

## Evidence-to-recommendation table

Problem		
Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>The ageing population means that the absolute numbers of those living with cognitive decline or dementia continue to rise, with an estimated prevalence of 75 million by 2030 and a new case of dementia diagnosed every three seconds<sup>(1)</sup>. Anything that could reduce the incidence of cognitive decline or dementia would have huge importance for individual health, society and health care providers.</p> <p>Hypertension is an extremely common condition that is associated with an increased risk of heart attacks, heart failure, stroke and kidney failure. <b>Hypertension in midlife has been found to be associated with an increased risk of late-life dementia</b><sup>(2)</sup>.</p>	
Desirable Effects		
How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> Trivial</li> <li><input type="radio"/> Small</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> Large</li> <li><input type="radio"/> Varies</li> <li><input checked="" type="radio"/> Don't know</li> </ul>	<p><i>Desirable effects</i></p> <p><b>Treatment of hypertension in the form of antihypertensive medication versus placebo or no intervention</b></p> <p>No data was available for MCI. For cognitive function and incident dementia the volume of evidence is low (3 RCTs for cognitive function and 4 RCT for dementia) and quality of evidence is low for both. The review conducted two meta-analyses and reported that the use of antihypertensive's did not significantly reduce cognitive decline (RR 0.96, 95% CI 0.87 to 1.06) or incidence of dementia (RR 0.90, 95% CI 0.76 to 1.07).</p> <p><b>Treatment for hypertension in the form of lifestyle interventions versus placebo or no intervention</b></p> <p>No data</p>	<p>New information presented at the Alzheimer's Association International Conference (AAIC) July 2018 is in agreement with previous findings.</p> <p>Peters et al <sup>(3)</sup>carried out a systematic review and meta-analysis and found no difference by antihypertensive classes for cognitive function but reported an OR0.65 (0.51:0.83) for incident dementia in favour of antihypertensive treatment compared to placebo in clinical trial populations aged &gt;65 years with ≥5 year follow up.</p> <p>Williamson et al <sup>(4)</sup>reported preliminary results from the Sprint Mind Trial showing a significantly lower rate of incident MCI (HR=0.81, 95% CI 0.70 to 0.95)</p>

