying potential adverse events from treatments (e.g. uric acid, abnormal electrolytes) 6. Compelling indications to pharmacological treatment				
Subgroup considerations	In patients with a history or exam findings that suggests being at high risk for comorbidities or who have severe HTN, testing and detailed assessment are more justified.				
Implementation considerations	Suggested laboratory tests include electrolytes, creatinine, lipogram, glucose, HBA1C, dipsticks urine, and ECG. In low-resourced areas or non-clinical settings where testing may not be implementable because of additional costs, access to laboratories and ECG, treatment should not be delayed and testing could be arranged to be done subsequently. Some meds like long-acting dihydropyridine CBB are more amenable to being started without testing compared to diuretic or renin-angiotensin-aldosterone system (RAAS) inhibitors.				
Monitoring and evaluation considerations	There is no guidance on how often these tests should be performed but analysis of the LIFE study showed regression/progression of ECG LVH or albuminuria was associated with improved/worse outcomes, independent of BP respectively.[25] [26]				
Research priorities	There needs to be greater understanding of the essential tests to be performed in all patients to reduce costs and improve outcomes.				

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

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE/PANEL INPUT
VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	Important uncertainty or variability ☐ / Possibly important uncertainty or variability ☒ / Probably no important uncertainty or variability ☐ / No important uncertainty or variability ☐ / No known undesirable outcomes ☐ **Detailed judgements**	**RESEARCH EVIDENCE** There is no scientific evidence about how patients or healthcare providers value conducting a CVD risk assessment prior to starting pharmacological treatment. **PANEL INPUT** Communication with patients may change their perspective. Patients' perspectives may vary on the setting. In high-resource settings, patients may put more value on long-term outcomes compared to patients in low-resource settings, where they may focus more on immediate treatment without having to bear more costs.
BENEFITS & HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	No included studies ☐ / Very low ☐ / Low ☒ / Moderate ☐ / High ☐ **Detailed judgements**	**RESEARCH EVIDENCE** The certainty of evidence is low/moderate for the outcome of CV events avoided. Risk assessment can potentially prevent 310 MACE events in 1000 people over five years. This evidence is indirect however, for many reasons. This benefit is moderate to large. These effects depend on BP at presentation (graphs diverge at higher level of BP, compared with starting meds without risk assessment).[27] No evidence is provided of undesirable anticipated effects. However, delay in initiating care and loss to follow up are important concerns to be considered, especially in low-resource settings. **PANEL INPUT** Benefits of risk assessment may not all be attributable to risk assessment per se, rather, to the various treatments provided for risk factors identified during risk assessment. It is not very clear whether non-lab-based risk assessment is inferior to more sophisticated or lab-based risk assessment.
	How substantial are the desirable anticipated effects?	Don't know ☐ / Trivial ☐ / Small ☐ / Moderate ☐ / large ☒ / Varies ☐ **Detailed judgements**	
	How substantial are the undesirable anticipated effects?	Don't know ☐ / Trivial ☐ / Small ☒ / Moderate ☐ / large ☐ / Varies ☐ **Detailed judgements**	

	Do the desirable effects outweigh the undesirable effects?	No ☐ Probably No ☐ Don't know ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	
RESOURCE USE	**How large are the resource requirements?**	Large costs ☐ Moderate costs ☐ Small ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Detailed judgements**	**RESEARCH EVIDENCE** The systematic review revealed moderate costs for treatment of HTN (USD 22/mth) as compared to treatment of CVD outcomes (up to USD 5000/episode) were HTN not treated.[28] However, the cost of implementation of CVD risk assessment should also include capacity building of healthcare providers and the time taken to do so for each patient.
	How large is the incremental cost relative to the net benefit?	Very large ICER ☐ Large ICER ☐ Moderate ICER ☐ Small ICER ☐ Savings ☐ Varies ☒ **Detailed judgements**	**RESEARCH EVIDENCE** There is no direct evidence of whether treatment of HTN with or without risk stratification is more cost effective. Cost of testing and delay in initiating care can be significant following a CVD risk stratification strategy in low-resource settings. Gaziano et al modelling 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, cost of care and travel time were not included in the analysis.[29] A meta analysis showed that proportional reduction in major CVD events from BP lowering did not differ substantially with the presence or absence of previous cardiovascular disease events, coronary heart disease, or cerebrovascular disease. Hence, the absolute benefit of BP lowering would be greatest in those with highest absolute risk of CVD.[30]
EQUITY	**What would be the impact on health inequities?**	Increased ☒ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies ☐ **Detailed judgements**	Studies show that in high-income countries such as the US, people at lower socioeconomic status (SES) have lower BP control and higher CVD risk over the years, as compared to people at higher SES.[31] Thus, in low-resource settings, adding one more step before initiating treatment may increase inequities since those patients who have limited access to healthcare services may suffer delays in treatment or even end up not receiving HTN treatment at all.

ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies ☒ **Detailed judgements**	In low-income settings, information on the availability of resources in health centres has reported their limited capacity to provide care for HTN, and the contribution of the private sector was also described as limited. Moreover, HTN management at district and commune levels is based mainly on measuring BP and rarely takes into account behavioral or metabolic risk factors (e.g. smoking, total blood cholesterol, and the presence or absence of diabetes mellitus).[21]
FEASIBILITY	**Is the option feasible to implement?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	A study in UK showed that primary care physicians found using chart-based risk stratification easy to use in busy practices.[32] Fewer than 30% of cardiologists do formal risk assessment. Depending on the risk stratification approach chosen, it may be more feasible or less feasible to apply this strategy in order to initiate HTN treatment. Another important factor would be the resources available in different settings. In general, especially in low-resource settings, the implementation of this strategy may be challenging. Non lab-based risk assessment is more feasible. Implementation in EMR improves feasibility and adherence.

Recommendation 3: CVD disease risk assessment

Recommendation	**WHO suggests CVD risk-stratification at or after the initiation of pharmacological treatment for hypertension, but only where feasible and does not delay treatment.**				
Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	**We suggest using the option**	We recommend the option
	☐	☐	☐	☒	☐
Justification	CVD risk stratification prior to initiating BP treatment may improve CVD mortality, especially at higher BP levels of >150/90 mmHg. Indirect evidence from modelling studies shows CVD risk-stratification to not only improve clinical outcomes, but also help with cost benefit. However, in the absence of resources, a delay in initiation of treatments, especially at BP levels >150/90 may be more harmful.				
Subgroup considerations	Risk stratification is more justified with higher levels of BP and in patients with multiple comorbidities				
Implementation considerations	If medications were started based on a threshold of SBP of 140, then risk assessment becomes most important in those with lower SBP (e.g. 130–139) Many CV risk-assessment systems are available.[33] [34] In the absence of a calibrated equation for the local population, the choice should depend of resources available, acceptability and feasibility of application. In any case, whenever risk stratification may threaten timing initiation of HTN treatment and/or patient's follow-up, it should be postponed, and included in the follow-up strategy, rather than taken as a first step to indicate treatment.				
Monitoring and evaluation considerations	In those people with an increased cardiovascular risk, appropriate management should be implemented according to the specific components that are affected, including lifestyle modification, pharmacological treatment, additional tests or referral, if needed.				
Research priorities	Future research in this area should explore key aspects concerning implementation of a risk-based approach to CVD prevention and BP-lowering pharmacological treatment.				

PICO questions 4–5: In adults with hypertension requiring pharmacological treatment, which drugs should be used as first-line agents? 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?

