

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?	<table border="0"> <tr> <td>Important uncertainty or variability</td> <td>Possibly important uncertainty or variability</td> <td>Probably no important uncertainty or variability</td> <td>No important uncertainty or variability</td> <td>No known undesirable outcomes</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table> <p>Detailed judgements</p>	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	No known undesirable outcomes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	No reliable data about patient values as it relates to a combination therapy vs another combination.
	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	No known undesirable outcomes								
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>									
BENEFITS AND HARMS OF THE OPTIONS	What is the overall certainty of the evidence of effects?	<table border="0"> <tr> <td>No included studies</td> <td>Very low</td> <td>Low</td> <td>Moderate</td> <td>High</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table> <p>Detailed judgements</p>	No included studies	Very low	Low	Moderate	High	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p><b>PANEL INPUT</b></p> <p>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.</p> <p>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.</p> <p>RAAS+CCB may have higher reduction of MACE and AE, yet may not be preferred in older individuals.</p>
	No included studies	Very low	Low	Moderate	High								
	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>								
How substantial are the desirable anticipated effects?	<table border="0"> <tr> <td>Don't know</td> <td>Trivial</td> <td>Small</td> <td>Moderate</td> <td>Large</td> <td>Varies</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table> <p>Detailed judgements</p>	Don't know	Trivial	Small	Moderate	Large	Varies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Don't know	Trivial	Small	Moderate	Large	Varies								
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Don't know	Trivial	Small	Moderate	Large	Varies								
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>								

	<b>Do the desirable effects outweigh the undesirable effects?</b>	No    Probably No    Don't know    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>RESOURCE USE</b>	<b>How large are the resource requirements?</b>	Glob    Moderate costs    Small    Moderate savings    Large savings    Varies <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <b>Detailed judgements</b>	Combination therapy is accompanied initially by a moderate increase in resource requirements, such as procurement, supply chain, and direct medication costs.
	<b>How large is the incremental cost relative to the net benefit?</b>	Very large ICER    Large ICER    Moderate ICER    Small ICER    Savings    Varies <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <b>Detailed judgements</b>	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.
<b>EQUITY</b>	<b>What would be the impact on health inequities?</b>	Increased    Probably increased    Uncertain    Probably reduced    Reduced    Varies <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <b>Detailed judgements</b>	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.
<b>ACCEPTABILITY</b>	<b>Is the option acceptable to key stakeholders?</b>	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>	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.
<b>FEASIBILITY</b>	<b>Is the option feasible to implement?</b>	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>	Clinical studies and real-world experience and data demonstrate that this option is clearly feasible.

## Partial recommendation 4: drug classes

<b>Partial recommendation</b>	<b>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.</b>				
<b>Type of recommendation</b>	We recommend against the option or for the alternative  <input type="checkbox"/>	We suggest not to use the option or to use the alternative  <input type="checkbox"/>	We suggest using either the option or the alternative  <input type="checkbox"/>	We suggest using the option  <input type="checkbox"/>	<b>We recommend the option</b>  <input checked="" type="checkbox"/>
<b>Justification</b>	<p>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.</p> <p>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.</p> <p>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.</p>				
<b>Subgroup considerations</b>					
<b>Implementation considerations</b>					

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**Monitoring and evaluation  
considerations**

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**Research priorities**

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