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they would not accept antihypertensive drug therapy.[35] **PANEL INPUT** Overall, the available survey data is limited, outdated, and of relatively poor quality.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.