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE/PANEL INPUT
VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	Important uncertainty or variability: ☐ Possibly important uncertainty or variability: ☒ Probably no important uncertainty or variability: ☐ No important uncertainty or variability: ☐ No known undesirable outcomes: ☐ **Detailed judgements**	**RESEARCH EVIDENCE** Shahaj et al.[22] synthesized six qualitative and 29 quantitative reviews and identified a range of individual and social factors, including familial (lack of support, need for separate meals) and environmental (sense of security, local amenities, healthy food availability), as challenges to treatment adherence. Differences between clinicians' and patients' beliefs were potential sources of confusion and mistrust and were related to both cultural and individual beliefs. (e.g. perceptions of symptoms, disease management, and treatment expectations). A review by Fragasso et al.[3] 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, due to drug prescription. There is limited survey evidence to document the value placed on antihypertensive therapy by patients and providers. Interviews were conducted in 110 of 1080 South Asian and 153 of 540 Caucasian adults (35–74 years) who were randomly sampled from the resident population of Sheffield, UK in 2005. Based on participant responses to dummy patient scenarios, general acceptance of antihypertensive drug therapy was documented, with greater acceptance in the context of higher dummy patient cardiovascular risk and higher survey participant SES. However, as many as 35% of the Caucasians and 20% of the South Asians in the two lowest categories of SES told their interviewer that they would not accept antihypertensive drug therapy.[35] **PANEL INPUT** Overall, the available survey data is limited, outdated, and of relatively poor quality. The value of antihypertensive therapy is well accepted by HTN "experts", professional societies, government agencies and most patients. There are, however, some individuals who are eligible for antihypertensive treatment who either evade efforts aimed at treatment or are prescribed a treatment but fail to take/adhere to the treatment. The asymptomatic nature of the disease could be a contributing factor. Patients may favor HCTZ due to cost, but older individuals may not like it, etc.

BENEFITS AND HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	No included studies ☐ Very low ☐ Low ☐ Moderate ☐ High ☒ **Detailed judgements**	**Benefits**: Per 1000 people, mortality and MACE reduction respectively: ACEi (23, 48), ARB (14, 1), CCB (8, 23), low dose HCTZ like (3,14), BB (2,8). Less stroke protection with BB. **AE**: >60 for diuretics and 113 for BB (per 1000). Withdrawal from ACEi 12 and cough 26. 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).[36] Drug vs drug, minimal differences in SBP or DBP (0.5–2 mmHg). Hard end point: smaller number of studies, some patterns noted such as less HF with RAAS, potentially increased stroke. RAAS superior to BB for diabetics (MACE, HF). The amount of BP reduction is the major determinant of reduction in cardiovascular events than the choice of antihypertensive drug (ALLHAT, VALUE, and CAMELOT trials). Diuretic trials are older; practice patterns have changed. DM and CKD spectrum in the trials is wide in term of severity/stage. In adults at high risk for CVD, there is certainty, varying from high for diuretics (thiazides and thiazide-like agents) to low to moderate for renin-angiotensin-aldosterone system (RASS) inhibitors (angiotensin converting enzyme inhibitors (ACEis) and angiotensin-receptor blockers (ARBs)), calcium channel blockers (CCB), and beta-blockers that agents from these classes prevent cardiovascular disease (CVD) compared to placebo and/or usual care.
	How substantial are the desirable anticipated effects?	Don't know ☐ Trivial ☐ Small ☐ Moderate ☐ Large ☒ Varies ☐ **Detailed judgements**	In general, the active agents have reduced the risk of coronary heart disease by about 20% compared to placebo/usual care in trials. The corresponding reduction in stroke has been about 30–40%.
	How substantial are the undesirable anticipated effects?	Don't know ☐ Trivial ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ **Detailed judgements**	Undesirable effects are recognized with agents from all classes of antihypertensive drugs. However, they are infrequent, usually mild, and can be managed or another agent can be substituted. ALLHAT suggested greater decrease in BP in blacks with chlorthalidone than lisinopril, and that stroke was significantly less likely with the diuretic than with the lisinopril in blacks but not in nonblacks.[37]

	Do the desirable effects outweigh the undesirable effects?	No ☐ Probably No ☐ Don't know ☐ Probably Yes ☐ Yes ☒ Varies ☐ **Detailed judgements**	The beneficial effects of antihypertensive drug therapy in preventing CVD events outweigh the undesirable effects, which are rare, usually mild, and can be managed by modifying the dosage or by addition or substitution of other agents.
RESOURCE USE	**How large are the resource requirements?**	Glob ☐ Moderate costs ☐ Small ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Detailed judgements**	Agents from all recommended classes of antihypertensive agents are available as generic drugs. In many countries, generic agents are available free of cost or at subsidized prices to all or a majority of patients with HTN. Other costs related to workforce requirements, provision of infrastructure, laboratory testing, lost work time etc. are real but modest. Countries not used to paying for NCD care may have more challenges even at generic prices, making the case for lower prices. This can vary by country, policy, health system; it is less feasible in smaller countries or when health care is paid for from out-of-pocket expenses. Standardized treatments bought at large volume can reduce cost. Affordability varies despite evidence of cost effectiveness.
	How large is the incremental cost relative to the net benefit?	Very large ICER ☐ Large ICER ☐ Moderate ICER ☐ Small ICER ☐ Savings ☒ Varies ☐ **Detailed judgements**	Numerous modelling studies are available and demonstrate cost effectiveness of antihypertensive therapy. Park et al conducted a systematic review of cost-effectiveness studies and all antihypertensives were cost effective compared with no treatment (dominant strategy, USD 19 945/QALY).[38] Treatment of HTN is very beneficial compared to costs in all countries but is especially beneficial in low- and middle-income countries with large numbers of adults with untreated high BPs (and high risk of CVD). For example, a study in Bangladesh suggested an almost 13-fold annual return on investment.[39] Models from Ghana, Nigeria and other countries are available.[4041]
EQUITY	**What would be the impact on health inequities?**	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies ☐ **Detailed judgements**	The commissioned reviews and literature include many studies that shows disparities in BP meds adherence and CV outcomes based on race or SES. The impact would be substantial. In studies where equally effective treatment has been delivered to underserved minorities the intermediate outcome (BP control) and prevention of CVD have been similar.
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	There is strong acceptance by health professionals and by governments when the health value and cost-effectiveness of antihypertensive therapy is recognized. WHO plays a major role in helping ministries of health to understand the value and practicality of effective recognition and treatment of high BP. From a patient standpoint, numerous studies show variable adherence, possibly due to the asymptomatic nature of HTN and long-term horizon for perceived benefit, and worry about AE.

FEASIBILITY	**Is the option feasible to implement?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐ **Detailed judgements**	Not only is high BP the most important major, modifiable risk factor for CVD, but BP reduction is one of the most feasible interventions for prevention of CVD.

Recommendation 4: drug classes to be used as first-line agents

Recommendation	**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 (ACEi)/angiotensin receptor blockers (ARB)** **3. long-acting dihydropyridine calcium channel blockers (CCB).**

Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	**We recommend the option**
	☐	☐	☐	☐	☒

Justification

Numerous aggregate patient data (study level data) systematic reviews are available and demonstrate effectiveness. In addition, a series of meta-analytic reports from the Blood Pressure Lowering Treatment Trialists Collaboration (starting in 2000 and continuing through 2019)[42] and network meta-analyses are also available (e.g. a network meta-analysis conducted by the 2017 ACC/AHA BP Guideline[43] Evidence Review Committee) and show similar conclusions. The benefits exceed adverse events, which are transient and mild in the majority of time. The intervention is likely feasible, acceptable and consistent with stakeholders values.

Numerous randomized controlled trials and meta-analysis of randomized trials have documented the efficacy of diuretics, renin-angiotensin-aldosterone system inhibitors (RASSi) (ACEis and ARBs), CCB, and beta-blockers compared to placebo and/or usual care. Almost all these trials have recruited adults either with CVD or at high risk for developing CVD. Many patients in clinical practice settings also tend to be at high risk for CVD,[44] although some are not.

