Guideline for the pharmacological treatment of hypertension in adults

WEB ANNEX A

Summary of evidence

World Health Organization

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PICO question 1: At what level of blood pressure should pharmacological therapy be started to prevent cardiovascular events?

Systematic review for desirable and undesirable effects

Evidence was considered in respect of the following components (Table 1) to determine at what level of blood pressure pharmacological therapy should be started to prevent cardiovascular events (Tables 3–15).

Table 1 Components for PICO question 1

Population	Intervention	Comparison	Outcome	Subgroup

Adults suspected of or who have hypertension	Specific systolic and diastolic blood pressure thresholds*:
	- Systolic (mm Hg):
	  - ≥120
	  - ≥130
	  - ≥140
	  - ≥150
	- Diastolic (mm Hg):
	  - ≥80
	  - ≥90
		- placebo
		- systolic or diastolic BP threshold that is higher than intervention thresholds
			- death (all-cause mortality)
			- cardiovascular death (death from MI, sudden cardiac death or stroke)
			- stroke
			- myocardial infarction
			- end-stage kidney disease
			- cognitive impairment/ dementia
			- heart failure events
			- adverse effects
				- based on different effect modifiers such as:
				- estimated cardiovascular risk (pre-existing cad)
				- stroke
				- diabetes
				- age
				- sex
				- chronic kidney disease
				- race/ethnicity

Table 2 Evidence profile 1a: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure 120–130 mmHg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
4	randomized trials	not serious	not serious	not serious	not serious a	none	141/4331 (3.3%)	149/4298 (3.5%)	RR 0.95 (0.76 to 1.18)	2 fewer per 1000 (from 8 fewer to 6 more)	⊕⊕⊕⊕ HIGH	–
Cardiovascular mortality (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
6	randomized trials	not serious	not serious	not serious	not serious [a]	none	58/3838 (1.5%)	49/3819 (1.3%)	RR 1.18 (0.81 to 1.74)	2 more per 1000 (from 2 fewer to 9 more)	⊕⊕⊕⊕ HIGH	–
Stroke (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
8	randomized trials	not serious	not serious	not serious	not serious [b]	none	155/5327 (2.9%)	198/5279 (3.8%)	RR 0.75 (0.56 to 1.01)	9 fewer per 1000 (from 17 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	–
Heart failure (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
5	randomized trials	not serious	not serious	not serious	not serious a	none	45/3875 (1.2%)	52/3849 (1.4%)	RR 0.91 (0.61 to 1.36)	1 fewer per 1000 (from 5 fewer to 5 more)	⊕⊕⊕⊕ HIGH	–
Myocardial infarction (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
4	randomized trials	not serious	not serious	not serious	serious [c]	none	46/1204 (3.8%)	51/1207 (4.2%)	RR 0.91 (0.62 to 1.36)	4 fewer per 1000 (from 16 fewer to 15 more)	⊕⊕⊕◯ MODERATE	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. Using a threshold of 1% as a small but important difference, the CI is precise around the line of no effect; b. The confidence interval of the absolute effect suggests the possibility of some benefit and no harm ; c. The absolute estimates suggest both important harm and benefit

Table 3 Evidence profile 1b: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure 130-140 mmHg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
14	randomized trials	not serious	not serious	not serious	not serious [a]	none	3759/44 599 (7.9%)	3904/44 254 (8.3%)	RR 0.98 (0.90 to 1.05)	2 fewer per 1000 (from 8 fewer to 4 more)	⊕⊕⊕⊕ HIGH	–
Cardiovascular mortality (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
15	randomized trials	not serious	not serious	not serious	not serious [a]	none	2636/44 861 (5.3%)	2697/44 911 (5.4%)	RR 0.98 (0.91 to 1.07)	1 fewer per 1000 (from 5 fewer to 4 more)	⊕⊕⊕⊕ HIGH	–
Stroke (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
17	randomized trials	not serious	not serious	not serious	not serious	none	1334/55 730 (2.6%)	1510/55 765 (3.0%)	RR 0.88 (0.76 to 1.01)	4 fewer per 1000 (from 7 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	–
Heart failure (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
12	randomized trials	not serious	serious [b]	not serious	not serious	none	1992/44 536 (4.6%)	2203/44 182 (5.1%)	RR 0.90 (0.82 to 0.98)	5 fewer per 1000 (from 9 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	–
Myocardial infarction (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
15	randomized trials	not serious	not serious	not serious	not serious [a]	none	2131/44 584 (4.3%)	2386/44 632 (4.8%)	RR 0.92 (0.83 to 1.02)	4 fewer per 1000 (from 8 fewer to 1 more)	⊕⊕⊕⊕ HIGH	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. Using a threshold of 1% as a small but important difference, the CI is precise around the line of no effect

b. Unexplained inconsistency exists between the studies.

Table 4 Evidence profile 1c: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure 120-140 mmHg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
20	randomized trials	not serious	not serious	not serious	not serious [a]	none	3936/55 930 (7.6%)	4053/55 552 (7.9%)	RR 0.97 (0.91 to 1.04)	2 fewer per 1000 (from 7 fewer to 3 more)	⊕⊕⊕⊕ HIGH	–
Cardiovascular mortality (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
22	randomized trials	not serious	not serious	not serious	not serious [a]	none	2694/55 699 (5.0%)	2746/55 730 (5.1%)	RR 0.99 (0.92 to 1.07)	1 fewer per 1000 (from 4 fewer to 4 more)	⊕⊕⊕⊕ HIGH	–
Stroke (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
28	randomized trials	not serious	serious [b]	not serious	not serious	none	1772/55 913 (3.0%)	1995/55 949 (3.3%)	RR 0.86 (0.78 to 0.96)	5 fewer per 1000 (from 7 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	–
Heart failure (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
17	randomized trials	not serious	not serious	not serious	not serious	none	2037/44 411 (4.3%)	2255/44 031 (4.8%)	RR 0.90 (0.83 to 0.97)	5 fewer per 1000 (from 8 fewer to 1 fewer)	⊕⊕⊕⊕ HIGH	–
Adverse events leading to discontinuation of the treatment (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
8	randomized trials	not serious	not serious	not serious	not serious	none	2262/11 867 (11.4%)	1758/11 221 (9.1%)	RR 1.35 (1.06 to 1.72)	32 more per 1000 (from 5 more to 66 more)	⊕⊕⊕⊕ HIGH	–
Myocardial infarction (follow up: range 0.25 months to 76 months; assessed with: Hong, 2018*(1)*)												
19	randomized trials	not serious	not serious	not serious	not serious [a]	none	2177/55 788 (4.3%)	2437/55 839 (4.8%)	RR 0.92 (0.84 to 1.01)	4 fewer per 1000 (from 8 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. Using a threshold of 1% as a small but important difference, the CI is precise around the line of no effect.

b. Unexplained inconsistency exists between the included studies.

Table 5 Evidence profile 1d: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure 140-159 mmHg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: median 4.4 years; assessed with: Sundstrom 2015(2))												
9	randomized trials	not serious	not serious	not serious	not serious	none	260/7337 (3.5%)	322/7090 (4.5%)	OR 0.79 (0.67 to 0.94)	9 fewer per 1000 (from 15 fewer to 3 fewer)	⊕⊕⊕⊕ HIGH	–
Cardiovascular mortality (follow up: median 4.4 years; assessed with: Sundstrom 2015(2))												
6	randomized trials	not serious	not serious	not serious	serious [a]	none	90/2859 (3.1%)	114/2666 (4.3%)	OR 0.77 (0.58 to 1.02)	10 fewer per 1000 (from 18 fewer to 1 more)	⊕⊕⊕◯ MODERATE	–
Stroke (follow up: median 4.4 years; assessed with: Sundstrom 2015(2))												
8	randomized trials	not serious	not serious	not serious	not serious [b]	none	90/5880 (1.5%)	109/5722 (1.9%)	OR 0.82 (0.62 to 1.09)	3 fewer per 1000 (from 7 fewer to 2 more)	⊕⊕⊕⊕ HIGH	–
Heart failure (follow up: median 4.4 years; assessed with: Sundstrom 2015(2))												
5	randomized trials	not serious	not serious	not serious	serious [a]	none	59/2588 (2.3%)	71/2585 (2.7%)	OR 0.81 (0.58 to 1.16)	5 fewer per 1000 (from 11 fewer to 4 more)	⊕⊕⊕◯ MODERATE	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; OR: Odds ratio

Explanations

a. The 95% CI crosses the threshold of a small but important benefit in one extreme, and suggests lack of important harm in the other.
b. The CI is precise around the null effect.

Table 6 Evidence profile 1e: Treatment compared to no treatment in patients with baseline BP 130–140 without CAD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Treatment	No treatment	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
12	randomized trials	serious [a,b]	not serious	not serious [c]	not serious [d]	none	2107/22 219 (8.0%)	2099/22 257 (8.0%)	RR 1.00 (0.95 to 1.06)	0 fewer per 1000 (from 4 fewer to 5 more)	⊕⊕⊕◯ MODERATE	–
MACE (follow up: mean 4.5 years; assessed with: Brunsrtom, 2019*(3)*)												
9	randomized trials	serious [a,b]	not serious	not serious [c]	not serious [d]	none	2379/22 741 (10.0%)	2366/22 805 (9.9%)	RR 1.01 (0.96 to 1.06)	1 more per 1000 (from 4 fewer to 6 more)	⊕⊕⊕◯ MODERATE	–
Cardiovascular mortality (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
8	randomized trials	serious [a,b]	not serious	not serious [c]	not serious [d]	none	2390/44 685 (4.8%)	1163/22 862 (4.7%)	RR 1.07 (0.95 to 1.21)	3 more per 1000 (from 2 fewer to 10 more)	⊕⊕⊕◯ MODERATE	–
Myocardial infarction (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
8	randomized trials	serious [a,b]	not serious	not serious [c]	not serious [d]	none	1092/44 682 (2.3%)	540/22 372 (2.3%)	RR 1.03 (0.91 to 1.15)	1 more per 1000 (from 2 fewer to 3 more)	⊕⊕⊕◯ MODERATE	–
Stroke (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
9	randomized trials	serious [a,b]	not serious	not serious [c]	not serious [d]	none	1536/44 546 (3.2%)	803/22 170 (3.5%)	RR 0.89 (0.73 to 1.09)	4 fewer per 1000 (from 9 fewer to 3 more)	⊕⊕⊕◯ MODERATE	–
Heart failure (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
6	randomized trials	serious [a,b]	not serious	not serious [c]	not serious [d]	none	1903/44 881 (4.2%)	1003/22 472 (4.5%)	RR 0.90 (0.81 to 1.00)	4 fewer per 1000 (from 8 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	–
Discontinuation due to adverse events (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
8	randomized trials	serious [a]	serious [e]	not serious [c]	not serious	none	1917/11 249 (10.5%)	1585/11 651 (9.0%)	RR 1.23 (1.03 to 1.47)	21 more per 1000 (from 3 more to 42 more)	⊕⊕◯◯ LOW	–
Hypotension related adverse events (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
6	randomized trials	serious [a]	serious [f]	not serious [c]	not serious	none	5141/44 058 (11.7%)	2245/22 038 (10.2%)	RR 1.71 (1.32 to 2.22)	72 more per 1000 (from 33 more to 124 more)	⊕⊕◯◯ LOW	–
Discontinuation due to renal impairment (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
8	randomized trials	serious [a,b]	not serious	not serious [c]	not serious [d]	none	992/44 627 (2.0%)	457/22 831 (1.8%)	RR 1.20 (0.93 to 1.55)	4 more per 1000 (from 1 fewer to 10 more)	⊕⊕⊕◯ MODERATE	–
Dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. According to the authors' assessment, the studies that contributed most of the weight for this outcome had unclear and or risk of bias in some of the domains..

b. For this assessment, we did not consider the judgements of unclear outcome assessment risk of bias judgment that the author's made.

c. The results were very similar when excluding trials in people with diabetes, trials of dual renin-angiotensin-aldosterone system (RAAS) inhibition, trials not reaching <130mm Hg in the intervention group, trials of previously treated/hypertensive patients, and trials of treatment of naïve patients. Therefore, these results are likely to be applicable to the general population.

d. Although the 95% confidence interval crosses the line of no effect, the absolute effect estimate is precise as it suggests the possibility of a trivial benefit in one extreme and a trivial harm in the other

e. The point estimates show different directions and magnitude of effect, and not all confidence intervals overlap. The I square is 81.7% and the p value of the chi square test for heterogeneity is statistically significant.

f. The point estimates suggest importantly different magnitudes of effect and not all confidence intervals overlap. The I square is 90.3%, and the p value of the chi square test for heterogeneity is statistically significant.

Table 7 Evidence profile 1f: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure 130–140 mmHg and CAD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (CAD studies) (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
6	randomized trials	serious [a,b]	not serious	not serious [c]	not serious	none	1490/11 025 (7.8%)	1650/11 024 (8.7%)	RR 0.91 (0.83 to 0.99)	8 fewer per 1000 (from 15 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	–
MACE (CAD studies) (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
6	randomized trials	serious [a,b]	not serious	not serious [c]	not serious	none	2024/11 025 (10.6%)	2374/11 024 (12.5%)	RR 0.85 (0.77 to 0.94)	19 fewer per 1000 (from 29 fewer to 7 fewer)	⊕⊕⊕◯ MODERATE	–
Cardiovascular mortality (CAD studies) (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
5	randomized trials	serious [a,b]	not serious	not serious [c]	not serious [d]	none	1802/33 589 (4.8%)	973/11 793 (5.2%)	RR 0.86 (0.74 to 1.00)	7 fewer per 1000 (from 13 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	–
Myocardial infarction (CAD studies) (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
5	randomized trials	serious [a,b]	not serious	not serious [c]	not serious	none	2367/22 893 (7.9%)	1076/11 933 (7.2%)	RR 0.83 (0.72 to 0.97)	12 fewer per 1000 (from 20 fewer to 2 fewer)	⊕⊕⊕◯ MODERATE	–
Stroke (CAD studies) (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
6	randomized trials	serious [a,b]	not serious	not serious [c]	not serious	none	943/33 049 (2.5%)	532/11 024 (2.8%)	RR 0.79 (0.66 to 0.94)	6 fewer per 1000 (from 10 fewer to 2 fewer)	⊕⊕⊕◯ MODERATE	–
Heart failure (CAD studies) (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
5	randomized trials	serious [a,b]	not serious	not serious [c]	not serious	none	412/11 796 (2.2%)	545/11 793 (2.9%)	RR 2.05 (1.62 to 2.61)	30 more per 1000 (from 18 more to 47 more)	⊕⊕⊕◯ MODERATE	–
Discontinuation due to adverse events (CAD studies) (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
5	randomized trials	serious [a,b]	serious [e]	not serious [c]	not serious	none	1321/11 796 (7.0%)	622/11 793 (3.3%)	RR 2.05 (1.62 to 2.61)	35 more per 1000 (from 21 more to 53 more)	⊕⊕◯◯ LOW	–
Hypotension related adverse events (CAD studies) (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
5	randomized trials	serious [a,b]	serious [f]	not serious [c]	not serious	none	793/22 817 (2.8%)	341/11 421 (2.4%)	RR 1.63 (1.01 to 2.63)	15 more per 1000 (from 0 fewer to 39 more)	⊕⊕◯◯ LOW	–
Discontinuation due to renal impairment (CAD studies) (follow up: mean 4.5 years; assessed with: Brunstrom, 2019*(3)*)												
1	randomized trials	serious [a,b]	not serious	not serious [c]	not serious [d]	none	20/6107 (0.3%)	16/6108 (0.3%)	RR 1.25 (0.65 to 2.41)	1 more per 1000 (from 1 fewer to 4 more)	⊕⊕⊕◯ MODERATE	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. According to the authors' assessment, the studies that contributed most of the weight for this outcome had unclear and or risk of bias in some of the domains.

b. For this assessment, we did not consider the judgments of unclear outcome assessment risk of bias judgment that the author's made.

c. The results were very similar when excluding trials in people with diabetes, trials of dual renin-angiotensin-aldosterone system (RAAS) inhibition, trials not reaching <130mm Hg in the intervention group, trials of previously treated/hypertensive patients, and trials of treatment naïve patients. Therefore, these results are likely to be applicable to the general population.

d. Although the 95% confidence interval crosses the line of no effect, the absolute effect estimate is precise as it suggests the possibility of a trivial benefit in one extreme and a trivial harm in the other.
e. The point estimates show different directions and magnitude of effect, and not all confidence intervals overlap. The I square is 79.0% and the p value of the chi square test for heterogeneity is statistically significant.
f. The point estimates show different directions and magnitude of effect, and not all confidence intervals overlap. The I square is 85.9% and the p value of the chi square test for heterogeneity is statistically significant.

