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.