Head-to-head studies and meta-analyses suggest superiority of the three recommended interventions. The largest (N=42,418), most comprehensive, and well-designed trial to test the comparative effectiveness of different first-step antihypertensive drugs was the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which compared a CCB (amlodipine), ACEi (lisinopril), and alpha-receptor blocker (doxazosin) to a diuretic (chlorthalidone). The doxazosin comparison was stopped early due to inferiority of doxazosin to chlorthalidone.[45] The primary outcome (fatal and non-fatal CHD) and all-cause mortality were similar for the amlodipine, lisinopril, and chlorthalidone groups. New onset heart failure was less common in the diuretic group, especially compared to the CCB group, but also compared to the ACEi group. New onset stroke was less common in the diuretic group compared to the ACEi group, especially in the black participants. The 2018 Reboussin et al network meta-analysis[46] of 58 randomized controlled trials provides the best evidence for recognition of differences in efficacy between antihypertensive treatment with diuretics, CCBs, ACEis, ARBs, and beta-blockers. Compared to diuretics, beta-blockers were less effective for prevention of major CVD events, and for prevention of fatal/non-fatal stroke, with a similar but non-significant inferiority trend for all-cause mortality, CVD mortality, and heart failure. Compared to diuretics, CCB were less effective for prevention of heart failure.

	In the 2015 Thomopoulos direct meta-analysis,[47] diuretics were superior to all other classes for prevention of heart failure, and beta-blockers were less effective for prevention of stroke. CCBs were most effective for prevention of stroke and all-cause mortality (but inferior for prevention of heart failure). ACEis were most effective for prevention of CHD but were less effective for prevention of stroke. ARBs were less effective for prevention of heart failure. Overall, analyses of randomized controlled trials are consistent in reporting that diuretics, CCB, and RASS inhibitors are superior to beta-blockers for first-line antihypertensive drug therapy. Beta-blockers should only be employed as first-line agents when there is a separate compelling indication for their use. The data further indicate that CCB and diuretics are the best agents for prevention of stroke, and diuretics are the best and CCB are the least effective agents for prevention of heart failure. Except for these differences, diuretics, CCB, and RASS inhibitors are similarly effective for first-step therapy of HTN.
Subgroup considerations	Indications to consider specific agents include diuretics or CCB in older or black patients, beta-blockers in patients with HTN who are post myocardial infarction, RAAS inhibitors in diabetes mellitus, heart failure or renal disease. [4849]
Implementation considerations	Critically important to ensure accurate diagnosis of HTN. Important to recognize masked and white coat HTN. Evidence supporting the efficacy of antihypertensive drug therapy has come from randomized controlled trials conducted in adults who were selected because they were at high risk for CVD/ASCVD. Because CVD risk increases with higher levels of BP and risk factors for CVD tend to track together, assumption of high CVD risk is reasonable in adults with a confirmed average SBP ≥140 mmHg and/or DBP ≥90 mmHg.
Monitoring and evaluation considerations	Adults being treated with antihypertensive drug therapy should be monitored for their BP response, symptoms, and selected laboratory values, if recommended and feasible. Laboratory monitoring is most desirable with diuretic therapy, especially long-acting diuretics, and least important with CCB.
Research priorities	An important research question is whether and to what extent laboratory evaluation is required in clinical and public health practice.

PICO question 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?

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE/PANEL INPUT
VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	Important uncertainty or variability ☐ / Possibly important uncertainty or variability ☒ / Probably no important uncertainty or variability ☐ / No important uncertainty or variability ☐ / No known undesirable outcomes ☐ **Detailed judgements**	**PANEL INPUT** Combination (two drug) therapy may be less acceptable in some settings if more expensive and may be more acceptable in a fixed dose. The main outcomes of controlling BP in adults with HTN using safe and effective pharmacologic medications such as improving BP control, medication adherence/persistence, and reducing major clinical outcomes of the hypertensive process, including cardiac, cerebral, and renal among others, is well accepted by individuals with HTN. Patients are concerned about the side-effect profile of each individual agent or combination of agents. Real-world data demonstrates that individuals with HTN accept and are comfortable with using combination antihypertensive agents in the intial pharmacologic management of HTN.
BENEFITS AND HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	No included studies ☐ / Very low ☒ / Low ☐ / Moderate ☐ / High ☐ **Detailed judgements**	There is very low certainty regarding the clinical outcomes of mortality, and CV morbidity and mortality, when monotherapy and combination therapy are compared in 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 a multiple-pill combination. Propensity-score-adjusted analysis suggests that an initial two-drug single-pill or multiple-pill combination was associated with significant reductions in the risk of death (−20%, 11% to 28%) and hospitalization for cardiovascular events (−16%, 10% to 21%) compared with initial monotherapy.[50] However, monotherapy is less likely to achieve the recommended BP targets.
	How substantial are the desirable anticipated effects?	Don't know ☐ / Trivial ☐ / Small ☐ / Moderate ☒ / Large ☐ / Varies ☐ **Detailed judgements**	Combination medication, particularly in a single pill, may improve other outcomes, such as patient adherence/persistence (with a single pill), proportion of individuals with BP control and, if complimentary classes of medications are given at lower doses, may reduce side-effects and increase patient acceptance

	How substantial are the undesirable anticipated effects?	Don't know ☐ Trivial ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ **Detailed judgements**	Consideration of undesirable effects of combination therapy, such as increased side-effects of combination therapy, are somewhat important. There is a wide range of results regarding side-effects of combination therapy from more to less, with the majority of data indicating that combination therapy results in fewer side-effects and greater adherence.
	Do the desirable effects outweigh the undesirable effects?	No ☐ Probably No ☐ Don't know ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	The desirable effects of improved BP control of combination antihypertensive therapy and possibly fewer side-effects due to use of lower doses of each drug, probably outweigh the undesirable effects such as side-effect profile.
RESOURCE USE	**How large are the resource requirements?**	Glob ☐ Moderate costs ☐ Small ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Detailed judgements**	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.
	How large is the incremental cost relative to the net benefit?	Very large ICER ☐ Large ICER ☐ Moderate ICER ☐ Small ICER ☒ Savings ☐ Varies ☐ **Detailed judgements**	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 likely faster with combination therapy. Many modelling studies that evaluated combination vs monotherapy used a fixed dose (a different PICO question, thus constitutes indirect evidence). One model from Japan used data from RCT 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.[51]
EQUITY	**What would be the impact on health inequities?**	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies ☐ **Detailed judgements**	Since HTN control rates would be greater in both high- and low-to-middle-income countries with combination antihypertensive therapy, when complementary classes of agents are used reductions in BP are equal in a diverse range of demographics such as age, sex, race and ethnicity, the impact on reducing health inequities is large.

ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	Initial combination therapy can be initially met with scepticism among stakeholders, including health care providers, although this is rapidly decreasing. Where implemented, the scepticism rapidly resolves and converts to acceptance.
FEASIBILITY	**Is the option feasible to implement?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐ **Detailed judgements**	Clinical studies and, more importantly, real-world experience and data demonstrate that this option is clearly feasible.