Table 8 Evidence profile 1g: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure <140 mmHg and diabetes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
14	randomized trials	serious [a]	not serious	not serious	serious [b]	none	[c]	582/7652 (7.6%) [c]	RR 1.05 (0.95 to 1.16)	4 more per 1000 (from 4 fewer to 12 more) [c]	⨁⨁◯◯ LOW	–
Cardiovascular mortality (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
10	randomized trials	serious [a]	not serious	not serious	not serious	none	[c]	307/7855 (3.9%) [c]	RR 1.15 (1.00 to 1.32)	6 more per 1000 (from 0 fewer to 13 more) [c]	⨁⨁⨁◯ MODERATE	–
Myocardial infarction (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
9	randomized trials	serious [a]	not serious	not serious	serious [b]	none	[c]	377/8579 (4.4%) [c]	RR 1.00 (0.87 to 1.15)	0 fewer per 1000 (from 6 fewer to 7 more) [c]	⨁⨁◯◯ LOW [c]	–
Stroke (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
8	randomized trials	serious [a]	not serious	not serious	serious [b]	none	[c]	230/8579 (2.7%) [c]	RR 0.87 (0.79 to 0.96)	3 fewer per 1000 (from 6 fewer to 1 fewer) [c]	⨁⨁◯◯ LOW	–
Heart failure (follow up: median 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
8	randomized trials	serious [a]	not serious	not serious	serious [b]	none	[c]	426/7625 (5.6%) [c]	RR 0.90 (0.79 to 1.02)	6 fewer per 1000 (from 12 fewer to 1 more) [c]	⨁⨁◯◯ LOW	–
End-stage kidney disease (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	[c]	157/7382 (2.1%) [c]	RR 0.97 (0.80 to 1.17)	1 fewer per 1000 (from 4 fewer to 4 more) [c]	⨁⨁⨁◯ MODERATE	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. All studies were judged to have unclear or high risk of bias in at least one domain

b. The CI crosses the line of no effect.

c. There are no absolute numbers reported in the systematic review. However, we abstracted the baseline risk from the 5 largest primary studies for each outcome.

Table 9 Evidence profile 1h: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure 140–150 mmHg and diabetes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
10	randomized trials	serious [a]	not serious	not serious	not serious	none	[b]	1427/11 430 (9.9%) [b]	RR 0.87 (0.78 to 0.98)	13 fewer per 1000 (from 22 fewer to 2 fewer) [b]	⨁⨁⨁◯ MODERATE	–
Cardiovascular mortality (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
9	randomized trials	serious [a]	not serious	not serious	serious [c]	none	[b]	841/11 430 (5.8%) [b]	RR 0.87 (0.71 to 1.05)	8 fewer per 1000 (from 17 fewer to 3 more) [b]	⨁⨁◯◯ LOW	–
Myocardial infarction (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	[b]	1216/11 430 (8.4%) [b]	RR 0.84 (0.76 to 0.93)	13 fewer per 1000 (from 20 fewer to 6 fewer) [b]	⨁⨁⨁◯ MODERATE	–
Stroke (follow up: median 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
9	randomized trials	serious [a]	not serious	not serious	serious [c]	none	[b]	658/11 430 (4.6%) [b]	RR 0.92 (0.83 to 1.01)	4 fewer per 1000 (from 8 fewer to 0 fewer) [b]	⨁⨁◯◯ LOW	–
Heart failure (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	[b]	522/8859 (5.9%) [b]	RR 0.80 (0.66 to 0.97)	12 fewer per 1000 (from 20 fewer to 2 fewer) [b]	⨁⨁⨁◯ MODERATE	–
End-stage kidney disease (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
6	randomized trials	serious [a]	not serious	not serious	serious [c]	none	[b]	41/9809 (0.4%) [b]	RR 0.91 (0.74 to 1.12)	0 fewer per 1000 (from 1 fewer to 1 more) [b]	⨁⨁◯◯ LOW	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. All included studies were judged at a high or unclear risk of bias in at least one domain

b. Absolute numbers are not reported in the systematic review. However, we abstracted the baseline risk from the 5 largest primary studies.

c. The confidence interval crosses the line of no effect

Table 10 Evidence profile 1i: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure >150 mmHg and diabetes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
16	randomized trials	serious [a]	not serious	not serious	not serious	none	[b]	434/3023 (14.4%) [b]	RR 0.89 (0.80 to 0.99)	16 fewer per 1000 (from 29 fewer to 1 fewer) [b]	⊕⊕⊕◯ MODERATE	–
Cardiovascular mortality (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
11	randomized trials	serious [a]	not serious	not serious	not serious	none	[b]	179/2154 (8.3%) [b]	RR 0.75 (0.57 to 0.99)	21 fewer per 1000 (from 36 fewer to 1 fewer) [b]	⊕⊕⊕◯ MODERATE	–
Myocardial infarction (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
13	randomized trials	serious [a]	not serious	not serious	not serious	none	[b]	195/2454 (7.9%) [b]	RR 0.74 (0.63 to 0.87)	21 fewer per 1000 (from 29 fewer to 10 fewer) [b]	⊕⊕⊕◯ MODERATE	–
Stroke (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
15	randomized trials	serious [a]	not serious	not serious	not serious	none	[b]	152/2454 (6.2%) [b]	RR 0.77 (0.65 to 0.91)	14 fewer per 1000 (from 22 fewer to 6 fewer) [b]	⊕⊕⊕◯ MODERATE	–
Heart failure (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
7	randomized trials	serious [a]	not serious	not serious	serious [c]	none	[b]	151/1152 (13.1%) [b]	RR 0.73 (0.53 to 1.01)	35 fewer per 1000 (from 62 fewer to 1 more)	⊕⊕◯◯ LOW	–
End-stage kidney disease (follow up: mean 3.7 years; assessed with: Brunstrom, 2016*(4)*)												
5	randomized trials	serious [a]	not serious	not serious	not serious	none	[b]	302/1721 (17.5%) [b]	RR 0.82 (0.71 to 0.94)	32 fewer per 1000 (from 51 fewer to 11 fewer) [b]	⊕⊕⊕◯ MODERATE	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. All studies were judged at unclear or high risk of bias in at least one domain

b. Absolute numbers were not reported in the systematic review. However, we abstracted the baseline risk from the 5 largest trials.

c. The confidence interval crosses the line of no effect.

Table 11 Evidence profile 1j: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure <120 mmHg and a history of stroke or transient ischemic attack

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
Recurrent stroke (assessed with: Zonneveld, 2018(5))												
1	randomized trials	not serious	not serious	not serious	serious [a]	none	12/174 (6.9%)	12/176 (6.8%)	RR 1.01 (0.47 to 2.19)	1 more per 1000 (from 36 fewer to 81 more)	⨁⨁⨁◯ MODERATE	–
Major cardiovascular event – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
All-cause mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. The 95% CI suggests important benefit and important harm. The total number of patients included is small and the optimal information size is not met.

Table 12 Evidence profile 1k: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure 120–139 mmHg and a history of stroke or transient ischemic attack

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
Recurrent stroke (assessed with: Zonneveld, 2018(5))												
1	randomized trials	not serious	not serious	not serious	serious [a]	none	95/898 (10.6%)	109/998 (10.9%)	RR 0.86 (0.67 to 1.12)	15 fewer per 1000 (from 36 fewer to 13 more)	⊕⊕⊕◯ MODERATE	–
Mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. The confidence interval suggests the possibility of important benefit and important harm.

Table 13 Evidence profile 1l: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure 140-159 mmHg and a history of stroke or transient ischemic attack

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
Recurrent stroke (assessed with: Zonneveld, 2018(5))												
2	randomized trials	not serious	not serious	not serious	not serious	none	115/1275 (9.0%)	164/1290 (12.7%)	RR 0.71 (0.57 to 0.89)	37 fewer per 1000 (from 55 fewer to 14 fewer)	⊕⊕⊕⊕ HIGH	–
Mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

None

Table 14 Evidence profile 1m: Blood pressure lowering drugs compared to no treatment in patients with baseline systolic blood pressure >160 mmHg and a history of stroke or transient ischemic attack

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	No treatment	Relative (95% CI)	Absolute (95% CI)		
Recurrent stroke (assessed with: Zonneveld, 2018(5))												
3	randomized trials	not serious	not serious	not serious	not serious	none	132/987 (13.4%)	198/967 (20.5%)	RR 0.65 (0.51 to 0.83)	72 fewer per 1000 (from 100 fewer to 35 fewer)	⊕⊕⊕⊕ HIGH	–
Mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

None

Evidence to decision for PICO question 1

Values and preferences

Fragasso, 2012*(6)*: 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.

Risso, 2015*(7)*: From a patient perspective, HTN is often a silent disease and patients may not take antihypertensive medications as directed because their positive effects are not as obvious as potential side-effects from the medications.

Resources required

Gu, 2015*(8)*: If the Chinese government systematically screened adults aged 35–84 years for hypertension, it would require an investment of about International Dollars 962 million (RMB 3.4 billion) in 2015 to screen adults unaware of an existing HTN diagnosis, and about International Dollars 65 billion annually (RMB 231 billion) to screen adults currently without HTN and all persons becoming 35 years of age after 2015 for incidence of HTN during 2015 to 2025.

Cost effectiveness

Richman and colleagues conducted a trial-based economic evaluation incorporating the effect estimates for treatment effects and adverse event rates from the SPRINT trial in a Markov model.*(9)* They compared intensive BP management (SBP <120 mmHg) with standard (SBP <140 mmHg) among 68-year-old high-risk adults with HTN but not diabetes. Model inputs were obtained from the Centers for Disease Control and Prevention (CDC) Life Table: Projected age- and cause-specific mortality, calibrated to rates reported in SPRINT. Population-based observational data was used for heart failure, MI, stroke and subsequent mortality. Utilities were obtained based on EQ-5D scores from a nationally representative sample. Costs were based on published sources. The base case ICER was USD 23 777 per QALY. The results were robust, ICERs with sensitivity analyses changing parameter inputs several-fold were < USD 50 000.

Howard*(10)* and colleagues constructed a cost-effectiveness study of screening and optimal management of HTN and diabetes and chronic kidney disease in an Australian setting. They found that an intensive management of previously uncontrolled HTN compared with usual care resulted in an ICER of AUD 2588. They do not specify the target BP for the comparisons.

Equity

Meiqari, 2019*(11)*: Barriers in access to HTN care in low-income settings include low patient health literacy and limited resources.

Acceptability

Shahaj, 2019*(12)*: Deliberately choosing to avoid or reduce medication (intentional nonadherence), rather than forgetfulness, was a theme in some studies. For some patients, symptoms acted as a guide for the seriousness of their HTN and guided their medication use; for example, they stopped treatment if symptoms disappeared. Some were guided by stress, using medication to manage worry or anxiety rather than HTN. Fear of dependency affected the amount of medication they took.

Shahaj, 2019*(12)*: 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, and treatment expectations).

Feasibility

Kuate, 2019*(13)*: In Cameroon, many individuals' HTN was untreated and uncontrolled. This may also reflect the high burden of undiagnosed HTN. The latter is consistent with enduring constraints in access to quality and affordable health care, poor public health facilities network coverage, scarcity of health professionals, frequent disruption of the supply of NCD drugs, very limited access to inexpensive and/or essential medicines, limited HTN knowledge among health professionals and patients, and poor adherence to medication among hypertensive patients under treatment.

Meiqari, 2019*(11)*: Many barriers in access to HTN care in low-income settings are due to overburdened health care providers; the lack of an organizational structure to accommodate a nonphysician as a primary care provider; the lack of confidence and/or policy towards the nonphysician providers' ability to manage uncomplicated and stable patients; and the lack of infrastructure for data collection and monitoring of clinical information on a periodic basis.

Gu, 2015*(8)*: While China rapidly expanded health insurance coverage nationally within the past decade, many Chinese adults still have limited access to HTN screening and follow up for HTN treatment and monitoring. For example, in the New Rural Cooperative Medical Scheme, which now covers over 95% of the rural population, most coverage is for inpatient hospitalizations, and the costs of basic medical services, including HTN education, screening, treatment, and monitoring, are not usually covered.

Outcome utilities See Table 15 below.

Table 15 Utilities per outcome for PICO question 1

Outcomes	Utility	Systematic review	Primary studies reported in the SR
Hypertension	0.96	Ren 2020*(14)*	Li 2015*(15)*
	0.98 (range: 1–0.95)	Kawalec 2015*(16)*	Burstrom 2001*(17)*, Sullivan 2008*(18)*, Wang 2008*(19)*
Type 2 diabetes mellitus	0.985	Gad 2020*(20)*	Salomon 2012*(21)*
MACE	Time NR: All CVD excluding stroke: 0.73 (95%CI: 0.69–0.76)	Kawalec 2015*(16)*	Lunde, 2013*(22)*
Stroke	First month after onset: 0.55	Ren 2020*(14)*	Li 2015*(15)*
	Days 1–3: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4–28: 0.88	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.65	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.70 (95%CI: 0.67-0.73)	Kawalec 2015*(16)*	Golicki 2010*(24)*
MI	First month after onset: 0.60	Ren 2020*(14)*	Li 2015*(15)*
	Days 1–3: 0.58	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4–28: 0.94	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.70	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: Disability weight 0.124	Gad 2020*(20)*	Salomon 2012*(21)*
ESRD	ESRD pre-dialysis: 0.73 (95% CI: 0.62–1)	Cooper 2020*(25)*	Jesky 2016*(26)*
	Hemodialysis: 0.75 (SD: 0.25)	Cooper 2020*(25)*	Briggs 2016*(27)*
Cognitive impairment/dementia	Patient rating: 0.85 (SD: 0.19)	NA	Rowen 2015*(28)*
	Patient rating: mild dementia 0.79 (SD: 0.22) moderate dementia: 0.72 (0.23)	NA	Orgeta 2015*(29)*
	Carer rating: mild dementia 0.63 (SD: 0.27) moderate dementia: 0.52 (0.27)	NA	Orgeta 2015*(29)*
HF events	First month after onset: 0.63	Ren 2020*(14)*	Li 2015*(15)*
	Chronic state: 0.73	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.79	Gad 2020*(20)*	Salomon 2012*(21)*
Adverse events	Common: 0.88	Gu 2015*(8)*	Clinical Judgement
	Infrequent: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*

PICO question 2: Is any laboratory testing necessary prior to initiation or during titration of pharmacological treatments?

Systematic review for desirable and undesirable effects

Background information

Prevalence of secondary HTN – There is limited data on community prevalence of secondary HTN (one study*(30)* that estimated primary and secondary HTN in a random population sample published in 1976 investigated those with a BP >175/115 mmHg on treatment – not relevant any more). Review articles commonly quote a prevalence of 5–10% in the general population.*(31)* Several studies assess the prevalence of secondary HTN in referral HTN clinics (patients referred for evaluation for secondary HTN) to be ~10%. Prevalence varies based on the population and included causes of secondary HTN (for example – obstructive sleep apnoea was considered as a cause in some studies, not others). Prevalence in the general population is significantly less than in these select population samples.