		<p>and a nonsignificant reduction in probable dementia (HR=0.83; 95% CI 0.67 to 1.04) in the intensive treatment group (SBP target of &lt;120 mmHg) versus the standard treatment group (SBP target of &lt;140 mmHg).</p> <p>Tully et al (5) carried out a systematic review and meta-analysis to look at the impact of diuretic use on incident dementia. The results of the meta-analysis for incident dementia (which combined adjusted published and unpublished data) showed a combined hazard ratio of 0.83 (95% CI 0.76 to 0.91) in favour of diuretic treatment</p> <p>Hussain et al (6) carried out a systematic review and meta-analysis to look at the impact of calcium channel blocker use on incident dementia. They carried out a meta-analysis including all 10 cohorts and reported a combined risk ratio of 0.70 (95% CI 0.58 to 0.85) for incident dementia in favour of calcium channel blocker use.</p> <p>Kane et al (7) carried out a peer reviewed systematic review of interventions to prevent age-related cognitive decline, mild cognitive impairment and clinical Alzheimer's type dementia. For hypertension and use of antihypertensives the review reported low strength evidence that 3 to 4.7 years of antihypertensive treatment versus placebo appears to have no benefit on cognitive test performance in adults with normal cognition. They also reported that the results for dementia were inconsistent. There was insufficient evidence to draw conclusions (only one study) in adults with MCI. For combination therapy (type not specified) vs placebo the review reports statistically significant difference in dementia diagnoses favouring combination therapy versus placebo (n=3228, up to 3.9 years follow up). No meta-analysis data provided</p> <p>Stuhec et al (8) carried out a systematic review of RCTs examining a population aged (on average) 65</p>
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		<p>years or older, without dementia and who were taking antihypertensive medication. The review reports that Angiotensin II receptor blockers improved cognitive functioning in the elderly, especially with regards to episodic memory, however the other antihypertensive drugs did not improve cognition.</p> <p>Fink et al carried out a systematic review which examined randomised and non-randomised controlled trials in those without dementia. The authors concluded that pharmacologic treatments neither improved nor slowed decline in cognitive test performance.</p> <p>Hernandorena et al(9) carried out a systematic search and presented a narrative review discussing the observational studies and clinical trials that have reported on the use of antihypertensives and outcomes of cognitive function, hippocampal atrophy and dementia. They concluded that most observational studies have suggested a potential preventive effect of antihypertensive therapies, however RCTs and meta-analyses provide more conflicting results.</p> <p>Weiss et al (10)carried out a systematic review to examine the benefits and harms of intensive blood pressure treatment in adults aged 60 and over and reported moderate strength evidence that the use of antihypertensive treatment to achieve moderately strict blood pressure control for up to five years does not worsen cognitive outcomes compared to less strict blood pressure control.</p>
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Undesirable Effects		
How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Large</li> <li>○ Moderate</li> <li>○ Small</li> <li>○ Trivial</li> <li>● Varies</li> <li>○ Don't know</li> </ul>	<p><i>Undesirable effects</i></p> <p><b>Treatment of hypertension in the form of antihypertensive medication versus placebo or no intervention</b></p> <p>For quality of life, the volume of evidence (4 RCTs) and quality of evidence is very low. For functional level, the volume of evidence is low (1 RCT) and the quality of evidence is very low. No meta-analyses were conducted. For quality of life, the review states "we found moderate strength evidence that use of antihypertensive therapy to achieve moderate BP control (SBP 140-150 mmHg) was not associated with deterioration in quality of life compared to less intensive blood pressure control". For functional level, the review states "we found low strength evidence from one large low risk of bias trial that moderate blood pressure control was not associated with deterioration in functional status compared to less intensive control." For adverse events the volume of evidence is moderate (19 RCTs) and the quality of evidence is very low. The review reports a wide range of adverse events (but cough and hypotension were most frequently reported) and mixed findings regarding whether antihypertensive intervention increases the frequency of adverse events. Overall drop out rates were not reported.</p> <p><b>Treatment for hypertension in the form of lifestyle interventions versus placebo or no intervention</b></p> <p>No data adverse events, quality of life, functional levels, or dropouts.</p>	<p>Adverse effects are highly dependant on the medication administered. See American Heart Association website for list of possible side effects for each class of antihypertensives (link: <a href="http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/MakeChangesThatMatter/Types-of-Blood-Pressure-Medications_UCM_303247_Article.jsp">http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/MakeChangesThatMatter/Types-of-Blood-Pressure-Medications_UCM_303247_Article.jsp</a>)</p>
Certainty of evidence		
What is the overall certainty of the evidence of effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Very low</li> <li>● Low</li> <li>○ Moderate</li> <li>○ High</li> <li>○ No included studies</li> </ul>	<p><b>Treatment of hypertension in the form of antihypertensive medication versus placebo or no intervention</b></p> <p><b>Findings:</b></p> <p>Certainty of the evidence is low for both cognitive function and incident dementia, which showed that antihypertensive therapy has no effect on cognitive decline or incidence of dementia. The certainty of evidence for adverse events is very low showing that antihypertensive therapy does not decrease quality of life or functional level. The certainty of evidence is very low showing mixed findings with regards to antihypertensive and adverse events. No evidence for MCI was available. No evidence on overall drop out rates.</p> <p><b>Treatment for hypertension in the form of lifestyle interventions versus placebo or no intervention</b></p> <p><b>Findings:</b></p>	