Partial recommendation 4: drug classes

Partial recommendation	**Conditional recommendation for two-medication combination over monotherapy. See beneath PICO question 8 for full wording of the recommendation.**				
Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	**We suggest using the option**	We recommend the option
	☐	☐	☐	☒	☐
Justification	Despite effective, safe, affordable, and available pharmacologic antihypertensive agents, the control rates of HTN are dismal in both high- and low-to-middle-income countries worldwide, and over the last five to 10 years have been decreasing in some high and low-to-middle-income countries in tandem with increasing major cardiovascular events. A combination therapy approach may have several advantages over the traditional up-titration monotherapy approach: 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 least additive of the two chosen agents) in comparison to full-dose monotherapy titration; lower doses of each agent are needed, which results in a reduction of side-effects due to use of lower doses for each agent and the fact that use of complementary classes of antihypertensive agents may mitigate the side-effects of each agent; clinical/therapeutic inertia is reduced; adherence to the agents is increased; a simpler dose schedule is possible; pill burden is reduced; BP is lowered equally across a broad range of demographic groups (sex, age, race and ethnicity); and logistics can be simplified, leading to fewer stock-outs and reduced pharmacy inventory.[52 53] It is important to note that, currently, comparative studies between combination and monotherapy 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. However, there is moderately convincing data which demonstrates that combination therapy leads to greater patient adherence to antihypertensive agents and persistence to therapy. These are highly desirable outcomes in the treatment of adults with HTN. An 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[54] and is a major component of the WHO Global HEARTS Programme and the PAHO HEARTS in the Americas Initiative.[55] Recently, combination antihypertensive medications in a single pill have been added to the WHO Essential Medication List.[56] This approach has demonstrated general acceptance by government, public, and private stakeholders and is demonstrating success in increasing HTN control rates in both high- and low-to-middle-income countries.				
Subgroup considerations	Certain combinations may be better when a specific medication is indicated for an individual with a co-morbidity or disease, such as HTN in persons with diabetes mellitus, chronic kidney disease, or coronary heart disease.				

Implementation considerations	Combination medication therapy may be especially valuable when the baseline BP is ≥20/10 mmHg than the goal BP. However, given the trend to recommending a lower BP goal than in the past, initial combination therapy may be desirable in most, if not in all, patients with untreated HTN.
Monitoring and evaluation considerations	Monitoring and follow up after initiation of combination therapy is needed, and it will likely be similar to monitoring after initiation of monotherapy.
Research priorities	The number of randomized trials that evaluated this question was small. Long term data about hard clinical endpoints compared between monotherapy and combination therapy are needed.

PICO question 7: In adults with hypertension requiring pharmacological treatment, which drugs 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?

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE/PANEL INPUT
VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	Important uncertainty or variability ☐ / Possibly important uncertainty or variability ☐ / Probably no important uncertainty or variability ☐ / No important uncertainty or variability ☒ / No known undesirable outcomes ☐ **Detailed judgementsDDetailed judgements**	No reliable data about patient values as it relates to a combination therapy vs another combination.
BENEFITS AND HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	No included studies ☐ / Very low ☒ / Low ☒ / Moderate ☒ / High ☐ **Detailed judgements**	**PANEL INPUT** Given that the three classes of antihypertensive agents are recommended as monotherapy for the initial treatment of the adult with HTN and the certainty about the clinical outcomes of mortality, CV mortality, BP level and adverse events of these classes, compared to other available classes, the certainty of using two of these classes of agents together is high. The desirable effects of greater adherence/persistence, improved BP control, and improved clinical outcomes of combinations of the three classes of antihypertensive therapy compared outweigh the undesirable effects such as side-effect profile. RAAS+CCB may have higher reduction of MACE and AE, yet may not be preferred in older individuals.
	How substantial are the desirable anticipated effects?	Don't know ☐ / Trivial ☐ / Small ☐ / Moderate ☒ / Large ☒ / Varies ☐ **Detailed judgements**	
	How substantial are the undesirable anticipated effects?	Don't know ☐ / Trivial ☐ / Small ☐ / Moderate ☒ / Large ☐ / Varies ☐ **Detailed judgements**	

	Do the desirable effects outweigh the undesirable effects?	No ☐ Probably No ☐ Don't know ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	
RESOURCE USE	**How large are the resource requirements?**	Glob ☐ Moderate costs ☐ Small ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Detailed judgements**	Combination therapy is accompanied initially by a moderate increase in resource requirements, such as procurement, supply chain, and direct medication costs.
	How large is the incremental cost relative to the net benefit?	Very large ICER ☐ Large ICER ☐ Moderate ICER ☐ Small ICER ☐ Savings ☐ Varies ☒ **Detailed judgements**	The net benefit of improved BP control and reduction of major events associated with the hypertensive process compared to the increase is cost is large.
EQUITY	**What would be the impact on health inequities?**	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies ☐ **Detailed judgements**	Since combination therapy of any of these three classes of medications should improve HTN control rates in high- and low-to-middle-income countries, and decrease major clinical events, and when complementary classes of agents are used BP is reduced equally in a diverse range of demographics such as age, sex, race, and ethnicity, the impact on health inequities is large.
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	Based on price and stakeholder. Treating physicians would favour faster BP control; patient perspective differs. Combination therapy can initially be met with scepticism among stakeholders, including health care providers. However, where implemented, this initial scepticism rapidly resolves and converts to acceptance.
FEASIBILITY	**Is the option feasible to implement?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	Clinical studies and real-world experience and data demonstrate that this option is clearly feasible.

Partial recommendation 4: drug classes

Partial recommendation	**Strong recommendation for two-drug combinations chosen from the following three drug classes: diuretics (thiazide or thiazide-like), angiotensin converting-enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB), and dihydropyridine calcium channel blockers (CCB); over other combination therapies. See beneath PICO question 8 for full wording of the recommendation.**				
Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	**We recommend the option**
	☐	☐	☐	☐	☒
Justification	It is important to note that only two-drug combinations, as opposed to three or more drugs, are the ones most studied and being recommended. Importantly, the pharmacologic treatment of the adult with HTN is currently the traditional method of starting one antihypertensive agent and maximizing its dose via titration and, if needed, then starting a second antihypertensive agent and maximizing its dose via titration, etc. Thus, this concern over the poor and perhaps even decreasing HTN control rates has given rise to an alternative pharmacologic strategy (discussed in a separate PICO) which utilizes initiating two antihypertensive agents at once in the initial treatment of the adult with HTN, the so-called, combination approach. This combination approach could be either in the form of two separate pills or in a single-pill combination. If this strategy is to be considered, it is important to delineate which two anti-HTN classes of agents should be used. In addressing this question, it is also important to note the discussion and recommendations in PICO 4 and 5, which recommend three classes: thiazide or thiazide-like diuretics, renin angiotensin system inhibitors (ACEi or ARB), and CCB agents as first-line treatment. Thus, if two antihypertensive agents are to be used in combination, two-drug combinations of these classes and agents within each class are recommended. While large and prolonged duration studies are lacking comparing a certain two-drug combination with a different two-drug combination, there is some data to suggest that a two-drug combination with renin-angiotensin system inhibitors and CCBs offer advantages over renin-angiotensin system inhibitors and thiazide diuretics. Less information regarding comparison to a combination of diuretics and CCBs is available. Thus, there is an urgent need for high-quality, randomized studies in this area. Initiating combination treatment with two-drug combinations of these classes, particularly combinations of renin-angiotensin system inhibitors, either an ACEi or ARB, plus a thiazide or thiazide-like agent or a CCB, have been employed for over 15 years in large health systems such as the Kaiser Permanente system in the United States and is a major component of the Global HEARTS Programme, including the HEARTS in the Americas Initiative in the initial treatment of HTN. In this initiative currently 12 countries are using a combination of these two classes in the initial treatment of HTN. This approach has demonstrated general acceptance by government, public, and private stakeholders, and is demonstrating success in increasing HTN control rates in both high- and low-to-middle-income countries.				
Subgroup considerations					
Implementation considerations					

Monitoring and evaluation considerations

Research priorities

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

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE/PANEL INPUT
VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	Important uncertainty or variability ☐ / Possibly important uncertainty or variability ☐ / Probably no important uncertainty or variability ☐ / No important uncertainty or variability ☒ / No known undesirable outcomes ☐ **Detailed judgements**	Considering the ease of using a single-pill combination over a multiple-pill combination and the anticipated impact on adherence and persistence, the Guidelines Development Group anticipates no important variability in patient or other stakeholder values about the critical outcomes. A systematic review demonstrated that simplifying dosing regimens results in significant improvements in medication adherence, ranging from 6–20%.[57] There are cost implications when single-pill combinations are expensive from a patient point of view.
BENEFITS AND HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	No included studies ☐ / Very low ☐ / Low ☒ / Moderate ☐ / High ☐ **Detailed judgements**	Evidence is limited in terms of hard endpoints or adverse effects. Evidence supporting single-pill vs multiple-pill combination is confounded by comparisons of monotherapy vs combination therapy, although the two concepts are tightly associated. Low certainty evidence shows that single-pill comination use was associated with better adherence and persistence rates.
	How substantial are the desirable anticipated effects?	Don't know ☐ / Trivial ☐ / Small ☐ / Moderate ☒ / Large ☐ / Varies ☐ **Detailed judgements**	Increased patient adherence and persistence with pharmacologic antihypertensive therapy could lead to increased BP control and improved clinical outcomes which are strongly desired. As with PICO questions 6 and 7, if complimentary classes of medications are included in the single-pill combination and given at lower doses, this may reduce side-effects of treatment.
	How substantial are the undesirable anticipated effects?	Don't know ☐ / Trivial ☐ / Small ☒ / Moderate ☐ / Large ☐ / Varies ☐ **Detailed judgements**	Consideration of undesirable side-effects of combination therapy are somewhat important. As above, the use of complementary classes together may decrease side-effects, although this has not been demonstrated with high certainty.