- In one prospective study, the prevalence was 9.1% among 1020 hypertensive patients visiting an outpatient clinic in Japan.*(32)*
- 10.2% in 4429 consecutively referred patients to a HTN clinic (to evaluate for secondary HTN) *(33)*
- In a study of consecutive patients evaluated in outpatient HTN clinics in Sao Paulo, Brazil, 32% had severe sleep apnoea, 5.6% had primary hyperaldosteronism, 2.4% had renal artery stenosis, 1.6% had eGFR <30 ml/min.*(34)*
- A meta-analysis of 20 observational studies and four RCTs with a total sample size of 991 035 estimated the prevalence of apparent treatment-resistant HTN in the observational studies to be 13.7% (95% CI, 11.2%–16.2%).*(35)*

Prevalence of comorbidities and end organ damage (e.g. DM, CVD, HF, cerebrovascular disease, CKD among patients with HTN); prevalence of CVD risk factors (e.g. hyperlipidaemia)

- HTN and insulin resistance have a common causal mechanism resulting in a high prevalence of DM in patients with HTN. An analysis of the 2011–2014 Medical Expenditure Panel Survey*(36)* revealed DM in 27.3% of hypertensive adults. Other comorbidities in individuals with HTN included hyperlipidaemia (55.9%), coronary heart disease (16.7%), renal disease (11.2%), heart rhythm disorders (6%), stroke (4.7%) and congestive heart failure (2.1%). A cross-sectional study of a sample of hypertensive patients recruited from three different university hospitals in Lebanon revealed a prevalence of diabetes of 27%.*(37)*
- From the 2020 AHA update of heart disease and stroke statistics*(35)*– in a meta-analysis including 95 772 US females and 30 555 US Males, each 10 mmHg higher SBP was associated with an effect size (RR or HR) for CVD of 1.25 (95% CI, 1.18–1.32) among females and 1.15 (95% CI, 1.1–1.19) for males; RR for CVD mortality was 1.16 among females and 1.17 among males.
- From the 2020 AHA update of heart disease and stroke statistics*(35)*– increased risk of heart failure (multivariable-adjusted HR, 1.86 (95%CI, 1.51-2.3).
- From the 2020 AHA update of heart disease and stroke statistics*(35)* – SBP/DBP ≥140/90 mmHg was associated with an OR for stroke of 2.98 (95% CI 2.72-3.28).

Adverse events after treatment (hyperkalaemia and AKI) – some of this may already be in the evidence profiles for PICO 4 and 5.

- A meta-analysis of randomized trials*(38)* documented discontinuation for adverse events attributed to different classes of antihypertensive drugs. They do not give specifics of adverse effects, just report on the percentage discontinuation. In this review, the probability of discontinuation over five years was 1.7% for centrally acting drugs, 2.9% for beta-blockers, 3.6% for diuretics, 7.7% for CCBs, 13.1% for ACEis and 15% for ARBs. The caveat is that the trials for centrally acting drugs, beta-blockers and diuretics are older and did not have other medications at baseline. Rate of discontinuation increased with increasing number of baseline drugs.
- Rates of individual adverse effects are probably best obtained for specific drugs.
- Of note, a recently published N-or-1 trial of statin, placebo or no treatment, found that 90% of symptom burden elicited by statins was also elicited by placebo.*(39)* May be relevant when considering disutility of taking pills.

Table 16 Components for PICO question 2

Study	Study population	Prevalence of secondary HTN
Berglund, 1976*(30)*	Among patients with BP>175/115:	- 40/689 (6%)
Rimoldi, 2013*(31)*	Among general HTN patients:	- 5–10%
Omura, 2004*(32)*	Among hypertensive outpatients:	- 93/1020 (9.1%)
Anderson, 1994*(33)*	among HTN patients sent for referral to investigate secondary HTN:	- 452/4429 (10.2%)
Pedrosa, 2011*(34)*	Among patients with resistant HTN:	- OSA: 80/125 (64.0%) - Severe OSA: 40/125 (32%) - Plasma aldosterone/renin >20: 14/125 (11.2%) (primary aldosteronism was confirmed in only 7 patients) - Renal artery stenosis screening test: 13/125 (10.4%) (renal artery stenosis was confirmed in 3 patients)
Virani 2020*(35)*	From the 2020 AHA update of heart disease and stroke statistics	- Among resistant HTN - A meta-analysis of 20 observational studies and 4 RCTs with a total sample size of 99 1035 estimated the prevalence of apparent treatment-resistant HTN in the observational studies to be 13.7% (95% CI, 11.2%–16.2%)
Park, 2017*(36)*	Among patients with HTN:	- No comorbidities: 4073/ 26 049 (14%) - One comorbidity: 6135/ 26 049 (23%) - Two comorbidities: 6310/ 26 049 (24.4%) - Three or more comorbidities: 9531/ 26 049 (38.7%) - Hyperlipidemia: 55.9% - Diabetes mellitus: 27.3% - Rheumatoid arthritis: 26.8% - Depression: 24.9% - Chronic pulmonary disease: 16.9% - CHD: 16.7% - Hypothyroidism: 12.5% - Renal disease: 11.2% - Heart rhythm disorder: 6.0% - Stroke: 4.7% - Fluid and electrolyte disorder: 2.6% - Congestive heart failure: 2.1% - Valvular heart disease: 1.5%
Chahoud, 2016*(37)*	Hypertension patients in Lebanon (LMIC)	- Diabetes mellitus 80/294 (27%)
Virani, 2020*(35)*	From the 2020 AHA update of heart disease and stroke statistics	- In a meta-analysis including 95 772 US females and 30 555 US Males, each 10 mmHg higher SBP was associated with an effect size (RR or HR) for CVD of 1.25 (95% CI, 1.18-1.32) among females and 1.15 (95% CI, 1.1-1.19) for males; RR for CVD mortality was 1.16 among females and 1.17 among males. - Increased risk of heart failure (multivariable-adjusted HR, 1.86 (95%CI, 1.51-2.3). - From the 2020 AHA update of heart disease and stroke statistics *(35)* – SBP/DBP ≥ 140/90 mmHg was associated with an OR for stroke of 2.98 (95% CI 2.72-3.28).
Thomopoulos, 2016*(38)*	Meta-analysis of RCTs	- A meta-analysis of randomized trials documented discontinuation for adverse events attributed to different classes of antihypertensive drugs. They do not give specifics of adverse effects, report on the % discontinuation. In this review, the probability of discontinuation over 5 years was 1.7% for centrally acting drugs, 2.9% for beta-blockers, 3.6% for diuretics, 7.7% for CCBs, 13.1% for ACEis and 15% for ARBs. The caveat is that the trials for centrally acting drugs, beta-blockers and diuretics are older and did not have other medications at baseline. Rate of discontinuation increased with increasing number of baseline drugs.
Wood, 2020*(39)*	Patients taking statins	- A recently published an N-or-1 trial of statin, placebo or no treatment found that 90% of symptom burden elicited by statins was also elicited by placebo. May be relevant when considering disutility of taking pills.

Evidence to decision for PICO question 2

Values and preferences

No research evidence

Resources required

No research evidence

Cost effectiveness

No research evidence

Equity

Baptist, 2018*(40)*: Health care among Haitians is very difficult to manage due to public-health challenges resulting from limited or lack of access to health care, economical constraints and the country's poor infrastructure. Haiti's health care system is highly dependent on episodic aid from nongovernmental organizations (NGOs) for health care provision. It is not uncommon for Haitians to travel a minimum of 10 km to access primary medical care. These limitations in access to health care outside urban areas have important implications when planning approaches to HTN management, particularly in rural areas and among those in lower socioeconomic groups, leading to lack of follow up for health care, which limits laboratory testing to titrate pharmacological treatment for HTN.

Risso, 2015*(7)*: In urban areas, patients found difficulty in taking time off work to attend the clinic: "Some of the private companies don't accept 'time-off', but we [doctors] cannot provide medical leave because [patients] were only here for a few hours." (HP)

Acceptability

Ogededgbe, 2006*(41)*: The reported magnitude of the differences in medication adherence between intervention and usual care, however, was larger for the complex interventions compared with the simple interventions.

Feasibility

Indirect evidence, Risso, 2015*(7)*: Commonly the MO will just "tell the patient to continue medication, sometimes without physical examination" (HP); they report having little time to talk with patients, and they simply "take their [the patient's] word" as to whether they are adhering to medication and modifying their lifestyle as the doctors have insufficient time to engage with them to ensure a shared understanding. In the public sector, a nurse will take the patient's blood pressure readings and any other tests required, which are then followed up by the MO as the nurse is not allowed to prescribe medications. However, physicians reported seeing 10 or more patients per hour, or 100 in a day, leaving inadequate time for meaningful interaction: "Many of healthcare providers [are] not able to sit down and have counselling session regarding their medications with their patients." (KI)

Outcome utilities

Please refer to Table 17 below.

Table 17 Utilities per outcome for PICO question 2

Outcomes	Utility	Systematic review	Primary studies reported in the SR
Hypertension	0.96	Ren 2020*(14)*	Li 2015*(15)*
	0.98 (range: 1–0.95)	Kawalec 2015*(16)*	Burstrom 2001*(17)*, Sullivan 2008*(18)*, Wang 2008*(19)*
Type 2 diabetes mellitus	0.985	Gad 2020*(20)*	Salomon 2012*(21)*
MACE	Time NR: All CVD excluding stroke: 0.73 (95%CI: 0.69–0.76)	Kawalec 2015*(16)*	Lunde, 2013*(22)*
Stroke	First month after onset: 0.55	Ren 2020*(14)*	Li 2015*(15)*
	Days 1–3: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4–28: 0.88	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.65	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.70 (95%CI: 0.67–0.73)	Kawalec 2015*(16)*	Golicki 2010*(24)*
MI	First month after onset: 0.60	Ren 2020*(14)*	Li 2015*(15)*
	Days 1–3: 0.58	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4–28: 0.94	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.70	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: Disability weight 0.124	Gad 2020*(20)*	Salomon 2012*(21)*
ESRD	ESRD pre-dialysis: 0.73 (95% CI: 0.62–1)	Cooper 2020*(25)*	Jesky 2016*(26)*
	Hemodialysis: 0.75 (SD: 0.25)	Cooper 2020*(25)*	Briggs 2016*(27)*
Cognitive impairment/dementia	Patient rating: 0.85 (SD: 0.19)	NA	Rowen 2015*(28)*
	Patient rating: mild dementia 0.79 (SD: 0.22) moderate dementia: 0.72 (0.23)	NA	Orgeta 2015*(29)*
	Carer rating: mild dementia 0.63 (SD: 0.27) moderate dementia: 0.52 (0.27)	NA	Orgeta 2015*(29)*
HF events	First month after onset: 0.63	Ren 2020*(14)*	Li 2015*(15)*
	Chronic state: 0.73	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.79	Gad 2020*(20)*	Salomon 2012*(21)*
Adverse events	Common: 0.88	Gu 2015*(8)*	Clinical Judgement
	Infrequent: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*

PICO question 3: Should cardiovascular risk assessment be used to guide initiation of antihypertensive medications?

Systematic review for desirable and undesirable effects

Table 18 Components for PICO question 3

Population	Intervention	Comparison	Outcome	Subgroups
Adult men and women without pre-identified cardiovascular disease	Initiating antihypertensives drug therapy based on a formal CVD risk estimation	Initiating antihypertensives drug therapy without formal CVD risk assessment (i.e., using only BP threshold)	- death (all-cause mortality) - CV death (death from MI, sudden cardiac death or stroke) - stroke - MI - end-stage kidney disease - HF events - cognitive impairment/ dementia - adverse events - proportion of people prescribed with antihypertensives - BP levels	BP levels

Table 19 Evidence Profile 3a: A formal cardiovascular risk estimation compared to no formal cardiovascular risk estimation in patients with hypertension without pre-identified cardiovascular disease who are starting antihypertensive medications

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	A formal cardiovascular risk estimation	No formal cardiovascular risk estimation	Relative (95% CI)	Absolute (95% CI)		
Major cardiovascular events avoided by treatment (composite of stroke [nonfatal or death from cerebrovascular disease], coronary heart disease [nonfatal myocardial infarction or death from CHD including sudden death], heart failure [causing death of admission to hospital] or cardiovascular disease death) (follow up: 5 years; assessed with: Karmali, 2018*(42)*)												
10	Secondary analysis of randomized trials [a]	serious [b]	not serious	not serious	not serious	none	The area under the curve quantifying the CV events avoided by treatment was (accuracy of avoiding cardiovascular events) – CVD risk strategy: 0.71 (95% CI, 0.70 to 0.72) – BP strategy: 0.54 (95% CI 0.53 to 0.55) The difference in accuracy was 0.17 (95% CI, 0.15 to 0.19). When doing the same analysis using the data from the SPRINT trial (Sundstrom & Karmali, 2019) results were qualitatively similar: CVD risk strategy: 0.58 (95% CI, 0.57 to 0.62)- BP strategy: 0.39 (95% CI, 0.34 to 0.92)- difference in accuracy: 0.19 (95% CI 0.12 to 0.29).[c,d]				⊕⊕⊕◯ MODERATE	–
Major cardiovascular events avoided for the same number of treated persons when treating at a BP threshold of 140 mmHg (follow up: 5 years; assessed with: Karmali, 2018*(42)*)												
10	Secondary analysis of randomized trials [a]	serious [b]	not serious	not serious	not serious	none	847/33 231 (2.2%)	821/33 231 (2.1%)	NE	310 more per 1000 (from 150 more to 500 more) [e]	⊕⊕⊕◯ MODERATE	–
Major cardiovascular events avoided for the same number of treated persons when treating at a BP threshold of 150 mmHg (follow up: 5 years; assessed with: Karmali, 2018*(42)*)												
10	Secondary analysis of randomized trials [a]	serious [b]	not serious	not serious	not serious	none	809/33 891 (2.4%)	698/33 891 (2.1%)	NE	158 more per 1000 (from 137 more to 183 more)[e]	⊕⊕⊕◯ MODERATE	–
Major cardiovascular events avoided for the same number of treated persons when treating at a BP threshold of 160 mmHg (follow up: 5 years; assessed with: Karmali, 2018*(42)*)												
10	Secondary analysis of randomized trials [a]	serious [b]	not serious	not serious	not serious	none	767/27 039 (2.8%)	557/22 039 (2.1%)	NE	376 more per 1000 (from 288 more to 402 more)[e]	⊕⊕⊕◯ MODERATE	–
Persons needed to treat to avoid the same number of cardiovascular events when treating at a BP threshold of 140 mm/Hg (follow up: 5 years; assessed with: Karmali, 2018*(42)*)												
10	Secondary analysis of randomized trials [a]	serious [b]	not serious	not serious	serious [f]	none	37 730/47 872 (78.8%)	39 231/47 872 (81.9%)	NE	38 fewer per 1000 (from 125 fewer to 72 more) [e]	⊕⊕◯◯ LOW	–
Persons needed to treat to avoid the same number of cardiovascular events when treating at a BP threshold of 150 mmHg (follow up: 5 years; assessed with: Karmali, 2018*(42)*)												

10	Secondary analysis of randomized trials [a]	serious [b]	not serious	not serious	not serious	none	24 225/47 872 (50.6%)	33 891/47 872 (70.8%)	NE	285 fewer per 1000 (from 311 fewer to 256 fewer)[e]	⊕⊕⊕◯ MODERATE	–
Persons needed to treat to avoid the same number of cardiovascular events when treating at a BP threshold of 160 mmHg (follow up: 5 years; assessed with: Karmali, 2018*(42)*)												
10	Secondary analysis of randomized trials [a]	serious [b]	not serious	not serious	not serious	none	17 484/47 872 (36.5%)	27 039/47 872 (56.5%)	NE	353 fewer per 1000 (from 499 fewer to 242 fewer)[e]	⊕⊕⊕◯ MODERATE	–
Mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval

Explanations

a. The original design of the studies was randomized trials; however the authors used the individual patient data to assess the outcomes of each patient had they been treated with one strategy or the other.

b. The question of interest is not the question randomization was done for. We decided to rate down only one level due to potential confounding bias, however, because the patients acted as their own control (although it is not clear how the data analysis accounted for this)

c. The ROC for the strategies cross at the 140 mmHg cut off, with the CV risk strategy being less accurate under that BP. The results of the SPRINT trial analysis, however, have ROC curves that do not cross at any point.

d. In the systematic review with individual patient meta-analysis in which the authors report how they built the CV risk-assessment model, they show that the relative effects of antihypertensive treatment is constant across risk groups, and that what changes is the absolute effect.

e. We used the numbers reported by the authors, who did not calculate a relative estimate of effect as they did not have two separate groups of patients.

f. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more.