	No data available, inestimable.	
<b>Values</b> Is there important uncertainty about or variability in how much people value the main outcomes?		
<b>JUDGEMENT</b>	<b>RESEARCH EVIDENCE</b>	<b>ADDITIONAL CONSIDERATIONS</b>
<ul style="list-style-type: none"> <li>○ Important uncertainty or variability</li> <li>○ Possibly important uncertainty or variability</li> <li>○ Probably no important uncertainty or variability</li> <li>● No important uncertainty or variability</li> </ul>	<p>A review conducted by Anderson et al 2009(11) on public perceptions about cognitive health in the United States revealed that a large proportion of the population were concerned about declines in cognition or memory. Further studies in Australia(12) and the United Kingdom(13) (UK) and have shown a general trend of individuals being fearful of developing dementia.</p> <p>There is no evidence showing that individuals would oppose dementia risk reduction, or view cognitive decline favourably.</p> <p>Data from low and middle income countries is unavailable.</p> <p>There is no reason to believe there is important uncertainty about or variability in how much people value reducing the risk of cognitive decline and/or dementia.</p>	<p>Additional sources like the Saga Survey(14) and Alzheimer's Research UK(15) have reported high percentage of people in the UK fear dementia, even more so than cancer, and feel a prognosis would mean their life is over (62%)</p>

Balance of effects		
Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● Don't know</li> </ul>	<p><b>Treatment of hypertension in the form of antihypertensive medication versus placebo or no intervention</b></p> <p>Does not favor either the intervention or the comparison (low quality evidence suggests no effect of antihypertensive therapy on cognitive decline or dementia, but intervention also does not lower quality of life or functional level, mixed results regarding adverse effects).</p> <p><b>Treatment for hypertension in the form of lifestyle interventions versus placebo or no intervention</b></p> <p>No data available, inestimable.</p>	<p>There is consistent indirect evidence in favour of these interventions. Drug specific adverse events may require change of one drug for another.</p>
Resources required		
How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>○ Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>● Varies</li> <li>○ Don't know</li> </ul>	<p>Various medications can be used to treat hypertension and costs are dependent the drug administered (see additional considerations).</p> <p>No data on resources required were reported by the systematic reviews described above.</p>	<p>The WHO(16) recommendations for antihypertensive medications are listed below. The prices are taken from the International Drug Price Indicator Guide(17) and are listed as price per unit.</p> <ul style="list-style-type: none"> <li>· Amlodipine</li> </ul> <p>Tablet: 5 mg (as maleate, mesylate or besylate); Median Price US\$ (Supplier/Buyer) = 0.0252/0.0094</p> <ul style="list-style-type: none"> <li>· Bisoprolol (includes atenolol, metoprolol and carvedilol as alternatives. Atenolol should not be used as a first-line agent in uncomplicated hypertension in patients &gt;60 years)</li> </ul>

		<p>Tablet: 1.25 mg (price not listed); 5 mg; Median Price US\$ (Supplier/Buyer) = not listed/0.0660</p> <ul style="list-style-type: none"> <li>· Enalapril</li> </ul> <p>Tablet: 2.5 mg (price not listed); 5 mg (as hydrogen maleate); Median Price US\$ (Supplier/Buyer) = 0.0165/0.0095</p> <ul style="list-style-type: none"> <li>· Hydralazine (Hydralazine is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines).</li> </ul> <p>Powder for injection: 20 mg (hydrochloride) in ampoule; Median Price US\$ (Supplier/Buyer) = 4.6717/4.1600</p> <p>Tablet: 25 mg; Median Price US\$ (Supplier/Buyer) = 0.0378/0.0475; 50 mg (hydrochloride); Median Price US\$ (Supplier/Buyer) = 0.1485/0.0557</p> <ul style="list-style-type: none"> <li>· Hydrochlorothiazide</li> </ul> <p>Oral liquid: 50 mg/5 mL (price not listed)</p> <p>Solid oral dosage form: 12.5 mg; Median Price US\$ (Supplier/Buyer) = not listed/0.0087; 25 mg; Median Price US\$ (Supplier/Buyer) = 0.0043/0.0094</p> <ul style="list-style-type: none"> <li>· Methyldopa (Methyldopa is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines).</li> </ul> <p>Tablet: 250 mg; Median Price US\$ (Supplier/Buyer) = 0.0313/0.0436</p> <ul style="list-style-type: none"> <li>· Losartan</li> </ul>
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<p><b>Certainty of evidence of required resources</b> What is the certainty of the evidence of resource requirements (costs)?</p>		
<b>JUDGEMENT</b>	<b>RESEARCH EVIDENCE</b>	<b>ADDITIONAL CONSIDERATIONS</b>
<ul style="list-style-type: none"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>● High</li> <li>○ No included studies</li> </ul>	<p>Antihypertensive medication is commonly prescribed as a treatment option for hypertension. They are included in the WHO model list of essential medicines<sup>(16)</sup> and their costs are listed in the International Drug Price Indicator Guide<sup>(17)</sup></p>	<p>The WHO<sup>(18)</sup> brief on hypertension states that:</p> <p>“Not all patients diagnosed with hypertension require medication, but those at medium to high risk will need one or more of eight essential medicines to lower their cardiovascular risk (a thiazide diuretic, an angiotensin converting enzyme inhibitor, a long-acting calcium channel blocker, a beta blocker, metformin, insulin, a statin and aspirin). The cost of implementing such a programme is low, at less than US\$ 1 per head in low-income countries, less than US\$ 1.50 per head in lower middle-income countries and US\$ 2.50 in upper middle-income countries.”</p>