	Do the desirable effects outweigh the undesirable effects?	No ☐ Probably No ☐ Don't know ☐ Probably Yes ☐ Yes ☒ Varies ☐ **Detailed judgements**	The desirable effects of greater adherence/persistence with the potential to improve BP control and clinical outcomes of A single-pill combination outweigh the undesirable effects such as side-effect profile.
RESOURCE USE	**How large are the resource requirements?**	Glob ☐ Moderate costs ☐ Small ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Detailed judgements**	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 for the single-pill combination strategy compared with the up-titration strategy, which may offset initial costs.[58] Single-pill combination therapy is accompanied initially by a moderate increase in resource requirements such as procurement, supply chain, and direct medication costs. Single-pill combination therapy is more expensive in some settings.
	How large is the incremental cost relative to the net benefit?	Very large ICER ☐ Large ICER ☐ Moderate ICER ☐ Small ICER ☐ Savings ☐ Varies ☒ **Detailed judgements**	The net benefit of improved BP control and reduction of major events associated with the hypertensive process compared to the increase is cost is large. Faster BP control can improve the cost-effectiveness of single-pill combination therapy. Countries with a pharmaceutical policy, using generic medications, standardized protocols, and centralized purchase mechanisms can reduce the prices of single-pill combination a lot. In one model from China, olmesartan/amlodipine single-pill combination was dominant compared with olmesartan and amlodipine multiple-pill combination and valsartan/amlodipine single-pill combination.[59] In a second study there was reduction in cost of therapy by 33% with a saving of USD 19 per patient/month after switching from multiple-pill combination to single-pill combination.[60]
EQUITY	**What would be the impact on health inequities?**	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies ☐ **Detailed judgements**	Since single-pill combination therapy increases medication adherence and persistence, which could improve HTN control rates in high- and low-to-middle-income countries and decrease major clinical events, and when complementary classes of agents are used BP is reduced equally in a diverse range of demographics such as age, sex, race, and ethnicity, the beneficial impact on health inequities is large.

ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	Combination therapy, including in a single-pill combination can initially be met with scepticism among stakeholders, including health care providers. However, where implemented, this initial scepticism rapidly resolves and converts to acceptance.
FEASIBILITY	**Is the option feasible to implement?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐ **Detailed judgements**	**RESEARCH EVIDENCE** Cinical studies and real-world experience and data demonstrate that this option is likely feasible. 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.[10] Thus, the intervention is feasible to implement. Angeli et al.[61] has suggested that the use of single-pill combinations implies less flexibility in modifying the doses of individual components and the exposure of patients to unnecessary therapy. Moreover, should a patient develop side-effects to one component, the entire combination should be discontinued and replaced by multiple pills. Using single-pill combinations, the physician cannot easily titrate one component without changing the other. None of the tablets currently available on the market are able to be broken to allow sufficient flexibility. Only specific manufacturing options might be suitable to achieve a successful titration in clinical practice. **PANEL INPUT** Supply chain and procurement become easier with a single-pill combination. Market and manufacturing considerations are critical. Single-pill combinations were added to the WHO Essential Medicines list (four options are currently available). Smaller doses of single-pill combinations are not always available to use as a starting dose or to treat milder levels of HTN.

Recommendation 5: combination therapy

Recommendation	**For adults with hypertension requiring pharmacological treatment, WHO suggests combination therapy, preferably with a single-pill combination 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 (ACEi)/angiotensin-receptor blocker (ARB), and dihydropyridine calcium channel blockers (CCB).**				
Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	**We suggest using the option**	We recommend the option
	☐	☐	☐	☒	☐
Justification	The available data on a single-pill combination vs multiple-pill combination does not provide certainty about hard end points. However, improved adherence and persistence and better BP control are suggested in the literature and in various programmes of HTN management. Improved medication adherence and persistence of treatment could result in a lower BP, resulting in an increase in BP control and a decrease in target organ damage of the hypertensive process. Over 30% of the world population has HTN and only 13.8% are considered controlled.[62] 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.[62 63 64 65] Single-pill combinations are likely acceptable and feasible in most settings. A combination approach in the initial treatment of the adult with HTN has been in place for over 15 years in large health systems such as the Kaiser Permanente system in the United States and is a major component of the Global HEARTS Programme, including the HEARTS in the Americas Initiative in the initial treatment of HTN. Many of these programmes use an initial single-pill combination treatment approach. This approach has demonstrated general acceptance for government, public, and private stakeholders and is demonstrating success in increasing HTN control rates in high-, low- and middle-income countries.				
Subgroup considerations	Any patients in which single-pill combination should not be used?				
Implementation considerations					

Monitoring and evaluation considerations	
Research priorities	It is also important to note that available data are in real-world experiences and research studies which are designed and statistically powered to determine if there is a difference in clinical outcomes such as reduction in major cardiovascular events and mortality between single-pill combinations versus individual treatment are lacking.

PICO question 9: What target BP should pharmacologic treatment aim to achieve?

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE/PANEL INPUT
VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	Important uncertainty or variability ☐ / Possibly important uncertainty or variability ☒ / Probably no important uncertainty or variability ☐ / No important uncertainty or variability ☐ / No known undesirable outcomes ☐ **Detailed judgements**	**PANEL INPUT** From a patient perspective, HTN is often a silent disease and patients may not take antihypertensive medications as directed because their positive effects are not as obvious as potential side-effects from the medications.[4] Society and patients want to avoid premature mortality or disability. Serious adverse events are feared also, but their duration and severity are often not well characterized in trials. Asymptomatic condition with short-term lack of direct signs of benefit is an issue for retaining patients in care and maintaining medication adherence.
BENEFITS AND HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	No included studies ☐ / Very low ☐ / Low ☐ / Moderate ☒ / High ☐ **Detailed judgements**	**RESEARCH EVIDENCE** Desirable/undesirable effects per 1000: 130 vs 140: 17 fewer HF and stroke but 20 more AE; 120 vs 130-139: 27 deaths, 1 more AE. In patients with comorbidity (CAD, DM, CKD): consistent benefit with lower targets (variable thresholds). The benefit is the final reduction in CV events, reaching WHO NCD targets. AE includes dizzziness in intensive control group. Lower targets can increase ischemia in patients with CAD. With lower BP target and older age the tradeoffs can shift towards larger harms. Lower target will be associated with less adherence. **PANEL INPUT** Summarizing evidence for "intensive versus standard" BP treatment targets is challenging – generalizing low and high across differently designed RCTs leads to heterogeneity; dividing up trials into specific targets leads to small numbers and imprecision. Summary results from the Murad[66] meta-analysis leads to the conclusion that treatment to a lower BP target in older individuals leads to a significant reduction in all-cause and CVD mortality, CKD, MI, or stroke outcomes. Despite using different trials and evidence synthesis approach, the Reboussin (ACC/AHA guideline reference 3) review yielded similar results.[46] Neither of these meta-analyses account for the very high risk of the trial cohorts reviewed – at least for SPRINT and ACCORD.[67] [68] We caution against applying this evidence to lower risk patients with raised BP or HTN – specifically, those not meeting eligibilty criteria for SPRINT, ACCORD, or SPS3.[69] Questions
	How substantial are the desirable anticipated effects?	Don't know ☐ / Trivial ☐ / Small ☐ / Moderate ☐ / Large ☒ / Varies ☐ **Detailed judgements**	
	How substantial are the undesirable anticipated effects?	Don't know ☐ / Trivial ☐ / Small ☐ / Moderate ☒ / Large ☐ / Varies ☐ **Detailed judgements**	
	Do the desirable effects outweigh the undesirable effects?	No ☐ / Probably No ☐ / Don't know ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐ **Detailed judgements**	