Evidence to decision for PICO question 3

Values and preferences

No research evidence

Resources required

Gheorghe, 2018*(43)*: The costs per episode for hypertension and generic CVD were generally homogeneous across studies, ranging between USD 500 and USD 1500. In contrast, for CHD and stroke, cost estimates were higher and more heterogeneous, with several estimates in excess of USD 5000 per episode. Most studies reported costs for hypertension, for a median of USD 22 per month across estimates. The medians for average monthly treatment costs for stroke and CHD were higher, but varied with study scope and economic perspective from as little as USD 50 per month (e.g. CHD, patient perspective) to over USD 1000 (e.g. CHD, provider perspective).

Cost effectiveness

No research evidence

Equity

Meiqari, 2019*(11)*: In low-income settings, information on the availability of resources in health centres has reported their limited capacity to provide care for HTN, and the contribution of the private sector was also described as limited. Patients, therefore, tended to bypass the commune level and go to more distant centres, which increases their costs; this impedes continuous support for disease management. Moreover, HTN management at district and commune levels is based mainly on measuring BP and rarely takes into account behavioural or metabolic risk factors (e.g. smoking, total blood cholesterol, and the presence or absence of DM).

Helmer, 2018*(44)*: Much research has been done to assess the best hypertensive treatment approaches in black patients; however, there is a paucity of high-quality data. Although there are no published data assessing clinical outcomes specifically in black patients using ACEi or ARB monotherapy, evidence from subgroup analyses and cohort studies suggests that these patients may have higher rates of cardiovascular and cerebrovascular outcomes compared with those taking other antihypertensives.

Risso, 2015*(7)*: In urban areas, patients found difficulty in taking time off work to attend the clinic: “Some of the private companies don’t accept ‘time-off’, but we [doctors] cannot provide medical leave because [patients] were only here for a few hours” (HP). This is likely to make it more difficult for these patients to undergo a CV risk assessment.

Acceptability

Indirect evidence, Ogededgbe, 2006*(41)*: The reported magnitude of the differences in medication adherence between intervention and usual care, was larger for the complex interventions compared with the simple interventions.

Feasibility

Gu, 2015*(8)*: While China rapidly expanded health insurance coverage nationally within the past decade, many Chinese adults still have limited access to HTN screening and follow up. For example, in the New Rural Cooperative Medical Scheme, which now covers over 95% of the rural population, most coverage is for inpatient hospitalizations, and the costs of basic medical services, including HTN education, screening, treatment, and monitoring, are not usually covered.

Outcome utilities

Please refer to Table 20 below.

Table 20 Utilities per outcome for PICO question 3

Outcomes	Utility	Systematic review	Primary studies reported in the SR
Hypertension	0.96	Ren 2020*(14)*	Li 2015*(15)*
	0.98 (range: 1 – 0.95)	Kawalec 2015*(16)*	Burstrom 2001*(17)*, Sullivan 2008*(18)*, Wang 2008*(19)*
Type 2 diabetes mellitus	0.985	Gad 2020*(20)*	Salomon 2012*(21)*
MACE	Time NR: All CVD excluding stroke: 0.73 (95%CI: 0.69–0.76)	Kawalec 2015*(16)*	Lunde, 2013*(22)*
Stroke	First month after onset: 0.55	Ren 2020*(14)*	Li 2015*(15)*
	Days 1-3: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4-28: 0.88	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.65	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.70 (95%CI: 0.67-0.73)	Kawalec 2015*(16)*	Golicki 2010*(24)*
MI	First month after onset: 0.60	Ren 2020*(14)*	Li 2015*(15)*
	Days 1-3: 0.58	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4-28: 0.94	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.70	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: Disability weight 0.124	Gad 2020*(20)*	Salomon 2012*(21)*
ESRD	ESRD pre-dialysis: 0.73 (95% CI: 0.62–1)	Cooper 2020*(25)*	Jesky 2016*(26)*
	Hemodialysis: 0.75 (SD: 0.25)	Cooper 2020*(25)*	Briggs 2016*(27)*
Cognitive impairment/dementia	Patient rating: 0.85 (SD: 0.19)	NA	Rowen 2015*(28)*
	Patient rating: mild dementia 0.79 (SD: 0.22) moderate dementia: 0.72 (0.23)	NA	Orgeta 2015*(29)*
	Carer rating: mild dementia 0.63 (SD: 0.27) moderate dementia: 0.52 (0.27)	NA	Orgeta 2015*(29)*
HF events	First month after onset: 0.63	Ren 2020*(14)*	Li 2015*(15)*
	Chronic state: 0.73	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.79	Gad 2020*(20)*	Salomon 2012*(21)*
Adverse events	Common: 0.88	Gu 2015*(8)*	Clinical Judgement
	Infrequent: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*

PICO question 4: In adults with hypertension requiring pharmacological treatment, which drugs should be used as first-line agents?

Systematic review for desirable and undesirable effects

Evidence was considered in respect of the following components (Table 1) to determine (Table 21) to determine which drugs should be used as first-line agents in adults with hypertension requiring pharmacological treatment..

Table 21 Components for PICO question 4

Population	Intervention	Comparison	Outcome	Subgroup
Adult men and women >18 years old with primary HTN requiring pharmacological treatment	BB, CCB, diuretics, ACEi, or ARB	Placebo	- death (all-cause mortality) - CVD death (death from MI, sudden cardiac death or stroke) - stroke - MI - end-stage renal disease - cognitive impairment/ dementia - heart failure events - adverse effects - BP reduction and control (if data on CVD events are absent)	Based on different effect modifiers such as: - estimated cardiovascular risk - pre-existing CAD - stroke - diabetes - age - sex - chronic kidney disease - race/ethnicity - level of baseline BP

Table 22 Evidence profile 4a: Antihypertensive drug therapy (a mix of different class of antihypertensives) compared to placebo in individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antihypertensive drug therapy	Placebo	Relative (95% CI)	Absolute (95% CI)		
Sudden cardiac death (mean follow up: 4.2 years) Taverny, 2016*(45)*												
15	randomized trials	not serious	not serious	not serious	not serious [a]	none	247/20 353 (1.2%)	246/19 555 (1.3%)	RR 0.96 (0.81 to 1.15)	1 fewer per 1000 (from 2 fewer to 2 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Non-fatal myocardial infarction (mean follow up 4.2 years) Taverny, 2016*(45)*												
15	randomized trials	not serious	not serious	not serious	not serious [a]	none	379/20 353 (1.9%)	395/19 555 (2.0%)	RR 0.85 (0.74 to 0.98)	3 fewer per 1000 (from 5 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Fatal myocardial infarction (mean follow up 4.2 years) Taverny, 2016*(45)*												
15	randomized trials	not serious	not serious	not serious	not serious [a]	none	202/20 353 (1.0%)	232/19 555 (1.2%)	RR 0.75 (0.62 to 0.90)	3 fewer per 1000 (from 5 fewer to 1 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Withdrawals due to adverse effects – Taverny, 2016*(45)*												
10	randomized trials	not serious	serious [b]	not serious	not serious [c]	none	1996/16 197 (12.3%)	983/15 829 (6.2%)	RR 2.06 (1.11 to 3.83)	66 more per 1000 (from 7 more to 176 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Stroke (combined single agents and combinations, average duration of follow up 3.5 years) Parsons, 2016*(46)*												
11 [d]	randomized trials	serious [e]	not serious	not serious	not serious	none	698/17 428 (4.0%)	1132/19 957 (5.7%)	RR 0.74 (0.67 to 0.82)	15 fewer per 1000 (from 19 fewer to 10 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Dementia (duration of follow up ranged from 2 to 9.8 years) van Middelaar, 2018*(47)*												
9 [f]	randomized trials	not serious [g]	not serious	not serious	not serious	none	1041/29 029 (3.6%)	1090/28 653 (3.8%)	RR 0.93 (0.84 to 1.02)	3 fewer per 1000 (from 6 fewer to 1 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Incident dementia (IPDA of 6 cohort studies with median follow up of 7–22 years) Ding, 2020*(48)*												
6 [h]	observational studies	not serious	not serious	not serious	not serious	none		13.0%	HR 0.88 (0.79 to 0.98)	15 fewer per 1000 (from 26 fewer to 2 fewer)	⊕⊕◯◯ LOW	IMPORTANT
All-cause mortality – not reported												

–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage renal disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio

Explanations

a. The 95% CI is precise around the line of no effect, suggesting trivial benefit or trivial harm.

b. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I square (97.51%)

c. Although the confidence interval is wide, it does not cross the null; hence not downgraded for imprecision.

d. Event rates for individual outcomes in control group not included in the paper. We contacted the authors and received the excel file for events in each trial. The event rates were calculated.

e. The Medical Research Council elderly HTN trial had a high loss-to-follow-up (25%), other included trials had loss-to-follow-up ranging from 9 to 20%.

f. Parsons and colleagues included the outcome of dementia in individuals with HTN >65 years old and reported similar effect estimate of 0.90 (95% CI 0.76-1.07). Their date of literature search was 2014 and they included 4 trials for this outcome.

g. Overall risk of bias was low. Two trials (combined 16.6% weight) were unblinded due to the nature of the intervention (lifestyle or combined intervention). In one trial (12.6% weight) the study sponsor was involved in study design, data collection, analysis and interpretation.

h. Events in control arm not provided. Overall there were 1865/14 520 (12.8%) cases for this comparison. A baseline risk of 13% was used to estimate absolute effect.

Table 23 Evidence profile 4b: Thiazide diuretics (low or high dose) compared to control in individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thiazide diuretics (low or high dose)	Control	Relative (95% CI)	Absolute (95% CI)		
Setting: Outpatient												
Source: Wright 2018*(49)*, Xiao 2018*(50)*												
All-cause mortality – Low dose (mean duration 4.1 years)												
8	randomized trials	serious [a]	not serious	not serious	not serious	none	894/9549 (9.4%)	1137/10325 (11.0%)	RR 0.89 (0.82 to 0.97)	12 fewer per 1,000 (from 20 fewer to 3 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
All-cause mortality – High dose (mean duration 4.1 years)												
11	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	221/7769 (2.8%)	377/12070 (3.1%)	RR 0.90 (0.76 to 1.05)	3 fewer per 1,000 (from 7 fewer to 2 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Total stroke (fatal and non-fatal) – Low dose (mean duration 4.1 years)												
8	randomized trials	serious [a]	not serious	not serious	not serious	none	399/9549 (4.2%)	638/10325 (6.2%)	RR 0.68 (0.60 to 0.77)	20 fewer per 1,000 (from 25 fewer to 14 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Total stroke (fatal and non-fatal) – High dose (mean duration 4.1 years)												
11	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	87/7769 (1.1%)	229/12070 (1.9%)	RR 0.47 (0.37 to 0.61)	10 fewer per 1,000 (from 12 fewer to 7 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Total coronary heart disease (coronary heart disease, fatal and non-fatal myocardial infarction, and sudden or rapid cardiac death) – Low dose (mean duration 4.1 years)												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	231/9123 (2.5%)	386/9899 (3.9%)	RR 0.72 (0.61 to 0.84)	11 fewer per 1,000 (from 15 fewer to 6 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total coronary heart disease (coronary heart disease, fatal and non-fatal myocardial infarction, and sudden or rapid cardiac death) – High dose (mean duration 4.1 years)												
11	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	212/7769 (2.7%)	327/12070 (2.7%)	RR 1.01 (0.85 to 1.20)	0 fewer per 1,000 (from 4 fewer to 5 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total cardiovascular events (total stroke, total CHD, hospitalization or death from congestive heart failure and other significant vascular deaths such as ruptured aneurysms) – Low dose (mean duration 4.1 years)												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	810/9123 (8.9%)	1279/9899 (12.9%)	RR 0.70 (0.64 to 0.76)	39 fewer per 1,000 (from 47 fewer to 31 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Total cardiovascular events (total stroke, total CHD, hospitalization or death from congestive heart failure and other significant vascular deaths such as ruptured aneurysms) – High dose (mean duration 4.1 years)												
11	randomized trials	serious [a]	not serious	not serious	not serious	none	311/7769 (4.0%)	611/12070 (5.1%)	RR 0.72 (0.63 to 0.82)	14 fewer per 1,000 (from 19 fewer to 9 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Withdrawal due to adverse effects – Low dose (mean duration 4.1 years)												
3	randomized trials	serious [a,c]	not serious [d]	not serious	not serious	none	467/3862 (12.1%)	248/5008 (5.0%)	RR 2.38 (2.06 to 2.75)	68 more per 1,000 (from 52 more to 87 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Withdrawal due to adverse effects – High dose (mean duration 4.1 years)												
7	randomized trials	serious [a,c]	not serious	not serious	not serious	none	497/5422 (9.2%)	214/9748 (2.2%)	RR 4.48 (3.83 to 5.24)	76 more per 1,000 (from 62 more to 93 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Fractures – Xiao 2018												
11 [e]	observational studies	not serious	serious [f]	not serious	not serious	none		3.0%	RR 0.86 (0.80 to 0.93)	4 fewer per 1,000 (from 6 fewer to 2 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Thiazide diuretics (low or high dose)	Control	Relative (95% CI)	Absolute (95% CI)		
Systolic blood pressure – Low dose (mean duration 4.1 years)												
8	randomized trials	serious [a,c]	not serious [g]	not serious	not serious	none			-	MD 12.56 lower (13.22 lower to 11.91 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Systolic blood pressure – High dose (mean duration 4.1 years)												
6	randomized trials	serious [a,c]	not serious [g]	not serious	not serious	none			-	MD 13.66 lower (14.4 lower to 12.91 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Diastolic blood pressure – Low dose (mean duration 4.1 years)												
8	randomized trials	serious [a,c]	not serious [g]	not serious	not serious	none			-	MD 4.73 lower (5.12 lower to 4.34 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Diastolic blood pressure – High dose (mean duration 4.1 years)												
10	randomized trials	serious [a,c]	not serious [g]	not serious	not serious	none			-	MD 6.82 lower (7.24 lower to 6.41 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Cardiovascular mortality – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
End stage renal disease – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Cognitive impairment /dementia – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. Lack of blinding, Incomplete outcome reporting and selective outcome reporting bias leading to high risk or unclear risk of bias in majority (responsible for >50% of weight) of included trials.
b. The 95% CI is precise around the line of no effect, suggesting trivial benefit or trivial harm.
c. High risk of selective reporting bias (3 out of 8 for low dose and 7 out of 11 for high dose report this outcome).
d. Even though there is statistical inconsistency, all estimates suggest the same direction of effect, only one of the CIs does not overlap.
e. Event rates and sample size for each outcome not included in this review. A conservative baseline risk estimate of 3% was imputed to estimate absolute effect.
f. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (58%).
g. Even though there is statistical inconsistency, all estimates suggest the same direction of effect.

Table 24 Evidence profile 4c: Loop diuretics compared to placebo in individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	loop diuretics	placebo	Relative (95% CI)	Absolute (95% CI)		
Systolic BP (4 to 12 weeks duration)												
9	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	–	–	–	MD 7.9 mmHg lower (10.4 lower to 5.4 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Diastolic BP (4 to 12 weeks duration)												
9	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	–	–	–	MD 4.4 mmHg lower (5.9 lower to 2.8 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Musini 2015*(51)* – Cochrane review – BP-lowering efficacy of loop diuretics for primary HTN												

CI: Confidence interval; MD: Mean difference

Explanations

a. All but one trials were at high risk of at least one item in the risk of bias including incomplete outcome reporting (attrition bias), selective reporting (reporting bias) and publication bias. All but one trial were unclear risk of random sequence generation and allocation concealment.

b. Total number of participants in all the trials combined was 460. In the control arm, SBP reduction ranged from – 3.3 to – 15.7 mmHg. In the control arm, SBP reduction ranged from -2 to – 6.7.

