

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?	<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 style="text-align: center;">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"/>	<p>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%.<sup>57</sup></p> <p>There are cost implications when single-pill combinations are expensive from a patient point of view.</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"/>									
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 type="checkbox"/></td> <td><input checked="" type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table> <p style="text-align: center;">Detailed judgements</p>	No included studies	Very low	Low	Moderate	High	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>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.</p> <p>Low certainty evidence shows that single-pill combination use was associated with better adherence and persistence rates.</p>	
	No included studies	Very low	Low	Moderate	High									
	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input 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 type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table> <p style="text-align: center;">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 type="checkbox"/>	<input type="checkbox"/>	<p>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.</p>
Don't know	Trivial	Small	Moderate	Large	Varies									
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How substantial are the undesirable 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 checked="" type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table> <p style="text-align: center;">Detailed judgements</p>	Don't know	Trivial	Small	Moderate	Large	Varies	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>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.</p>
Don't know	Trivial	Small	Moderate	Large	Varies									
<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>									

	<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 type="checkbox"/>    <input checked="" type="checkbox"/>    <input type="checkbox"/></p> <p><b>Detailed judgements</b></p>	<p>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.</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>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.<sup>58</sup></p> <p>Single-pill combination therapy is accompanied initially by a moderate increase in resource requirements such as procurement, supply chain, and direct medication costs.</p> <p>Single-pill combination therapy is more expensive in some settings.</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 type="checkbox"/>    <input type="checkbox"/>    <input checked="" 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>Faster BP control can improve the cost-effectiveness of single-pill combination therapy.</p> <p>Countries with a pharmaceutical policy, using generic medications, standardized protocols, and centralized purchase mechanisms can reduce the prices of single-pill combination a lot.</p> <p>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.<sup>59</sup> 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.<sup>60</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 checked="" type="checkbox"/>    <input type="checkbox"/>    <input type="checkbox"/></p> <p><b>Detailed judgements</b></p>	<p>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.</p>

ACCEPTABILITY	Is the option acceptable to key stakeholders?	<p>No    Probably    Uncertain    Probably    Yes    Varies</p> <p>      No                                  Yes</p> <p><input type="checkbox"/>    <input type="checkbox"/>    <input type="checkbox"/>    <input checked="" type="checkbox"/>    <input type="checkbox"/>    <input type="checkbox"/></p> <p style="text-align: center;">Detailed judgements</p>	<p>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.</p>
FEASIBILITY	Is the option feasible to implement?	<p>No    Probably    Uncertain    Probably    Yes    Varies</p> <p>      No                                  Yes</p> <p><input type="checkbox"/>    <input type="checkbox"/>    <input type="checkbox"/>    <input type="checkbox"/>    <input checked="" type="checkbox"/>    <input type="checkbox"/></p> <p style="text-align: center;">Detailed judgements</p>	<p><b>RESEARCH EVIDENCE</b></p> <p>Cinical studies and real-world experience and data demonstrate that this option is likely feasible.</p> <p>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.<sup>10</sup> Thus, the intervention is feasible to implement.</p> <p>Angeli et al.<sup>61</sup> 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.</p> <p><b>PANEL INPUT</b></p> <p>Supply chain and procurement become easier with a single-pill combination. Market and manufacturing considerations are critical.</p> <p>Single-pill combinations were added to the WHO Essential Medicines list (four options are currently available).</p> <p>Smaller doses of single-pill combinations are not always available to use as a starting dose or to treat milder levels of HTN.</p>

## Recommendation 5: combination therapy

<b>Recommendation</b>	<p>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).</p>				
<b>Type of recommendation</b>	<p>We recommend against the option or for the alternative</p>	<p>We suggest not to use the option or to use the alternative</p>	<p>We suggest using either the option or the alternative</p>	<p><b>We suggest using the option</b></p>	<p>We recommend the option</p>
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Justification</b>	<p>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.</p> <p>Over 30% of the world population has HTN and only 13.8% are considered controlled.<sup>62</sup> 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.<sup>62 63 64 65</sup></p> <p>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.</p>				
<b>Subgroup considerations</b>	<p>Any patients in which single-pill combination should not be used?</p>				
<b>Implementation considerations</b>					

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**Monitoring and evaluation considerations**

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**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.

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