			about exclusion of frail elderly in these trials persist, though SPRINT did arguably include older and frail elderly ppts. Small sample size meant uncertainty in detecting differences in this overall finding by age, diabetes, or CKD status. Nonetheless, there was no clear difference by age 65–74 vs ≥75 years. Network meta-analyses found a similar direction of effect but more optimistic effect sizes regarding intensive treatment benefit.[70] [71]
RESOURCE USE	**How large are the resource requirements?**	Large costs ☐ Moderate costs ☒ Small ☐ Moderate savings ☐ Large savings ☐ Varies ☐ **Detailed judgements**	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. This translates to about USD 13 000 more per patient over their remaining lifetime.[72] [73] Costs are much less in countries other than US (SPRINT). Treating to lower targets will have diminishing returns as the magnitude of benefit becomes smaller and shifts focus to a smaller number of patients.
	How large is the incremental cost relative to the net benefit?	Very large ICER ☐ Large ICER ☐ Moderate ICER ☒ Small ICER ☐ Savings ☐ Varies ☐ **Detailed judgements**	A cost-effectiveness study of screening and optimal management of HTN and DM and CKD in an Australian setting found that an intensive management of previously uncontrolled HTN compared with usual care resulted in an ICER of AUD 2588 (Australian). They do not specify the target BP for the comparisons.[74] SPRINT trial analysis provides similar inferences.[73] [74]

EQUITY	**What would be the impact on health inequities?**	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies ☐ **Detailed judgements**	**RESEARCH EVIDENCE** HTN is a "disease of poverty", at least in some countries. Even using the <140/90 goal, "many barriers in access to HTN care in low-income settings are low patient health literacy; overburdened health-care providers; the lack of an organizational structure to accommodate a nonphysician as a primary care provider; the lack of confidence and/or policy towards the nonphysician providers' ability to manage uncomplicated and stable patients; the lack of infrastructure for data collection and monitoring of clinical information on a periodic basis as a more intensive target seems to requires more data collection and monitoring; and finally, limited resources."[21] **PANEL INPUT** Focus on intensifying treatment in patients already under care and with lower BP but not if goal may divert attention and resources away from treating people who are unaware/untreated/uncontrolled – the result could be exacerbating inequities in health outcomes. Treating BP can reduce equity because preventing CV events reduces mortality in the society in general. Uncontrolled HTN might be over-represented in vulnerable populations. So, improving HTN treatment and control through better treatment and lower BP targets could reduce inequality in the long term. It varies based on the budget and whether it is fixed. In an overloaded health system, standard of care may suffer. In a well-resourced system, it will be easier. This is an opportunity to expand access and resources and look at models other than physician-centric ones.

ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	**RESEARCH EVIDENCE** Acceptable to health care systems and providers in principle, yes, though governments and health systems are often distracted by more acute demands and higher priority placed on acute conditions and health emergencies. 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 in selected high-risk patients. Many well-known barriers to access to HTN care in low-income settings exist.[22] **PANEL INPUT** 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 targets in the general public are less acceptable to stakeholders. Most available evidence is from high-risk patients receiving intensive treatment and not from the general public. Patients may find more intensive treatment for a chronic asymptomatic condition unacceptable. Taking one additional medication on average may lead to more side-effects (even if not serious AEs), may lead to more out of pocket medications costs, and may lead to the inconvenience of more office visits. People at risk have likely been seen in various settings and are better informed.

FEASIBILITY	**Is the option feasible to implement?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	If risk stratification was not easy, implementation becomes difficult. A few countries in the world have good control, which suggests that it is not feasible. Intensive BP treatment requires more resources and should be the goal of HTN programmes that are already achieving control <140 across the entire population. Risk of concentrating resources on the "high achiever" patients and providers is a concern. From Risso, 2015: The guidelines envisage that all clinics should manage patients with HTN, with staff undergoing specific training in screening and HTN management. BP is not routinely checked during attendance at primary care clinics for other problems, contrary to national guidelines; however some doctors do measure BP in all patients visiting the clinics.[4] Additional evidence of feasibility can be inferred from the WHO, Resolve to Save Lives initiative that included improving the control of HTN using the WHO HEARTS technical package. Five components are necessary for a successful HTN control programme: drug- and dose-specific treatment protocols; access to quality-assured medications and BP monitors; team-based care; patient-centred care delivered in the community, and information systems to enable quality improvement. This programmatic experience of protocol-based treatment of more than 3 million persons from 18 countries was done over a short period.[75]

Recommendation 6: target blood pressure

Recommendations	**WHO recommends a target BP treatment goal <140/90 mmHg in all patients with hypertension without comorbidities.** **WHO recommends a target systolic BP treatment goal <130 mmHg in patients with hypertension and known CVD** **WHO suggests a target systolic BP treatment goal <130 mmHg in high risk patients with hypertension (those with high CVD risk, diabetes, chronic kidney disease).**				
Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	**We recommend the option**
	☐	☐	☐	☐	☒
Justification	Trial evidence is convincing, but feasibility, equity, opportunity cost considerations count against a recommendation to pursue intensive BP treatmen in all jurisdictions..				
Subgroup considerations	• Lack of statistical power to define RR in subgroups, including DM, CKD • No interaction between "old" (65–74) and "very old" (75+) in Murad[66], potentially due to lack of power. • Because some of the major intensive BP treatment trials reviewed selected patients based on high risk (SPRINT, ACCORD, SP3), caution is needed regarding extrapolating these findings to the general population or even intermediate CVD risk groups.				
Implementation considerations	Intensive BP in selected high-risk patients is more justified in countries, subnational areas, or health systems with demonstrated success in controlling BP <140/90 mmHg in the general population living with HTN. Considering the failure of most nations and health care systems to reach population HTN control goals of >50% controlled <140/90 mmHg, putting a priority on intensive treatment in high-risk patients risks focusing more effort on high-risk people when many moderate-risk people are untreated or treated but uncontrolled. The latter are more likely younger and in their productive years, supporting families. Our contention is that intensive BP treatment is "extra credit" and not the main goal. European guidelines frame this prioritization better than US guidelines. 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 and the potential for therapeutic inertia, especially for health workers with more limited training and/or autonomy.				

Monitoring and evaluation considerations	More monitoring resources are needed to reach intensive BP goals in terms of number of medications, number of monitoring visits. Trials have not tested the roles of task shifting or out of office/home monitoring in pursuit of more intensive BP goals. A systems approach to programme evaluation will be needed. For example, trials or simulation studies should examine the impact of increased service intensity to achieve intensive treatment for selected high-risk patients on the access to primary care visits and loss-to-follow up among the remainder of HTN patients (who are "not yet" high risk, and likely to be of working age).
Research priorities	• Better to characterize serious AEs in trials of intensive vs standard BP treatment (severity, duration, costs, utilities) • Quantification of the resource commitment required for more intensive treatment in LICs and MICs and consideration of opportunity cost of directing resources away from primary care by focus on achieving <140/90 in all hypertensives to focus on specialized HTN treatment in high-risk patients • Research needed on the feasibility, acceptability, and efficacy of intensive treatment in high-risk LIC and MIC populations • Inclusion of cognitive outcomes in trials (note provocative results from ACCORD and SPRINT in terms of cognitive outcomes) • More implementation research to demonstrate intensive treatment is feasible in real clinical practice.