Table 25 Evidence profile 4d: Diuretic antihypertensive therapy compared to placebo in individuals with hypertension (mix of different diuretics – outcome of incident dementia and falls)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diuretic (any) antihypertensive therapy	Placebo	Relative (95% CI)	Absolute (95% CI)		
Incident dementia – (follow up – 2.2 to 4.5 years) Tully 2016*(52)*												
4 [a]	randomized trials	not serious	not serious	not serious	not serious	none	–	4.0%	HR 0.88 (0.78 to 0.99)	5 fewer per 1000 (from 9 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Incident dementia – (length of follow up 3 to 9 years) Tully 2016*(52)*												
11 [a]	observational studies	not serious	not serious	not serious	not serious	none	–	4.0%	HR 0.79 (0.70 to 0.89)	8 fewer per 1000 (from 12 fewer to 4 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Incident dementia (IPDA of 6 cohort studies with median follow up of 7–22 years) Ding 2020*(48)*												
6 [b]	observational studies	not serious	not serious	not serious	not serious	none	–	9.0%	HR 0.97 (0.76 to 1.24)	3 fewer per 1000 (from 21 fewer to 20 more)	⊕⊕◯◯ LOW	IMPORTANT
Falls – Ang 2018*(53)*												
38 [c]	observational studies	not serious [d]	serious [e]	not serious	not serious	none	–	5.0%	OR 1.05 (0.92 to 1.20)	2 more per 1000 (from 4 fewer to 9 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Injurious falls – Ang 2018*(53)*												
29 [c]	observational studies	not serious [d]	serious [e]	not serious	not serious	none	–	5.0%	OR 0.98 (0.88 to 1.08)	1 fewer per 1000 (from 6 fewer to 4 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Recurrent falls – Ang 2018*(53)*												
8 [c]	observational studies	not serious [d]	serious [f]	not serious	serious [g]	none	–	5.0%	OR 1.15 (0.95 to 1.40)	7 more per 1000 (from 2 fewer to 19 more)	⊕◯◯◯ VERY LOW	IMPORTANT
All-cause mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
New outcome												
–	–	–	–	–	–	–	–		NE	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial Infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage renal disease – not reported												

–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio

Explanations

a. Event rates and sample size for each outcome not included in this review. Baseline risk estimate was imputed (for estimating absolute effect) from the incidence in a control group in a different systematic review.

b. Events in control arm not provided. Overall there were 934/10 623 (8.8%) cases for this comparison. A baseline risk of 9% was used to estimate absolute effect.

c. A conservative estimate of 5% falls in the control arm was used to calculate absolute effects.

d. The authors used the NOS to assess study quality. The studies were a mix of high quality (27%), moderate quality (50%) and low quality (23%). Sensitivity analysis including only high quality trials yielded comparable results to the overall analysis.

e. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (96%).

f. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (55%).

g. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

Table 26 Evidence profile 4e: Beta-blocker (BB) compared to placebo in individuals with high BP

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BB	Placebo	Relative (95% CI)	Absolute (95% CI)		
Total mortality (mean duration 5.3 years) Wright 2018*(49)*												
5	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	461/6967 (6.6%)	769/12 346 (6.2%)	RR 0.96 (0.86 to 1.07)	2 fewer per 1000 (from 9 fewer to 4 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Total stroke (fatal and non-fatal) (mean duration 5.3 years) Wright 2018*(49)*												
5	randomized trials	serious [a]	not serious	not serious	not serious	none	248/6967 (3.6%)	414/12 346 (3.4%)	RR 0.83 (0.72 to 0.97)	6 fewer per 1000 (from 9 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Total coronary heart disease (coronary heart disease, fatal and non-fatal myocardial infarction, and sudden or rapid cardiac death) (mean duration 5.3 years) Wright 2018*(49)*												
5	randomized trials	serious [a]	not serious	not serious	serious [c]	none	303/6967 (4.3%)	538/12 346 (4.4%)	RR 0.90 (0.78 to 1.03)	4 fewer per 1000 (from 10 fewer to 1 more)	⊕⊕◯◯ LOW	IMPORTANT
Total cardiovascular events (total stroke, total CHD, hospitalization or death from congestive heart failure and other significant vascular deaths such as ruptured aneurysms) (mean duration 5.3 years) Wright 2018*(49)*												
5	randomized trials	serious [a]	serious [d]	not serious	not serious	none	545/6967 (7.8%)	941/12 346 (7.6%)	RR 0.89 (0.81 to 0.98)	8 fewer per 1000 (from 14 fewer to 2 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Incident dementia (IPDA of 6 cohort studies with median follow up of 7-22 years) Ding 2020*(48)*												
5 [e]	observational studies	not serious	not serious	not serious	serious [f]	none	–	9.0%	HR 0.96 (0.77 to 1.20)	3 fewer per 1000 (from 20 fewer to 17 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Withdrawal due to adverse effects (mean duration 5.3 years) Wright 2018*(49)*												
4	randomized trials	serious [a]	serious [g]	not serious	not serious	none	1022/6609 (15.5%)	376/11 956 (3.1%)	RR 4.59 (4.11 to 5.13)	113 more per 1000 (from 98 more to 130 more)	⊕⊕◯◯ LOW	IMPORTANT
Systolic BP change (mean duration 5.3 years) Wright 2018*(49)*												
5	randomized trials	serious [a]	serious [g]	not serious	not serious	none	–	–	–	MD 9.51 lower (10.16 lower to 8.85 lower)	⊕⊕◯◯ LOW	IMPORTANT
Diastolic BP change (mean duration 5.3 years) Wright 2018*(49)*												
5	randomized trials	serious [a]	serious [g]	not serious	not serious	none	–	–	–	MD 5.64 lower (6.06 lower to 3.77 lower)	⊕⊕◯◯ LOW	IMPORTANT
Falls – Ang 2018*(53)*												
18	observational studies	not serious [h]	not serious [d]	not serious	not serious	none	–	5.0%	OR 1.04 (0.94 to 1.15)	2 more per 1000 (from 3 fewer to 7 more)	⊕⊕◯◯ LOW	IMPORTANT
Injurious falls (Falls requiring medical attention) – Ang 2018*(53)*												
8	observational studies	not serious [h]	serious [d]	not serious	not serious	none	–	5.0%	OR 0.84 (0.76 to 0.93)	8 fewer per 1000 (from 12 fewer to 3 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Recurrent falls – Ang 2018*(53)*												
4	observational studies	not serious [h]	not serious	not serious	serious [i]	none	–	5.0%	OR 1.19 (0.90 to 1.58)	9 more per 1000 (from 5 fewer to 27 more)	⊕◯◯◯ VERY LOW	IMPORTANT

End-stage renal disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio; OR: Odds ratio

Explanations

a. Three large trials included in this comparison were not blinded, resulting in high risk of performance / detection bias, blinding was unclear in a 4th trial. 2 of included trials had a high risk of attrition bias.
b. The 95% CI is precise around the line of no effect, suggesting trivial benefit or trivial harm.
c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.
d. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (54%).
e. Events in control arm not provided. Overall there were 888/9826 (9%) cases for this comparison. A baseline risk of 9% was used to estimate absolute effect .
f. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower ends of the 95% CI crossed this threshold, suggesting that there may be an important benefit or harm.
g. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (>85%)
h. The authors used the NOS to assess study quality. The studies were a mix of high quality (27%), moderate quality (50%) and low quality (23%). Sensitivity analysis including only high-quality trials yielded comparable results to the overall analysis.
i. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

Table 27 Evidence profile 4f: Angiotensin converting enzyme inhibitor (ACEi) compared to placebo in treatment of hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACEi	Placebo	Relative (95% CI)	Absolute (95% CI)		
Total mortality (mean duration 4.9 years) Wright 2018*(49)*												
3	randomized trials	serious [a]	not serious	not serious	not serious	none	343/3043 (11.3%)	402/2959 (13.6%)	RR 0.83 (0.72 to 0.95)	23 fewer per 1000 (from 38 fewer to 7 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Total stroke (fatal and non-fatal) (mean duration 4.9 years) Wright 2018*(49)*												
3	randomized trials	serious [a]	not serious	not serious	not serious	none	119/3043 (3.9%)	177/2959 (6.0%)	RR 0.65 (0.52 to 0.82)	21 fewer per 1000 (from 29 fewer to 11 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Total coronary heart disease (coronary heart disease, fatal and non-fatal myocardial infarction, and sudden or rapid cardiac death) (mean duration 4.9 years) Wright 2018*(49)*												
2	randomized trials	serious [a]	not serious	not serious	not serious	none	288/2612 (11.0%)	343/2533 (13.5%)	RR 0.81 (0.70 to 0.94)	26 fewer per 1000 (from 41 fewer to 8 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Total cardiovascular events (total stroke, total CHD, hospitalization or death from congestive heart failure and other significant vascular deaths such as ruptured aneurysms) (mean duration 4.9 years) Wright 2018*(49)*												
2	randomized trials	serious [a]	not serious	not serious	not serious	none	399/2612 (15.3%)	510/2533 (20.1%)	RR 0.76 (0.67 to 0.85)	48 fewer per 1000 (from 66 fewer to 30 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Incident dementia (IPDA of 6 cohort studies with median follow up of 7-22 years) Ding 2020*(48)*												
6 [b]	observational studies	not serious	not serious	not serious	serious [c]	none	–	8.0%	HR 1.03 (0.83 to 1.27)	2 more per 1000 (from 13 fewer to 20 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Systolic BP (mean duration 4.9 years) Wright 2018*(49)*												
2	randomized trials	serious [a]	not serious [d]	not serious	not serious	none	–	–	–	MD 21.14 lower (23.13 lower to 19.15 lower)	⊕⊕⊕◯ MODERATE	NOT IMPORTANT
Diastolic BP (mean duration 4.9 years) Wright 2018*(49)*												
2	randomized trials	serious [a]	not serious [d]	not serious	not serious	none	–	–	–	MD 9.64 lower (10.7 lower to 8.58 lower)	⊕⊕⊕◯ MODERATE	NOT IMPORTANT
Falls Ang 2018*(53)*												
9	observational studies	not serious [e]	not serious	not serious	not serious	none	–	5.0%	OR 1.02 (0.95 to 1.10)	1 more per 1000 (from 2 fewer to 5 more)	⊕⊕◯◯ LOW [f]	IMPORTANT
Injurious falls (Falls requiring medical attention) Ang 2018*(53)*												
5	observational studies	not serious [e]	not serious	not serious	not serious	none	–	5.0%	OR 0.85 (0.81 to 0.89)	7 fewer per 1000 (from 9 fewer to 5 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Recurrent falls Ang 2018*(53)*												
3 [f]	observational studies	not serious [e]	not serious	not serious	serious [g]	none	–	5.0%	OR 1.13 (0.91 to 1.40)	6 more per 1000 (from 4 fewer to 19 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Risk of fractures Kunutsor 2017*(54)*												
5 [h]	observational studies	not serious	serious [i]	not serious	serious [g]	none	–	3.0%	RR 1.09 (0.89 to 1.33)	3 more per 1000 (from 3 fewer to 10 more)	⊕◯◯◯ VERY LOW	IMPORTANT

End-stage renal disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

Setting: Outpatients

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio; OR: Odds ratio

Explanations

a. High risk of attrition bias in one of the three trials (~30% of participants discontinued the study medication). This study had a 70% weight in the meta-analysis. Lack of blinding in another trial.
b. Events in control arm not provided. Overall there were 895/11 112 (8%) cases for this comparison. A baseline risk of 8% was used to estimate absolute effect.
c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower ends of the 95% CI crossed this threshold, suggesting that there may be an important benefit or harm.
d. Even though there is statistical inconsistency, all estimates suggest the same direction of effect.
e. The authors used the NOS to assess study quality. The studies were a mix of high quality (27%), moderate quality (50%) and low quality (23%). Sensitivity analysis including only high-quality trials yielded comparable results to the overall analysis.
f. A conservative estimate of 5% falls in the control arm was used to calculate absolute effects.
g. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
h. The review did not provide event rates with forest plots, a 3% baseline risk was imputed to obtain absolute effect.
i. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. I-squared not provided.

Table 28 Evidence profile 4g: Angiotensin receptor blocker (ARB) compared to placebo in individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (Range 2 to 5 years) Dimou 2019*(55)*												
1 [a]	randomized trials	serious [b]	not serious [c,d]	not serious	serious [e]	none	–	402/2959 (13.6%)	RR 0.90 (0.75 to 1.08)	14 fewer per 1000 (from 34 fewer to 11 more)	⊕⊕◯◯ LOW [f]	CRITICAL
Cardiovascular mortality (Range 2 to 5 years) Dimou 2019*(55)*												
2 [g]	randomized trials	serious [b]	not serious [d,h]	not serious	serious [e]	none	–	297/2959 (10.0%)	RR 0.91 (0.72 to 1.15)	9 fewer per 1000 (from 28 fewer to 15 more)	⊕⊕◯◯ LOW [f]	CRITICAL
Myocardial infarction (fatal and non-fatal) (Range 2 to 5 years) Dimou 2019*(55)*												
2 [i]	randomized trials	serious [b]	not serious [d]	not serious	serious [e]	none	–	275/2959 (9.3%)	RR 0.90 (0.71 to 1.13)	9 fewer per 1000 (from 27 fewer to 12 more)	⊕⊕◯◯ LOW [f]	CRITICAL
Stroke (Range 2 to 5 years) Dimou 2019*(55)*												
2 [i]	randomized trials	serious [b]	not serious [d]	not serious	serious [e]	none	–	177/2959 (6.0%)	RR 0.80 (0.67 to 0.96)	12 fewer per 1000 (from 20 fewer to 2 fewer)	⊕⊕◯◯ LOW [f]	CRITICAL
Heart failure (development of or hospitalization for heart failure) (Range 2 to 5 years) Dimou 2019*(55)*												
1 [j]	randomized trials	serious [b]	not serious [d]	not serious	serious [e]	none	–	214/2959 (7.2%)	RR 1.05 (0.82 to 1.35)	4 more per 1000 (from 13 fewer to 25 more)	⊕⊕◯◯ LOW [f]	IMPORTANT
Incident dementia (IPDA of 6 cohort studies with median follow up of 7-22 years) Ding 2020*(48)*												
3 [k]	observational studies	not serious	not serious	not serious	serious [l]	none	–	9.4%	HR 0.78 (0.50 to 1.22)	20 fewer per 1000 (from 46 fewer to 19 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Falls (adverse effects) Ang 2018*(53)*												
5	observational studies	not serious	not serious	not serious	serious [e]	none	–	5.0%	OR 0.96 (0.87 to 1.06)	2 fewer per 1000 (from 6 fewer to 3 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Injurious falls (falls requiring medical attention) Ang 2018*(53)*												
3	observational studies	not serious	not serious	not serious	serious [m]	none	–	5.0%	OR 0.74 (0.53 to 1.03)	13 fewer per 1000 (from 23 fewer to 1 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Recurrent falls Ang 2018*(53)*												
1	observational studies	not serious	not serious	not serious	serious [e]	none	–	5.0%	OR 1.17 (0.80 to 1.71)	8 more per 1000 (from 10 fewer to 33 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Fractures Kunutsor 2017*(54)*												

5	observational studies	not serious	serious [n]	not serious	not serious	none	–	3.0%	RR 0.87 (0.76 to 1.01)	4 fewer per 1000 (from 7 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
End-stage renal disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio; OR: Odds ratio

Explanations

a. These results are from a network meta-analysis that included one trial directly comparing ARB to placebo, three trials comparing ACEi to placebo and two trials comparing ACEi to ARB with a total of 6 trials in the network.
b. Included trials had an intermediate risk of selection (random sequence generation/allocation bias) and attrition bias.
c. Q decomposition indicated heterogeneity (within designs Q 6.76, df:3, p:0.08).
d. Adequate data to assess inconsistency and incoherence was not provided in this manuscript. We reached out to the authors for clarification/additional data, the authors have not responded.
e. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm
f. This review did not provide baseline risk or Forest plots; baseline risk is imputed based on the rate in control arms of some of the other antihypertensive trials.
g. These results are from a network meta-analysis that included two trials directly comparing ARB to placebo, two trials comparing ACEi to placebo and one trial comparing ACEi to ARB with a total of five trials in the network.
h. Q decomposition indicated inconsistency (between designs Q:5.83, df:1, p:0.02).
i. These results are from a network meta-analysis that included two trials directly comparing ARB to placebo, three trials comparing ACEi to placebo and one trial comparing ACEi to ARB with a total of six trials in the network.
j. These results are from a network meta-analysis that included one trial directly comparing ARB to placebo, three trials comparing ACEi to placebo and one trial comparing ACEi to ARB with a total of five trials in the network.
k. Events in control arm not provided. Overall there were 476/5073 (9.4%) cases for this comparison. A baseline risk of 9.4% was used to estimate absolute effect.
l. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower ends of the 95% CI crossed this threshold, suggesting that there may be an important benefit or harm.
m. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit
n. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap, I-squared not provided.

