

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?	<p>Important uncertainty or variability <input type="checkbox"/></p> <p>Possibly important uncertainty or variability <input checked="" type="checkbox"/></p> <p>Probably no important uncertainty or variability <input type="checkbox"/></p> <p>No important uncertainty or variability <input type="checkbox"/></p> <p>No known undesirable outcomes <input type="checkbox"/></p> <p style="text-align: center;">Detailed judgements</p>	<p><b>PANEL INPUT</b></p> <p>Combination (two drug) therapy may be less acceptable in some settings if more expensive and may be more acceptable in a fixed dose.</p> <p>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 initial pharmacologic management of HTN.</p>
	What is the overall certainty of the evidence of effects?	<p>No included studies <input type="checkbox"/></p> <p>Very low <input checked="" type="checkbox"/></p> <p>Low <input type="checkbox"/></p> <p>Moderate <input type="checkbox"/></p> <p>High <input type="checkbox"/></p> <p style="text-align: center;">Detailed judgements</p>	<p>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.</p> <p>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.<sup>50</sup></p> <p>However, monotherapy is less likely to achieve the recommended BP targets.</p>
BENEFITS AND HARMS OF THE OPTIONS	How substantial are the desirable anticipated effects?	<p>Don't know <input type="checkbox"/></p> <p>Trivial <input type="checkbox"/></p> <p>Small <input type="checkbox"/></p> <p>Moderate <input checked="" type="checkbox"/></p> <p>Large <input type="checkbox"/></p> <p>Varies <input type="checkbox"/></p> <p style="text-align: center;">Detailed judgements</p>	<p>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</p>

	<p><b>How substantial are the undesirable anticipated effects?</b></p> <p>Don't know   Trivial   Small   Moderate   Large   Varies</p> <p><input type="checkbox"/>   <input type="checkbox"/>   <input checked="" type="checkbox"/>   <input type="checkbox"/>   <input type="checkbox"/>   <input type="checkbox"/></p> <p><b>Detailed judgements</b></p>	<p>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.</p>
	<p><b>Do the desirable effects outweigh the undesirable effects?</b></p> <p>No   Probably No   Don't know   Probably Yes   Yes   Varies</p> <p><input type="checkbox"/>   <input type="checkbox"/>   <input type="checkbox"/>   <input checked="" type="checkbox"/>   <input type="checkbox"/>   <input type="checkbox"/></p> <p><b>Detailed judgements</b></p>	<p>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.</p>
RESOURCE USE	<p><b>How large are the resource requirements?</b></p> <p>Glob   Moderate costs   Small   Moderate savings   Large savings   Varies</p> <p><input type="checkbox"/>   <input type="checkbox"/>   <input type="checkbox"/>   <input type="checkbox"/>   <input type="checkbox"/>   <input checked="" type="checkbox"/></p> <p><b>Detailed judgements</b></p>	<p>Combination therapy is accompanied initially by a moderate increase in resource requirements such as procurement, supply chain, and direct medication costs.</p> <p>Some combinations may be expensive, or not allow for exact dosing of both agents.</p>
	<p><b>How large is the incremental cost relative to the net benefit?</b></p> <p>Very large ICER   Large ICER   Moderate ICER   Small ICER   Savings   Varies</p> <p><input type="checkbox"/>   <input type="checkbox"/>   <input type="checkbox"/>   <input checked="" type="checkbox"/>   <input type="checkbox"/>   <input type="checkbox"/></p> <p><b>Detailed judgements</b></p>	<p>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.</p> <p>BP control is likely faster with combination therapy.</p> <p>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.<sup>51</sup></p>
EQUITY	<p><b>What would be the impact on health inequities?</b></p> <p>Increased   Probably increased   Uncertain   Probably reduced   Reduced   Varies</p> <p><input type="checkbox"/>   <input type="checkbox"/>   <input type="checkbox"/>   <input type="checkbox"/>   <input checked="" type="checkbox"/>   <input type="checkbox"/></p> <p><b>Detailed judgements</b></p>	<p>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.</p>

<b>ACCEPTABILITY</b>	<b>Is the option acceptable to key stakeholders?</b>	<table style="width: 100%; border: none;"> <tr> <td style="text-align: center;">No</td> <td style="text-align: center;">Probably No</td> <td style="text-align: center;">Uncertain</td> <td style="text-align: center;">Probably Yes</td> <td style="text-align: center;">Yes</td> <td style="text-align: center;">Varies</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> <tr> <td colspan="6" style="text-align: center;"><b>Detailed judgements</b></td> </tr> </table>	No	Probably No	Uncertain	Probably Yes	Yes	Varies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<b>Detailed judgements</b>						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.
No	Probably No	Uncertain	Probably Yes	Yes	Varies																
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																
<b>Detailed judgements</b>																					
<b>FEASIBILITY</b>	<b>Is the option feasible to implement?</b>	<table style="width: 100%; border: none;"> <tr> <td style="text-align: center;">No</td> <td style="text-align: center;">Probably No</td> <td style="text-align: center;">Uncertain</td> <td style="text-align: center;">Probably Yes</td> <td style="text-align: center;">Yes</td> <td style="text-align: center;">Varies</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> <tr> <td colspan="6" style="text-align: center;"><b>Detailed judgements</b></td> </tr> </table>	No	Probably No	Uncertain	Probably Yes	Yes	Varies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<b>Detailed judgements</b>						Clinical studies and, more importantly, real-world experience and data demonstrate that this option is clearly feasible.
No	Probably No	Uncertain	Probably Yes	Yes	Varies																
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>																
<b>Detailed judgements</b>																					

## Partial recommendation 4: drug classes

<b>Partial recommendation</b>	<b>Conditional recommendation for two-medication combination over monotherapy. See beneath PICO question 8 for full wording of the recommendation.</b>				
<b>Type of recommendation</b>	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	<b>We suggest using the option</b>	We recommend the option
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Justification</b>	<p>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.<sup>52 53</sup></p> <p>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<sup>54</sup> and is a major component of the WHO Global HEARTS Programme and the PAHO HEARTS in the Americas Initiative.<sup>55</sup> Recently, combination antihypertensive medications in a single pill have been added to the WHO Essential Medication List.<sup>56</sup> 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.</p>				
<b>Subgroup considerations</b>	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.				

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**Implementation considerations**    Combination medication therapy may be especially valuable when the baseline BP is  $\geq 20/10$  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.

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**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.

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**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.

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