PICO question 10: In adults with hypertension given pharmacological treatment, when should BP be reassessed?

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE/PANEL INPUT
VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ No known undesirable outcomes ☐ **Detailed judgements**	**RESEARCH EVIDENCE** Overall, society and patients want to reduce risk of premature mortality or morbidity. Many patients, particularly older ones or those living alone, are reassured by more frequent monitoring of BP. Patients became less fearful of being alone, or not picking up an important clinical sign that their condition may be deteriorating.[76] However, younger, less symptomatic, patients do not request repeat readings at follow-up visits since HTN is a "silent disease" that they do not feel. Despite existing evidence on the effectiveness of telemonitoring for patients experiencing HTN, there is no empirical evidence of its potential success over longer periods of time as well as its generalizability to patients with various backgrounds and educational levels who might react differently to this approach, though several studies identified potential savings and a reduction in the number of visits to health care providers.[77] Busy primary care physicians often fail to ask about adherence and frequently do not adjust medications for uncontrolled patients.[78] **PANEL INPUT** Providers in LICs and MICs are overwhelmed, seeing up to 100 cases per day, and anything that can reduce visits without affecting control would be welcomed. Self-monitoring and remote monitoring are likely to be preferred by patients.

BENEFITS AND HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	No included studies ☐ Very low ☐ Low ☒ Moderate ☐ High ☐ **Detailed judgements**	ACCORD and SPRING followed patients initially for one month. Longer follow-up times can lead to loss to follow up. There appears to be limited data to address this specific question. One RCT compared three months of follow-up to six months after patients were controlled and found no significant difference.[79] One well-conducted retrospective cohort study[80] reported two important findings: for those who were newly diagnosed or on new medications: 1. For those newly diagnosed with HTN those with >1.4 months prior to initiation of treatment had HR of 1.12 (1.05–1.2, p < 0.009) for MACE compared to those started <1.4 months. 2. For those with initiated treatment, those who waited >2.7 months before re-evaluation had HR 1.18 (1.11–1.25, p <0.0001) for MACE compared to those reassessed <2.7 months.
	How substantial are the desirable anticipated effects?	Don't know ☐ Trivial ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ **Detailed judgements**	
	How substantial are the undesirable anticipated effects?	Don't know ☐ Trivial ☐ Smallt ☐ Moderate ☐ Large ☐ Varies ☒ **Detailed judgements**	
	Do the desirable effects outweigh the undesirable effects?	No ☐ Probably No ☐ Don't know ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	
RESOURCE USE	**How large are the resource requirements?**	Large costs ☐ Moderate costs ☐ Small ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Detailed judgements**	No comparative data were identified. Input from panel suggests that many patients in LICs and MICs require monthly clinic visits to pick up medicines, while in HICs the frequency is less. For newly diagnosed and newly initiated on therapy this may be no change in resources in LICs and MIC. However, this would be offset by less frequent visits over the long term if stable patients did not require visits more frequently than twice per year.
	How large is the incremental cost relative to the net benefit?	Very large ICER ☐ Large ICER ☐ Moderate ICER ☐ Small ICER ☐ Savings ☐ Varies ☒ **Detailed judgements**	No comparative data were identified. Input from panel suggests that there would be increased costs seeing newly diagnosed patients frequently that would likely be offset by reducing visit frequency of stable patients. This pattern would lead to overall reductions in costs and better control

EQUITY	**What would be the impact on health inequities?**	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☐ Varies ☒ **Detailed judgements**	Meigari et al. suggest that it will be difficult in low income countries to increase frequency of visits but may be feasible if community HCWs or other workers can be involved in management of BP. Use of home monitoring may be useful.[21] It may reduce inequities when you have a structured follow up framework. However, when system barriers exist, it may worsen.
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	Older and more vulnerable patients would appreciate more frequent monitoring but it will have implications on health systems.[4 76]
FEASIBILITY	**Is the option feasible to implement?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	Will require use of Community HCWs or other health professionals and some evidence of benefit of telemonitoring to increase frequencies to less than a month. This has been demonstrated to be acceptable to patients.

Recommendation 7: frequency of assessment

Recommendation	**WHO suggests a monthly follow up after initiation or a change in antihypertensive medications until patients reach target.** **WHO suggests a follow up every 3–6 months for patients whose blood pressure is under control.**				
Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	**We suggest using the option**	We recommend the option
	☐	☐	☐	☒	☐
Justification	Data suggests that initiating treatment early after diagnosis improves outcomes and that delaying evaluation after initiation also may increase risk of MACE. Once a patient is established in care and BP is under control the frequency of visits is less important. One study showed that there was no statistical difference in measured BP if seen every three months vs six months.[79]				
Subgroup considerations	Older patients with more comorbidities may require more frequent visits relative to younger patients on fewer overall medications.				
Implementation considerations	• Initiation of HTN treatment should occur within four weeks of diagnosis of HTN. If BP level is high or accompanying evidence of end organ damage, initiation of treatment should be faster • Will require system that can track appointments over time and the staffing necessary to meet needs of number of visits and/or use of remote monitoring and task-sharing to achieve increased visits				
Monitoring and evaluation considerations	BP monitoring and data capture mechanisms. System linking pharmacy records to visits for evaluation.				
Research priorities	Evidence that remote monitoring and use of community HCWs/navigators can assist in management of BP. Effectiveness of community/home-based monitoring of BP.				

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

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE/PANEL INPUT
VALUES	**Is there important uncertainty or variability about how much people value the main outcomes?**	Important uncertainty or variability: ☒ Possibly important uncertainty or variability: ☐ Probably no important uncertainty or variability: ☐ No important uncertainty or variability: ☐ No known undesirable outcomes: ☐ **Detailed judgements**	Patient perspective: • In some studies in which BP was managed by nonphysicians, there was good patient satisfaction and high retention, suggesting at least willingness, if not preference, to having BP managed by nonphysicians. An example is a study in which 130 patients managed by nonphysicians and pharmacists with similar (28 mmHg) reductions and high retention in the programme >80%.[81] Many studies have suggested safety of nonphysician prescribing and how it is associated with patient satisfaction.[82] • 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.[83] Another study from Scotland explored patients' perspective on pharmacist prescribing and reported high patient satisfaction but 65% stated that they would prefer to consult a doctor.[84] Health profesionals perspective: • Numerous studies have shown that nurses and pharmacists had improved job satisfaction as a benefit of prescribing, as well as evidence of safety and competency. • Nurses have reported that prescribing is associated with increased workload, work-related stress and continuous need to update competencies, and an additional documentation burden.[85] • Physicians' perspective summarized in one systematic review was overall supportive but included concerns over pharmacists' lack of clinical assessment and diagnosis skills and access to patient medical records, legal concerns, a potential negative effect on the physician–patient relationship, and potential miscommunication between the members of the multidisciplinary team.[86] • Overall society and patients want to reduce 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 MDs vs other providers, which was the primary question.