Table 29 Evidence profile 4h: Calcium channel blocker (CCB) compared to placebo in individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	Placebo	Relative (95% CI)	Absolute (95% CI)		
Total mortality (2.5 years follow up) Wright 2018*(49)*												
1	randomized trials	serious [a]	serious [b]	not serious	not serious	none	123/2398 (5.1%)	137/2297 (6.0%)	RR 0.86 (0.68 to 1.09)	8 fewer per 1000 (from 19 fewer to 5 more)	⊕⊕◯◯ LOW	CRITICAL
Total stroke (fatal and non-fatal) (2.5 years follow up) Wright 2018*(49)*												
1	randomized trials	serious [a]	serious [b]	not serious	not serious	none	47/2398 (2.0%)	77/2297 (3.4%)	RR 0.58 (0.41 to 0.84)	14 fewer per 1000 (from 20 fewer to 5 fewer)	⊕⊕◯◯ LOW	CRITICAL
Total coronary heart disease (coronary heart disease, fatal and non-fatal myocardial infarction, and sudden or rapid cardiac death) (2.5 years follow up) Wright 2018*(49)*												
1	randomized trials	serious [a]	not serious [b]	not serious	serious [c]	none	58/2398 (2.4%)	72/2297 (3.1%)	RR 0.77 (0.55 to 1.09)	7 fewer per 1000 (from 14 fewer to 3 more)	⊕⊕◯◯ LOW	CRITICAL
Total cardiovascular events (total stroke, total CHD, hospitalization or death from congestive heart failure and other significant vascular deaths such as ruptured aneurysms) (2.5 years follow up) Wright 2018*(49)*												
1	randomized trials	serious [a]	not serious [b]	not serious	not serious	none	137/2398 (5.7%)	186/2297 (8.1%)	RR 0.71 (0.57 to 0.87)	23 fewer per 1000 (from 35 fewer to 11 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Heart failure (2.5 years follow up) Wright 2018*(49)*												
1	randomized trials	serious [a]	not serious [b]	not serious	serious [c]	none	31/2398 (1.3%)	42/2297 (1.8%)	RR 0.71 (0.45 to 1.12)	5 fewer per 1000 (from 10 fewer to 2 more)	⊕⊕◯◯ LOW	CRITICAL
Dementia in the elderly (>60 years) Median 8.2 years follow up – Hussain 2018*(56)*												
10	observational studies	not serious	serious [d]	serious [e]	not serious	none	–	4.0%	RR 0.70 (0.58 to 0.85)	12 fewer per 1000 (from 17 fewer to 6 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Incident dementia (IPDA of 6 cohort studies with median follow up of 7-22 years) Ding 2020*(48)*												
6 [f]	observational studies	not serious	not serious	not serious	serious [g]	none	–	8.0%	HR 0.92 (0.75 to 1.14)	6 fewer per 1000 (from 19 fewer to 11 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Systolic BP (2.5 years follow up) Wright 2018*(49)*												
1 [h]	randomized trials	not serious [a]	not serious [b]	not serious	not serious	none	–	–	–	MD 8.9 mmHg lower (10.14 lower to 7.66 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Diastolic BP (2.5 years follow up) Wright 2018*(49)*												
1	randomized trials	not serious [a]	not serious [b]	not serious	not serious	none	–	–	–	MD 4.5 mmHg lower (5.1 lower to 3.9 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Falls Ang 2018*(53)*												
11	observational studies	not serious [i]	not serious	not serious	not serious	none	–	5.0%	OR 1.00 (0.91 to 1.11)	0 fewer per 1000 (from 4 fewer to 5 more)	⊕⊕◯◯ LOW [j]	IMPORTANT
Injurious falls (falls requiring medical attention) Ang 2018*(53)*												
8	observational studies	not serious [i]	serious [k]	not serious	not serious	none	–	5.0%	OR 0.81 (0.74 to 0.90)	9 fewer per 1000 (from 13 fewer to 5 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Recurrent falls Ang 2018*(53)*												

3	observational studies	not serious [i]	not serious	not serious	serious [l]	none	–	5.0%	OR 1.25 (0.98 to 1.59)	12 more per 1000 (from 1 fewer to 27 more)	⨁◯◯◯ VERY LOW	IMPORTANT
End-stage renal disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio; MD: Mean difference; OR: Odds ratio

Explanations

a. Percentage not on assigned therapy at study end – placebo 28%, treatment group 18%.

b. Only one trial with evidence for this comparison with >4600 participants.

c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.

d. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (88%).

e. Comparator not identified (most were observational studies of individuals with HTN, the antihypertensive used in the control arm was not identified).

f. Events in control arm not provided. Overall there were 900/11 174 (8%) cases for this comparison. A baseline risk of 8% was used to estimate absolute effect.

g. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower ends of the 95% CI crossed this threshold, suggesting that there may be an important benefit or harm.

h. Seeley 2020 reviewed available evidence for pharmacotherapy of HTN in sub-Saharan Africa. Network meta-analysis with random effects was used to compare the effects across interventions. 32 studies with 2860 patients were included, median size – 42 participants/study. Nearly all studies were at some or high risk of bias. 50% of studies reported per-protocol results. Data were incomplete for 30 studies. Five studies failed to report any measure of variance. Very low quality data suggested that CCBs were the most efficacious first line agent with 18.46/11.6 mmHg reduction, no data on morbidity and mortality outcomes was available.

i. The authors used the NOS to assess study quality. The studies were a mix of high quality (27%), moderate quality (50%) and low quality (23%). Sensitivity analysis including only high-quality trials yielded comparable results to the overall analysis.

j. Event rate in the control arm was not provided. A conservative estimate of 5% falls in the control arm was used to calculate absolute effects.

k. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (75%).

l. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

Table 30 Evidence profile 4i: Antihypertensive drug therapy compared to placebo or no therapy in individuals aged 18 to 59 years with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antihypertensive drug therapy	Placebo or no therapy	Relative (95% CI)	Absolute (95% CI)		
Source												
Musini 2017*(57)* – Cochrane review – Pharmacotherapy for HTN in adults aged 18–59 years												
All-cause mortality (mean duration 5 years)												
5	randomized trials	serious [a]	not serious	not serious	not serious	none	194/8419 (2.3%)	204/8357 (2.4%)	RR 0.94 (0.77 to 1.13)	1 fewer per 1000 (from 6 fewer to 3 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Cardiovascular mortality plus morbidity (included fatal and nonfatal stroke, fatal and nonfatal MI, sudden death, hospitalization or death from congestive heart failure and other significant vascular deaths such as ruptured aneurysms) (mean duration 5 yeas)												
6	randomized trials	very serious [a,b]	not serious	not serious	not serious	none	277/8672 (3.2%)	351/8606 (4.1%)	RR 0.78 (0.67 to 0.91)	9 fewer per 1000 (from 13 fewer to 4 fewer)	⊕⊕◯◯ LOW	CRITICAL
Cerebrovascular mortality plus morbidity (fatal and nonfatal stroke) (mean duration 5 years)												
6	randomized trials	very serious [a,b]	not serious	not serious	not serious	none	55/8672 (0.6%)	116/8606 (1.3%)	RR 0.46 (0.34 to 0.64)	7 fewer per 1000 (from 9 fewer to 5 fewer)	⊕⊕◯◯ LOW	CRITICAL
Coronary heart disease mortality plus morbidity including fatal and non-fatal MI, sudden or rapid cardiac death (mean duration 5 years)												
4	randomized trials	very serious [a,b]	not serious	not serious	not serious	none	208/8134 (2.6%)	210/8107 (2.6%)	RR 0.99 (0.82 to 1.19)	0 fewer per 1000 (from 5 fewer to 5 more)	⊕⊕◯◯ LOW	CRITICAL
Withdrawal due to adverse events (follow up 10 years for the one trial that informed this outcome)												
3	randomized trials	very serious [a,b,c]	not serious	not serious	serious [d]	none	19/626 (3.0%)	4/597 (0.7%)	RR 4.82 (1.67 to 13.92)	26 more per 1000 (from 4 more to 87 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Reduction in systolic BP (mean duration 5 years)												
3	randomized trials	very serious [a,b,e]	not serious [f]	not serious	not serious	none	–	–	–	MD 14.98 mmHg lower (20.44 lower to 9.52 lower)	⊕⊕◯◯ LOW	NOT IMPORTANT
Reduction in diastolic BP (mean duration 5 years)												
4	randomized trials	very serious [a,b,g]	not serious [f]	not serious	not serious	none	–	–	–	MD 7.62 mmHg lower (10.55 lower to 4.69 lower)	⊕⊕◯◯ LOW	NOT IMPORTANT
End-stage renal disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. Attrition bias – in the largest trial included in this analysis (MRC-TMH 1985 – weighted between 65% to 86.4% for outcomes except for BP outcomes where the weight was ~ 30%), approximately 40% of the participants either stopped taking their assigned treatment during study follow up or were lost to follow up.
b. Lack of blinding of physician and participants in three trials (including the MRC-TMH 1985).
c. Only three out of seven included trials reported this outcome; in two out of these three no adverse events reported. MRC-TMH 1985 (the largest trial included) did not report on this outcome.
d. Results represent events in one trial only. Number of events is very low.
e. Change in SBP in the control group ranged from increase by 1.5 mmHg to decrease from 9-14 mmHg.
f. I-squared = 95% and some of the confidence intervals do not overlap. Even though there is statistical inconsistency, all estimates suggest the same direction of effect and only one of the CIs does not overlap with the others.
g. Decrease in DBP in the control group ranged from 0.6 mmHg to 7 mmHg.

Table 31 Evidence profile 4j: Antihypertensive drug therapy compared to placebo or no active comparator therapy in individuals over 60 years with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antihypertensive drug therapy	Placebo or no active comparator therapy	Relative (95% CI)	Absolute (95% CI)		
Source												
Musini 2019*(57)* – Cochrane review – Pharmacotherapy for HTN in adults 60 years or older												
Total mortality (mean duration 3.8 years)												
13	randomized trials	serious [a]	not serious	not serious	not serious	none	1290/13 368 (9.6%)	1376/12 564 (11.0%)	RR 0.91 (0.85 to 0.97)	10 fewer per 1000 (from 16 fewer to 3 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Fatal stroke (mean duration 3.7 years)												
11	randomized trials	serious [a]	not serious	not serious	not serious	none	143/13 287 (1.1%)	202/12 476 (1.6%)	RR 0.67 (0.54 to 0.82)	5 fewer per 1000 (from 7 fewer to 3 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Fatal coronary heart disease (mean duration 3.7 years)												
10	randomized trials	serious [a]	not serious	not serious	not serious	none	296/12 428 (2.4%)	374/12 050 (3.1%)	RR 0.78 (0.67 to 0.91)	7 fewer per 1000 (from 10 fewer to 3 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Cardiovascular mortality and morbidity including total stroke, total coronary heart disease, hospitalization or death from congestive heart failure, and other significant vascular deaths such as ruptured aneurysm (mean duration 3.8 years)												
15	randomized trials	serious [a]	not serious [b]	not serious	not serious	none	1312/13 778 (9.5%)	1759/12 969 (13.6%)	RR 0.72 (0.68 to 0.77)	38 fewer per 1000 (from 43 fewer to 31 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Cerebrovascular mortality and morbidity including fatal and non-fatal stroke (mean duration 3.7 years)												
13	randomized trials	serious [a]	not serious	not serious	not serious	none	453/13 424 (3.4%)	659/12 618 (5.2%)	RR 0.66 (0.59 to 0.74)	18 fewer per 1000 (from 21 fewer to 14 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Coronary heart disease mortality and morbidity including fatal and non-fatal myocardial infarction and sudden or rapid cardiac death (mean duration 2.9 years)												
11	randomized trials	serious [a]	not serious	not serious	not serious	none	456/12 466 (3.7%)	576/12 093 (4.8%)	RR 0.78 (0.69 to 0.88)	10 fewer per 1000 (from 15 fewer to 6 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Withdrawal due to adverse effects (mean duration 4.6 years)												
4	randomized trials	serious [a,c]	serious [d]	not serious	not serious	none	865/5803 (14.9%)	297/5507 (5.4%)	RR 2.91 (2.56 to 3.30)	103 more per 1000 (from 84 more to 124 more)	⊕⊕◯◯ LOW	IMPORTANT
End-stage renal disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. Lack of blinding, incomplete outcome reporting and selective outcome reporting in the majority (example – 11 of 13 for total mortality) of trials. Four large trials were funded by industry.
b. I-squared 65 %, even though there is statistical inconsistency, all estimates suggest the same direction of effect and only one of the CIs does not overlap with the others
c. Only four of 16 trials reported this outcome
d. The point estimates vary and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (97%).

Table 32 Evidence profile 4k: Antihypertensive drug therapy compared to placebo or no treatment in individuals over 80 years with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antihypertensive drug therapy	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Source												
Musini 2019*(57)* – Cochrane review – Pharmacotherapy for HTN in adults 60 years or older												
Total mortality (follow up between 2 and 5 years)												
8	randomized trials	serious [a]	not serious [b]	not serious	serious [c]	none	462/3617 (12.8%)	439/3084 (14.2%)	RR 0.97 (0.87 to 1.10)	4 fewer per 1000 (from 19 fewer to 14 more)	⨁⨁◯◯ LOW	CRITICAL
Cardiovascular mortality and morbidity (follow up between 2 and 5 years)												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	296/3547 (8.3%)	344/2999 (11.5%)	RR 0.75 (0.65 to 0.87)	29 fewer per 1000 (from 40 fewer to 15 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Cerebrovascular mortality and morbidity (follow up between 2 and 5 years)												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	120/3547 (3.4%)	157/2999 (5.2%)	RR 0.66 (0.52 to 0.83)	18 fewer per 1000 (from 25 fewer to 9 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Coronary heart disease mortality and morbidity (follow up between 2 and 5 years)												
6	randomized trials	serious [a]	not serious	not serious	not serious [d]	none	48/2690 (1.8%)	53/2573 (2.1%)	RR 0.82 (0.56 to 1.20)	4 fewer per 1000 (from 9 fewer to 4 more)	⨁⨁⨁◯ MODERATE	CRITICAL
End-stage renal disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Discontinuation due to adverse effects – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. Lack of blinding, incomplete outcome reporting and selective outcome reporting in the majority (example – 11 of 13 for total mortality) of trials. Three trials were funded by industry.
b. Even though there is statistical inconsistency (I-squared 52%), all estimates suggest the same direction of effect and only one of the CIs does not overlap with the others.
c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.
d. The 95% CI is precise around the line of no effect, suggesting trivial benefit or trivial harm.

Table 33 Evidence profile 4l: Dual alpha- and beta-blockers compared to placebo in individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dual alpha- and beta-blockers	Placebo	Relative (95% CI)	Absolute (95% CI)		
Source												
Wong 2015*(58)* – Cochrane Review – BP-lowering efficacy of dual alpha- and beta-blockers for primary HTN												
Systolic BP												
8	randomized trials	serious [a]	not serious	not serious	not serious	none	–	–	–	MD 5.59 mmHg lower (7.47 lower to 3.7 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Diastolic BP												
8	randomized trials	serious [a]	not serious	not serious	not serious	none	–	–	–	MD 3.88 mmHg lower (4.95 lower to 2.82 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT
Heart rate												
7	randomized trials	serious [a]	not serious	not serious	not serious	none	–	–	–	MD 4.62 beats/min lower (5.71 lower to 3.54 lower)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Pulse pressure												
8	randomized trials	serious [a]	not serious	not serious	not serious	none	–	–	–	MD 1.89 mmHg lower (3.58 lower to 0.2 lower)	⨁⨁⨁◯ MODERATE	NOT IMPORTANT
Withdrawal due to adverse effects												
5	randomized trials	serious [a]	not serious	not serious	not serious	none	–	–	RR 0.88 (0.54 to 1.42)	1 fewer per 1000 (from 1 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. High risk of detection bias due to breaking of blinding.