<b>Cost effectiveness</b>		
Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
<b>JUDGEMENT</b>	<b>RESEARCH EVIDENCE</b>	<b>ADDITIONAL CONSIDERATIONS</b>
<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	<p>Various medications can be used to treat hypertension and costs are dependent the drug administered, however there is evidence to show that antihypertensives can be cost-effective in the treatment of hypertension<sup>8</sup> (see additional considerations). No data on cost effectiveness were reported by the systematic reviews described above.</p>	<p>The cost effectiveness of stroke and ischemic and hypertensive heart disease interventions in adults (retrieved from the WHO guidelines Package of Essential Noncommunicable (PEN) Disease: Interventions for Primary Health Care in Low-Resource Settings (2010) p.64(19)):</p> <ul style="list-style-type: none"> <li>· Intervention = Combination treatment with aspirin, betablocker, thiazide, ACE inhibitor and statin in district hospital</li> </ul> <p>à Cost Effectiveness = 2128 US\$/DALY</p> <p>Retrieved from the Cost-Effectiveness Analysis in Disease Control Priorities, Third Edition<sup>(20)</sup>:</p> <p>“[A] way to address the availability and affordability of medications for hypertension and dyslipidemia is to use a combination of generic CVD medications or a polypill for all adults with significant risk for CVD. This single intervention could reduce IHD events by as much as 50 percent.”</p>
<b>Equity</b>		
What would be the impact on health equity?		
<b>JUDGEMENT</b>	<b>RESEARCH EVIDENCE</b>	<b>ADDITIONAL CONSIDERATIONS</b>
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>○ Probably reduced</li> <li>○ Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>○ Varies</li> </ul>	<p>A report from the Institute of Health on inequalities in cognitive impairment and dementia among older persons<sup>(21)</sup> studies health equities in England, They found that individuals with lower socioeconomic status (SES) were at increased risk of earlier onset of dementia, cognitive dysfunction at earlier stages of cognitive decline and impairment, and tend to have fewer resources to cope with symptoms, as compared to higher SES groups. Further, lower SES groups are likely to live and age in environments that are physically and economically less supportive of social connection physical activity or mental stimulation, which can increase the risk of cognitive impairment and dementia in later life.</p> <p>Based on this it is likely that interventions to reduce risk of cognitive decline and dementia will increase equity in health.</p>	<p>Health inequity in hypertensive treatment should be addressed</p>

● Don't know		
<b>Acceptability</b>		
Is the intervention acceptable to key stakeholders?		
<b>JUDGEMENT</b>	<b>RESEARCH EVIDENCE</b>	<b>ADDITIONAL CONSIDERATIONS</b>
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Varies; Drug-related side effects are a key consideration in acceptability of the intervention. There is no other apparent reasons for which pharmacological interventions for hypertension to reduce the risk of cognitive decline and/or dementia would not be acceptable to key stakeholders.	
<b>Feasibility</b>		
Is the intervention feasible to implement?		
<b>JUDGEMENT</b>	<b>RESEARCH EVIDENCE</b>	<b>ADDITIONAL CONSIDERATIONS</b>
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Yes, medication already available and used in individuals with hypertension.	Feasibility for lifestyle interventions to reduce blood pressure may limited by local circumstances

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