			• Limited information provided mixed results, where some patients appreciated 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.
BENEFITS AND HARMS OF THE OPTIONS	**What is the overall certainty of the evidence of effects?**	No included studies ☐ Very low ☐ Low ☒ Moderate ☐ High ☐ **Detailed judgements**	Data are available about BP managed by a pharmacist, nurse, dietitian, community HCW and about self-management (primarily self-monitoring). All of the community HCW-led intervention studies included focused on life-style education and health promotion, mainly at home or in community settings. No hard endpoints, data mainly consisted of BP control measures such as percentage controlled, adherence and mean SBP/DBP (as expected in such programmes). Magnitude of effect: better control in 91 to 264 more per 1000, pharmacist, SMP/DBP reduction of 1–8 mmHg, nurse/HCW/dietitian. Evidence is from HICs and may not apply to other settings. The nonphysician training is some countries is quite variable. Although the certainty of evidence was in general low, no study showed that nonphysician management was inferior. In fact, all the data that were limited to either pharmacy, nurse or community HCW-led care was found to be either no different or improved compared to usual care (physician-led care). Scirica et al studied 5000 patients in Boston manged remotely by navigators under pharmacist supervision. No office visits with MD. BP reduction of up to 30 mmHg.[87] The two studies by Scirica and Fisher are two examples of managing over 5000 patients with a non-clinical navigator supervised by a nurse and/or pharmacist and with no clinical visits – all with home BP cuffs with electronic transmission of data and no in-person visits. Prabhakar and others in India and China are conducting similar work with CHWs and show no sign of loss of safety.[81] [87] A systematic review by Greer et al. of pharmacy-managed care led to better BP control (RR 1.44 or 170 more controlled per 1000) with no obviously reported difference in adherence or clinical events or QOL.[88] A systematic review by Anand has shown that in LICs and MICs, task sharing with pharmacists led to 8 mmHg SBP and 3.74 mmHg DBP reductions. Task-sharing with nurses (5.34 mmHg lower), dieticians (4.67 mmHg lower), and CHWs (3.67 mmHg lower) yielded similar results.[89] A systematic review by Tucker[90] 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. Study limited by ability to adequately
	How substantial are the desirable anticipated effects?	Don't know ☐ Trivial ☐ Small ☐ Moderate ☒ Large ☐ Varies ☐ **Detailed judgements**	
	How substantial are the undesirable anticipated effects?	Don't know ☐ Trivial ☐ Small ☒ Moderate ☐ Large ☐ Varies ☐ **Detailed judgements**	
	Do the desirable effects outweigh the undesirable effects?	No ☐ Probably No ☐ Don't know ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	

			blind. Effect likely real but improved when supplemented with education, counseling and telecommunication.
RESOURCE USE	**How large are the resource requirements?**	Large costs ☐ Moderate costs ☐ Small ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Detailed judgements**	Jacob et al.[91] [92] synthesize data from 31 studies (24 in the US) and suggest studies that use community team approaches cost around USD 200/person/yr to implement but with cost-savings for prevention of negative CVD outcomes such that net costs had a median cost of USD 65/person/yr with 10 studies, with negative or cost-savings overall. Most cost/QALY estimates were between USD 3888–24 000/QALY, with pharmacist led more cost-effective than nurse led. Only two were > USD 50 000/QALY out of 28 studies. Most of the remaining cost data presented was related to self-monitoring and not to the question of physician vs nonphysician led care. However, if it is assumed that nonphysician salaries are lower, then potentially costs will be lower, but that assumes that physicians only have limited effort involved in any oversight of nonphysicians. Kulchaitanaroai et al found similar results with physician-MD collaborative system.[93] For self-monitoring or use of home BP monitoring, both training and access to inexpensive devices will need to be ensured for this to be feasible. Reimbursement and incentives must be aligned to encourage this type of care but could be effective in achieved. A reduction in the cost of the technology and an increase in the use of smart phones is likely to increase the use of home monitoring over time.
	How large is the incremental cost relative to the net benefit?	Very large ICER ☐ Large ICER ☐ Moderate ICER ☒ Small ICER ☐ Savings ☐ Varies ☐ **Detailed judgements**	The two available analyses mentioned above focused on team-based interventions as opposed to specifically physician vs other provider, and it is not clear if ICERs fit all countries, nor the willingness-to-pay thresholds was for countries analysed. All values appear to be below USD 50 000/QALY. For the US the results were highly cost-effectively, with most estimates well under USE 50 000/QALY. It is unclear exactly how these might be translated in LICs and MICs, but even at $10 000/QALY this would be acceptable for most MICs, though perhaps not all LICs. However, if the costs of direction by nurse or pharmacists was the same, compared to physicians, then there is likely to be a cost-saving.

EQUITY	**What would be the impact on health inequities?**	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies ☐ **Detailed judgements**	Unclear, but presumably equity is enhanced since task-shifting in public sector increases access to those using public health vs private health. Increasing access in underserved areas can improve inequities.
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies ☒ **Detailed judgements**	Numerous studies are available about telemonitoring that included management by nonphysicians. However, the focus was on the question of telemonitoring. Response to telemonitoring appears mixed, with some finding advantages and other disadvantages. Walker et al. found that providing management by nonphysicians and telemonitoring can make patients concerned that their care could become more focused on clinical data rather than on personal interaction, and that this might lead to fewer face-to-face consultations with clinicians. This personal contact was important to patients as it helped to establish trust and allowed for better communication. Patients also felt being able to discuss their monitoring data made them feel empowered and a more equal partner in their care, allowing them to be "better equipped to engage with health care services". Remote monitoring provided patients with peace of mind and reduced their anxiety and stress.[94]
FEASIBILITY	**Is the option feasible to implement?**	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ **Detailed judgements**	A systematic review by Cheema et al. described the UK model of community pharmacies where pharmacists are able to deliver some aspects of primary care.[95] The evidence is mixed, with some high-income countries having access to self-monitoring and care or assistance with pharmacists; thus suggesting feasibility in some settings.

Recommendation 8: treatment by nonphysician professionals

Recommendation	**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.**				
Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	**We suggest using the option**	We recommend the option
	☐	☐	☐	☒	☐
Justification	All studies reviewed showed that when either a team-based approach or nurse, pharmacists, or community HCWs were evaluated, the result was either no difference or in favour over usual care with a physician alone. Increasing access to HTN care to the nearly 900 million globally who are not under control by using pharmacists or nurses and CHWs under proper supervision justifies expanding BP management to nonphysicians.				
Subgroup considerations	Studies that looked at how telemonitoring of BP could impact care suggested that in most cases patient satisfaction is high and that it led to improved adherence especially with increasing age.[77] [96] [97]				
Implementation considerations	Community HCWs can assist through an established collaborative care model. 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. The interventions studied in the literature are multifaceted and focus on task sharing, therefore implementation should have a similar infrastructure. In order for nonphysicians to help with BP management, there must be legal/regulatory authority for them to either prescribe independently or under the license of a registered physician. Use of home-monitoring devices has extra costs and requires some level of technical proficiency (which is increasing globally), but when it occurs it can aid control of BP.[87] [81]				
Monitoring and evaluation considerations	The primary question is whether nonphysicians can deliver care as effectively as physicians. However, most available data were about how telemonitoring can aid in the management of either set of providers as long as it can be done in a cost-effective way. Innovations in bluetooth and wi-fi-based home BP cuffs can enhance the care of any provider helping to managing HTN.				

Research priorities	• Evaluation of implementing various home-based monitoring programmes with different technologies to relay data to provider, be it a physician, nurse, pharmacist or CHW. • Assessing in more detail which tasks specifically ought to be shifted to different providers and/or technologies, separating the tasks of screening, treatment algorithms, prescribing authority, clinical decision supports, medication availability and delivery.

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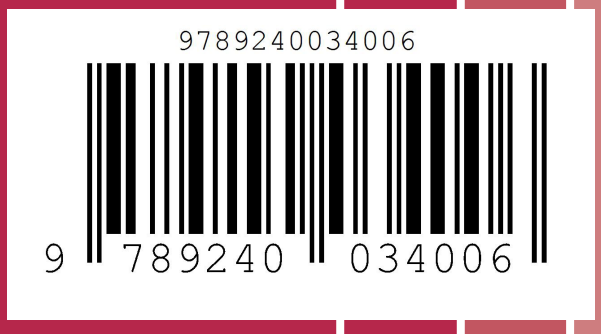
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