Table 34 Evidence profile 4m: Beta-1 selective beta-blocker compared to placebo in individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-1 selective beta-blocker	Placebo	Relative (95% CI)	Absolute (95% CI)		
Source												
Wong 2016*(58)* – Cochrane review – BP-lowering efficacy of beta-1 selective beta-blocker for primary HTN												
Systolic BP												
47	randomized trials	serious [a]	serious [b]	not serious	not serious	none	–	–	–	MD 10.4 mmHg lower (11.1 lower to 9.7 lower)	⊕⊕◯◯ LOW	IMPORTANT
Diastolic BP												
48	randomized trials	serious [a]	serious [b]	not serious	not serious	none	–	–	–	MD 8.3 mmHg lower (8.7 lower to 7.8 lower)	⊕⊕◯◯ LOW	IMPORTANT
Heart rate												
33	randomized trials	serious [a]	serious [b]	not serious	not serious	none	–	–	–	MD 10.9 beats/min lower (11.5 lower to 10.4 lower)	⊕⊕◯◯ LOW	IMPORTANT
Pulse pressure												
47	randomized trials	serious [a]	serious [b]	not serious	not serious	none	–	–	–	MD 1.8 mmHg lower (2.3 lower to 1.2 lower)	⊕⊕◯◯ LOW	NOT IMPORTANT
Withdrawal due to adverse effects												
3	randomized trials	serious [a]	serious [b]	not serious	not serious	none	–	–	RR 0.9 (0.5 to 1.5)	1 fewer per 1000 (from 2 fewer to 1 fewer)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. High risk of detection bias due to loss of blinding.

b. Significant heterogeneity – I-squared > 50%.

Table 35 Evidence profile4n: Angiotensin-converting enzyme inhibitor (ACEi) compared to placebo for non-dialysis chronic kidney disease stages 3–5

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACEi	Placebo	Relative (95% CI)	Absolute (95% CI)		
Source												
Zhang 2020*(59)* (Network meta-analysis)												
Kidney events (defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in GFR, or ESKD) (follow up >6 months)[a]												
13 [b]	randomized trials	not serious [c]	not serious [d]	not serious [e]	not serious	none	–	9.2% [f]	OR 0.54 (0.41 to 0.73)	40 fewer per 1000 (from 52 fewer to 23 fewer)	⊕⊕⊕⊕ HIGH	–
Cardiovascular events (follow up >6 months)[g]												
13 [b]	randomized trials	not serious [c]	not serious [d]	not serious	not serious	none	–	20.6% [f]	OR 0.73 (0.64 to 0.84)	47 fewer per 1000 (from 64 fewer to 27 fewer)	⊕⊕⊕⊕ HIGH	–
Cardiovascular death (follow up >6 months)												
13 [b]	randomized trials	not serious [c]	not serious [d]	not serious	not serious	none	–	10.6% [f]	OR 0.73 (0.63 to 0.86)	26 fewer per 1000 (from 36 fewer to 13 fewer)	⊕⊕⊕⊕ HIGH	–
All-cause mortality (follow up >6 months)[h]												
13 [b]	randomized trials	not serious [c]	not serious [d]	not serious	not serious	none	–	15.9% [f]	OR 0.77 (0.66 to 0.91)	32 fewer per 1000 (from 48 fewer to 12 fewer)	⊕⊕⊕⊕ HIGH	–
Hyperkalaemia (follow up >6 months)[i]												
13 [b]	randomized trials	serious [j]	not serious [d]	not serious	serious [k]	none	–	2.3% [f]	OR 1.55 (0.93 to 2.59)	12 more per 1000 (from 2 fewer to 34 more)	⊕⊕◯◯ LOW	–
Cough (follow up >6 months)												
13 [b]	randomized trials	serious [j]	not serious [d]	not serious	not serious	none	–	1.4% [f]	OR 2.90 (1.76 to 4.77)	26 more per 1000 (from 10 more to 49 more)	⊕⊕⊕◯ MODERATE	–
Hypotension (follow up >6 months)												
13 [b]	randomized trials	serious [j]	not serious [d]	not serious	serious [k]	none	–	0.6% [f]	OR 1.79 (1.05 to 3.04)	5 more per 1000 (from 0 fewer to 12 more)	⊕⊕◯◯ LOW	–
Oedema (follow up >6 months)												
13 [b]	randomized trials	serious [j]	not serious [d]	not serious	very serious [k]	none	–	0.3% [f]	OR 2.11 (0.33 to 13.53)	3 more per 1000 (from 2 fewer to 36 more)	⊕◯◯◯ VERY LOW	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												

–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction and control – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; OR: Odds ratio

Explanations

a. The OR of kidney events for ACEi vs placebo is 0.86 (0.37,2.01) for the subgroup of patients with diabetic kidney disease.

b. The total number of trials informing direct comparisons is 13. It is not clear from the review which of these trials examined the outcome of interest.

c. The weight of each of the included studies was not provided. However, five of the 13 included studies were judged to be at unclear risk of bias in the domains of random sequence generation, allocation concealment, blinding of outcome assessors and selective outcome reporting. However, we did not downgrade risk of bias because subgroup analysis including studies with low risk of bias showed consistent results.

d. The review does not provide I-squared or the confidence intervals of individual studies to assess heterogeneity. The review states "Loop-specific inconsistency approach was used to assess the disagreement between direct and indirect evidence in the loop, and the consistency results were considered not significant when 95% CIs of inconsistency factors included zero or ROR included one. ROR is defined as the difference that OR value of direct evidence minus OR value of indirect evidence."

e. We did not downgrade indirectness because 50% drop in eGFR and doubling in serum creatinine are validated surrogates for ESKD.

f. The baseline risk wasn't reported in the network meta-analysis. The values were abstracted directly from the included studies.

g. The OR of cardiovascular events for ACEi vs placebo is 0.89 (0.74,1.07) for the subgroup of patients with diabetic kidney disease.

h. The OR of All-cause mortality for ACEi vs placebo is 0.88 (0.73,1.06) for the subgroup of patients with diabetic kidney disease.

i. The OR of hyperkalemia for ACEi vs placebo is 2.08 (0.68,6.33) for the subgroup of patients with diabetic kidney disease.

j. The weight of each of the included studies was not provided. However, five of the 13 included studies were judged to be at unclear risk of bias in the domains of random sequence generation, allocation concealment, blinding of outcome assessors and selective outcome reporting.

k. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

Table 36 Evidence profile 4o Angiotensin II receptor blocker (ARB) compared to placebo for non-dialysis chronic kidney disease stages 3–5

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	Placebo	Relative (95% CI)	Absolute (95% CI)		
Source												
Zhang 2020*(59)* (Network meta-analysis)												
Kidney events (defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in GFR, or ESKD) (follow up >6 months)[a]												
3 [b]	randomized trials	not serious	not serious [c]	not serious [d]	serious [e]	none	–	385/1797 (21.4%)	OR 0.76 (0.58 to 1.00)	43 fewer per 1000 (from 78 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	–
Cardiovascular events (follow up >6 months)[f]												
2 [g]	randomized trials	not serious	not serious [c]	not serious	serious [e]	none		187/1035 (18.1%)	OR 0.83 (0.70 to 0.98)	26 fewer per 1000 (from 47 fewer to 3 fewer)	⊕⊕⊕◯ MODERATE	–
Cardiovascular mortality (follow up >6 months)												
2 [g]	randomized trials	not serious	not serious [c]	not serious	very serious [h]	none	–	86/1035 (8.3%)	OR 1.16 (0.88 to 1.53)	12 more per 1000 (from 9 fewer to 39 more)	⊕⊕◯◯ LOW	–
All-cause mortality (follow up >6 months)[i]												
3 [b]	randomized trials	not serious	not serious [c]	not serious	very serious [h]	none	–	298/1797 (16.6%)	OR 1.01 (0.82 to 1.25)	1 more per 1000 (from 26 fewer to 33 more)	⊕⊕◯◯ LOW	–
Hyperkalaemia (follow up >6 months)[j]												
3 [b]	randomized trials	not serious	not serious [c]	not serious	not serious	none	–	36/1797 (2.0%)	OR 2.08 (1.44 to 2.99)	21 more per 1000 (from 9 more to 38 more)	⊕⊕⊕⊕ HIGH	–
Hypotension (follow up >6 months)												
1 [k]	randomized trials	not serious	not serious [c]	not serious	serious [l]	none	–	6/751 (0.8%)	OR 1.12 (0.43 to 2.90)	1 more per 1000 (from 5 fewer to 15 more)	⊕⊕⊕◯ MODERATE	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction and control – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; OR: Odds ratio

Explanations

a. The OR of kidney events for ARB vs placebo is 0.82 (0.72,0.95) for the subgroup of patients with diabetic kidney disease.
b. The total number of trials informing direct comparisons is three.
c. The review does not provide I-squared or the confidence intervals of individual studies to assess heterogeneity. The review states "Loop-specific inconsistency approach was used to assess the disagreement between direct and indirect evidence in the loop, and the consistency results were considered not significant when 95% CIs of inconsistency factors included zero or RoR included one. RoR is defined as the difference that OR value of direct evidence minus OR value of indirect evidence."
d. We did not downgrade indirectness because 50% drop in eGFR and doubling in serum creatinine are validated surrogates for ESKD.
e. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.
f. The OR of cardiovascular events for ARB vs placebo is 0.87 (0.75,1.01) for the subgroup of patients with diabetic kidney disease.
g. 2 is the total number of trials informing direct comparisons.
h. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower end of the 95% CI crossed this threshold, suggesting that there may be important harm and benefit.
i. The OR of All-cause mortality for ARB vs placebo is 0.98 (0.81,1.18) for the subgroup of patients with diabetic kidney disease.
j. The OR of hyperkalemia for ARB vs placebo is 2.15 (1.25,3.69) for the subgroup of patients with diabetic kidney disease.
k. 1 is the total number of trials informing direct comparisons.
l. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

Table 37 Evidence profile 4p: BP-lowering drugs compared to placebo or no treatment for patients with a history of stroke or transient ischaemic attack

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP-lowering drugs	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Source												
Zonneveld 2018*(5)* (BP-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack)												
Recurrent stroke of any type (median follow up 12 to 47 months)[ab]												
8	randomized trials	serious [c]	not serious	not serious	not serious	none	1525/17 594 (8.7%)	1773/17 516 (10.1%)	RR 0.81 (0.70 to 0.93)	19 fewer per 1000 (from 30 fewer to 7 fewer)	⊕⊕⊕◯ MODERATE	–
Time to recurrent stroke (median follow up 12 to 47 months)												
3	randomized trials	not serious	not serious	not serious	serious [d]	none	–	–	RR 0.82 (0.65 to 1.03)	1 fewer per 1000 (from 1 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	–
Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause) (median follow up 12 to 47 months)[e]												
4	randomized trials	serious [f]	not serious	not serious	serious [g]	none	1941/14 301 (13.6%)	2168/14 329 (15.1%)	RR 0.90 (0.78 to 1.04)	15 fewer per 1000 (from 33 fewer to 6 more)	⊕⊕◯◯ LOW	–
Myocardial infarction (median follow up 12 to 47 months)												
6	randomized trials	serious [h]	not serious	not serious	not serious	none	330/17 374 (1.9%)	364/17 373 (2.1%)	RR 0.90 (0.72 to 1.11)	2 fewer per 1000 (from 6 fewer to 2 more)	⊕⊕⊕◯ MODERATE	–
Vascular death (median follow up 12 to 47 months)												
6	randomized trials	serious [i]	not serious	not serious	not serious	none	690/17 374 (4.0%)	810/17 373 (4.7%)	RR 0.85 (0.76 to 0.95)	7 fewer per 1000 (from 11 fewer to 2 fewer)	⊕⊕⊕◯ MODERATE	–
Death by any cause (median follow up 12 to 47 months)												
8	randomized trials	serious [j]	not serious	not serious	not serious	none	1363/17 594 (7.7%)	1386/17 516 (7.9%)	RR 0.98 (0.91 to 1.05)	2 fewer per 1000 (from 7 fewer to 4 more)	⊕⊕⊕◯ MODERATE	–
Dementia (median follow up 12 to 47 months)												
2	randomized trials	not serious	not serious	not serious	serious [g]	none	196/3320 (5.9%)	224/3351 (6.7%)	RR 0.88 (0.73 to 1.06)	8 fewer per 1000 (from 18 fewer to 4 more)	⊕⊕⊕◯ MODERATE	–
Ischaemic stroke (median follow up 12 to 47 months)												
3	randomized trials	not serious	not serious	not serious	serious [g]	none	1026/13 367 (7.7%)	1136/13 334 (8.5%)	RR 0.86 (0.70 to 1.05)	12 fewer per 1000 (from 26 fewer to 4 more)	⊕⊕⊕◯ MODERATE	–
Haemorrhagic stroke (median follow up 12 to 47 months)												

2	randomized trials	not serious	not serious	not serious	not serious	none	96/13 197 (0.7%)	143/13 240 (1.1%)	RR 0.66 (0.39 to 1.12)	4 fewer per 1000 (from 7 fewer to 1 more)	⊕⊕⊕⊕ HIGH	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse effects – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction and control – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. Subgroup analysis by intervention showed that the relative risk for recurrent stroke of any type for ACEi vs placebo is 0.73 with CI of [0.64, 0.84]. Subgroup analysis by intervention showed that the RR for recurrent stroke of any type for ARBs vs placebo is 0.95 with CI of [0.87, 1.03]. Subgroup analysis by intervention showed that the RR for recurrent stroke of any type for beta-blockers vs placebo is 0.94 with CI of [0.75, 1.18]. Subgroup analysis by intervention showed that the RR for recurrent stroke of any type for CCBs vs placebo is 0.55 with CI of [0.18, 1.67]. Subgroup analysis by intervention showed that the RR for recurrent stroke of any type for diuretics vs placebo is 0.72 with CI of [0.59, 0.87].

b. Subgroup analysis based on type of index event showed that Relative risk of BP-lowering drugs (BPLDs) versus placebo or no treatment (subgroups) for the outcome of TIA is 0.77 with CI of [0.50, 1.18], for the outcome of Ischaemic stroke is 0.76 with CI of [0.64, 0.89], and for Intracerebral haemorrhage is 0.59 with CI of [0.39, 0.89].

c. The trials that have more than 50% of the weight of the pooled estimate were judged to be at high/unclear risk of bias in the domain of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

d. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or no effect. The events rate is not available.

e. Subgroup analysis by intervention showed that the relative risk for major vascular events for ACEi vs placebo is 0.76 with CI of [0.68, 0.85]. Subgroup analysis by intervention showed that the RR for major vascular events for ARBs vs placebo is 0.94 with CI of [0.88, 1.01]. Subgroup analysis by intervention showed that the RR for major vascular events for beta-blocker is 1.01 with CI of [0.84, 1.21].

f. Two of the included trials which have more than 30% of the weight of pooled estimate were judged to be at high/unclear risk of bias in the domains of blinding of participants and personnel and selective reporting.

g. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.

h. The trials that have around 44.5% of the weight of the pooled estimate were judged to be at unclear risk of bias in the domain of blinding of participants and personnel and at high/unclear risk of bias in the domain of selective reporting and incomplete outcome data.

i. The trials that have around 44.5% of the weight of the pooled estimate were judged to be at high/unclear risk of bias in the domain of selective reporting and incomplete outcome data.

j. The trial that have around 23% of the weight of effect estimate were judged to be at high/unclear risk of bias in the domains of random sequence generation, allocation concealment, selective reporting and incomplete outcome data.

Table 38 Evidence profile 4q: Antihypertensive drug therapy compared to placebo or no treatment in individuals with pre-hypertensive levels of BP (systolic BP 120–139 mmHg and diastolic BP <90 mmHg)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antihypertensive drug therapy	Placebo or no treatment	Relative (95% CI)	Absolute (95% CI)		
Source												
Hong 2018*(1)* – Effects of antihypertensive treatment on major cardiovascular events in populations within pre-hypertensive levels: a systematic review and meta-analysis												
All-cause mortality (pooled analysis) mean intervention time 3.4 years												
19	randomized trials	serious [a]	not serious	not serious	not serious	none	3936/51 930 (7.6%)	4053/51 552 (7.9%)	RR 0.97 (0.91 to 1.04)	2 fewer per 1000 (from 7 fewer to 3 more)	⊕⊕⊕◯ MODERATE	CRITICAL
All-cause mortality (average SBP 120-130) mean intervention time 3.4 years												
5	randomized trials	serious [a]	not serious	not serious	serious [b]	none	–	7.9%	RR 0.95 (0.76 to 1.18)	4 fewer per 1000 (from 19 fewer to 14 more)	⊕⊕◯◯ LOW	CRITICAL
All-cause mortality (average SBP 130-139) mean intervention time 3.4 years												
14	randomized trials	serious [a]	serious [c]	not serious	not serious	none	–	7.9%	RR 0.98 (0.90 to 1.05)	2 fewer per 1000 (from 8 fewer to 4 more)	⊕⊕◯◯ LOW	CRITICAL
Cardiovascular mortality												
22	randomized trials	serious [a]	not serious	not serious	not serious	none	2694/53 699 (5.0%)	2746/53 730 (5.1%)	RR 0.99 (0.92 to 1.07)	1 fewer per 1000 (from 4 fewer to 4 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Myocardial infarction												
19	randomized trials	serious [a]	not serious	not serious	serious [c]	none	2177/50 788 (4.3%)	2437/50 839 (4.8%)	RR 0.92 (0.84 to 1.01)	4 fewer per 1000 (from 8 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL
Stroke												
28	randomized trials	serious [a]	serious [d]	not serious	not serious	none	1772/59 913 (3.0%)	1995/59 949 (3.3%)	RR 0.86 (0.76 to 0.96)	5 fewer per 1000 (from 8 fewer to 1 fewer)	⊕⊕◯◯ LOW	CRITICAL
Heart failure												
17	randomized trials	serious [a]	not serious	not serious	serious [c]	none	2037/47 411 (4.3%)	2255/47 031 (4.8%)	RR 0.90 (0.83 to 0.97)	5 fewer per 1000 (from 8 fewer to 1 fewer)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

a. Data inadequate to assess allocation concealment (selection bias). Over 25% of trials did not blind participants and investigators (performance and detection bias). over 25% did not report intention to treat analysis. b. Rating the certainty that there is no important effect (using a threshold of 1%), the lower end of the 95% CI crossed this threshold suggesting that there may be an important benefit.

c. Confidence interval crosses the clinical decision threshold between recommending and not recommending treatment. d. For heterogeneity. Confidence intervals do not overlap. I-squared >50%.

PICO question 5: 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?

Systematic review for desirable and undesirable effects

Evidence was considered in respect of the following components (Table 39) to determine 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 in adults with hypertension requiring pharmacological treatment (Table 40–Table 66).

Table 39 Components for PICO question 5

Population	Intervention	Comparison	Outcome	Subgroup
Adult men and women >18 years old with primary HTN requiring pharmacological treatment	BB, CCB, diuretics, ACEi, or ARB	BB, CCB, diuretics, ACEi, or ARB (head-to-head studies)	- death (all-cause mortality) - cardiovascular death (death from MI, sudden cardiac death or stroke) - stroke - myocardial infarction - end-stage renal disease - cognitive impairment/ dementia - heart failure events - adverse effects - BP reduction and control (if data on CVD events are absent)	Based on different effect modifiers such as: - estimated cardiovascular risk - pre-existing CAD - stroke - diabetes - age - sex - chronic kidney disease - race/ethnicity - level of baseline BP

Table 40 Evidence profile 5a: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to calcium channel blocker (CCB) for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi	CCB	Relative (95% CI)	Absolute (95% CI)		
Setting												
Outpatient with mean follow-up of 4.9 years												
Source												
Chen 2018*(60)*: First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for HTN												
All-cause death (mean follow-up of 4.5 years)												
5	randomized trials	serious [a]	not serious	not serious	serious [b]	none	2258/17 648 (12.8%)	2175/17 578 (12.4%)	RR 1.03 (0.98 to 1.09)	4 more per 1000 (from 2 fewer to 11 more)	⊕⊕◯◯ LOW	CRITICAL
Cardiovascular events (mean follow-up of 4.5 years)												
6	randomized trials	serious [a]	serious [c]	not serious	serious [d]	none	3064/17 646 (17.4%)	3124/17 577 (17.8%)	RR 0.98 (0.93 to 1.02)	4 fewer per 1000 (from 12 fewer to 4 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Heart failure events (mean follow-up of 4.5 years)												
5	randomized trials	serious [a]	not serious [e]	not serious	not serious	none	1051/17 606 (6.0%)	1256/17 537 (7.2%)	RR 0.83 (0.77 to 0.90)	12 fewer per 1000 (from 16 fewer to 7 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Myocardial infarction (mean follow-up of 4.5 years)												
5	randomized trials	serious [a]	serious [f]	not serious	not serious	none	1203/17 557 (6.9%)	1192/17 486 (6.8%)	RR 1.01 (0.93 to 1.09)	1 more per 1000 (from 5 fewer to 6 more)	⊕⊕◯◯ LOW	IMPORTANT
Stroke (mean follow-up of 4.5 years)												
4	randomized trials	serious [a]	not serious	not serious	not serious	none	810/17 371 (4.7%)	676/17 302 (3.9%)	RR 1.19 (1.08 to 1.32)	7 more per 1000 (from 3 more to 13 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
End-stage kidney disease (mean follow-up of 4.5 years)												
4	randomized trials	serious [g]	not serious	not serious	not serious	none	218/9784 (2.2%)	245/9767 (2.5%)	RR 0.88 (0.74 to 1.05)	3 fewer per 1000 (from 7 fewer to 1 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Systolic BP change (mean follow-up of 4.5 years)												
20	randomized trials	serious [a]	not serious	not serious	not serious	none	18 249	18 188	–	MD 1.23 mmHg higher (0.9 higher to 1.56 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Diastolic BP change (mean follow-up of 4.5 years)												
20	randomized trials	serious [a]	not serious	not serious	not serious	none	18 249	18 188	-	MD 0.98 mmHg higher (0.79 higher to 1.18 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Cardiovascular death – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The VALUE trial (which has 26-41% of the weight of the pooled estimates) has a high risk of bias due to differential co-interventions. The other studies have unclear risk of bias in multiple domains.
b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
c. The point estimates vary with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (71%).
d. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.
e. Even though there is statistical inconsistency, all estimates suggest the same direction of effect and only 1 of the CIs does not overlap with the others.
f. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (82%).
g. The trial that has significant weight of the pooled estimate (42.7%) was judged at unclear risk of bias in the domains of random sequence generation, allocation concealment and blinding of outcome assessment.

Table 41 Evidence profile 5b: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to thiazide for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi	Thiazide	Relative (95% CI)	Absolute (95% CI)		
Source												
Chen 2018*(60)*												
All-cause mortality (mean follow-up of 4.9 years)												
1	randomized trials	serious [a]	not serious	not serious	serious [b]	none	1314/9054 (14.5%)	2203/15 255 (14.4%)	**RR 1.00** (0.94 to 1.07)	**0 fewer per 1000** (from 9 fewer to 10 more)	⊕⊕◯◯ LOW	CRITICAL
Cardiovascular events (mean follow-up of 4.9 years)												
2	randomized trials	serious [c]	not serious	not serious	serious [b]	none	1851/9100 (20.3%)	2959/15 279 (19.4%)	**RR 1.05** (1.00 to 1.11)	**10 more per 1000** (from 0 fewer to 21 more)	⊕⊕◯◯ LOW	IMPORTANT
Heart failure events (mean follow-up of 4.9 years)												
1	randomized trials	serious [a]	not serious	not serious	not serious	none	612/9054 (6.8%)	870/15 255 (5.7%)	**RR 1.19** (1.07 to 1.31)	**11 more per 1000** (from 4 more to 18 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Myocardial infarction (mean follow-up of 4.9 years)												
2	randomized trials	serious [c]	not serious	not serious	serious [d]	none	781/9100 (8.6%)	1414/15 279 (9.3%)	**RR 0.93** (0.86 to 1.01)	**6 fewer per 1000** (from 13 fewer to 1 more)	⊕⊕◯◯ LOW	IMPORTANT
Stroke (mean follow-up of 4.9 years)												
1	randomized trials	serious [a]	not serious	not serious	not serious	none	457/9054 (5.0%)	675/15 255 (4.4%)	**RR 1.14** (1.02 to 1.28)	**6 more per 1000** (from 1 more to 12 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
End-stage kidney disease (mean follow-up of 4.9 years)												
1	randomized trials	serious [a]	not serious	not serious	serious [e]	none	126/9054 (1.4%)	193/15 255 (1.3%)	**RR 1.10** (0.88 to 1.37)	**1 more per 1000** (from 2 fewer to 5 more)	⊕⊕◯◯ LOW	IMPORTANT
Systolic BP change (mean follow-up of 4.9 years)												
10	randomized trials	serious [f]	serious [g]	not serious	not serious	none	10 135	16 247	–	MD **1.6 mmHG higher**	⊕⊕◯◯ LOW	IMPORTANT

										(1.2 higher to 1.99 higher)		
Diastolic BP change (mean follow-up of 4.9 years)												
9	randomized trials	serious [f]	serious [h]	not serious	not serious	none	10 101	16 234	–	MD **0.12 mmHg lower** (0.36 lower to 0.13 higher)	⊕⊕◯◯ LOW	IMPORTANT
Cardiovascular death – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The trial ALLHAT 2002 was judged at unclear risk of bias in blinding outcome assessment and selective reporting in another review (Olde Engberink 2015).

b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

c. The ALLHAT 2002 was considered to have unclear risk of bias in blinding outcome assessment and selective reporting in another review (Olde Engberink 2015). The Schram 2005 was judged by authors to have unclear risk of bias in multiple domains including random sequence generation, allocation concealment and blinding of outcome assessment.

d. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.

e. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more. The extremes of confidence interval will lead to different decisions.

f. The trial that has most of the weight of the pooled estimate (>80%) was judged at unclear risk of bias at unclear risk of bias in blinding outcome assessment and selective reporting in another review (Olde Engberink 2015).

g. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (80%).

h. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (70%).

Table 42 Evidence profile 5c: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to beta-blocker (BB) for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi	BB	Relative (95% CI)	Absolute (95% CI)		
Source												
Chen 2018*(60)*												
All-cause mortality (mean follow-up of 4.8 years)												
1	randomized trials	serious [a]	not serious	not serious	serious [b]	none	383/4605 (8.3%)	431/4588 (9.4%)	RR 0.89 (0.78 to 1.01)	10 fewer per 1000 (from 21 fewer to 1 more)	⊕⊕◯◯ LOW	CRITICAL
Cardiovascular events (mean follow-up of 4.8 years)												
2	randomized trials	serious [a]	not serious	not serious	not serious	none	584/4628 (12.6%)	659/4611 (14.3%)	RR 0.88 (0.80 to 0.98)	17 fewer per 1000 (from 29 fewer to 3 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Heart failure (mean follow-up of 4.8 years)												
1	randomized trials	serious [a]	not serious	not serious	serious [c]	none	153/4605 (3.3%)	161/4588 (3.5%)	RR 0.95 (0.76 to 1.18)	2 fewer per 1000 (from 8 fewer to 6 more)	⊕⊕◯◯ LOW	IMPORTANT
Myocardial infarction (mean follow-up of 4.8 years)												
2	randomized trials	serious [a]	not serious	not serious	serious [d]	none	199/4628 (4.3%)	189/4611 (4.1%)	RR 1.05 (0.86 to 1.27)	2 more per 1000 (from 6 fewer to 11 more)	⊕⊕◯◯ LOW	IMPORTANT
Stroke (mean follow-up of 4.8 years)												
1	randomized trials	serious [a]	not serious	not serious	not serious	none	232/4605 (5.0%)	309/4588 (6.7%)	RR 0.75 (0.63 to 0.88)	17 fewer per 1000 (from 25 fewer to 8 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
End-stage kidney disease (mean follow-up of 4.8 years)												
1	randomized trials	not serious	not serious	not serious	very serious [e]	none	0/23 (0.0%)	1/23 (4.3%)	RR 0.33 (0.01 to 7.78)	29 fewer per 1000 (from 43 fewer to 295 more)	⊕⊕◯◯ LOW	IMPORTANT
Systolic BP change (mean follow-up of 4.8 years)												
16	randomized trials	serious [f]	serious [g]	not serious	not serious	none	5449	5456	–	MD 0.55 mmHg lower (1.22 lower to 0.11 higher)	⊕⊕◯◯ LOW	IMPORTANT
Diastolic BP change (mean follow-up of 4.8 years)												
16	randomized trials	serious [f]	serious [h]	not serious	not serious	none	5449	5456	–	MD 0.48 mmHg higher (0.14 higher to 0.83 higher)	⊕⊕◯◯ LOW	IMPORTANT
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												

–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The trial that has most of the weight of the pooled estimate (LIFE trial) >99% was judged to have unclear risk of bias for allocation concealment.
b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.
c. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more. The extremes of the confidence interval will lead to different decisions.
d. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
e. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be important benefit and harm.
f. The trial that has most of the weight of the pooled estimate (LIFE trial) >70% was judged to have unclear risk of bias for allocation concealment.
g. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is statistical heterogeneity, as reflected by the I-squared (45%).
h. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (60%).

Table 43 Evidence profile 5d: Angiotensin converting enzyme inhibitor (ACEi) compared to angiotensin receptor blocker (ARB) in individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACEi	ARB	Relative (95% CI)	Absolute (95% CI)		
Source												
Dimou 2019*(55)*. Only adverse event outcome is from Xu 2015*(61)*.												
All-cause mortality (treatment duration was between 6 and 156 weeks)												
2 [a]	randomized trials	serious [b]	not serious [c,d]	not serious	serious [e]	none	–	402/2959 (13.6%)	RR 0.96 (0.80 to 1.14)	5 fewer per 1000 (from 27 fewer to 19 more)	⊕⊕◯◯ LOW [f]	CRITICAL
Cardiovascular mortality (treatment duration was between 6 and 156 weeks)												
1 [g]	randomized trials	serious [b]	not serious [d,h]	not serious	serious [e]	none	–	297/2959 (10.0%)	RR 0.87 (0.67 to 1.14)	13 fewer per 1000 (from 33 fewer to 14 more)	⊕⊕◯◯ LOW [f]	CRITICAL
Myocardial Infarction (fatal and nonfatal) (treatment duration was between 6 and 156 weeks)												
1 [a]	randomized trials	serious [b]	not serious [d]	not serious	serious [e]	none	–	275/2959 (9.3%)	RR 1.02 (0.75 to 1.37)	2 more per 1000 (from 23 fewer to 34 more)	⊕⊕◯◯ LOW [f]	CRITICAL
Stroke (fatal and nonfatal) (treatment duration was between 6 and 156 weeks)												
1 [a]	randomized trials	serious [b]	not serious [d]	not serious	serious [i]	none	–	177/2959 (6.0%)	RR 1.13 (0.87 to 1.46)	8 more per 1000 (from 8 fewer to 28 more)	⊕⊕◯◯ LOW [f]	CRITICAL
Development and/or hospitalization for heart failure (treatment duration was between 6 and 156 weeks)												
1 [j]	randomized trials	serious [b]	not serious [d]	not serious	not serious	none	–	214/2959 (7.2%)	RR 0.71 (0.54 to 0.93)	21 fewer per 1000 (from 33 fewer to 5 fewer)	⊕⊕⊕◯ MODERATE [f]	IMPORTANT
Reduction in systolic BP (treatment duration was between 6 and 156 weeks)												
28	randomized trials	serious [b]	not serious	not serious	not serious	none	–	–	–	MD 0.59 mmHg higher (0.21 lower to 1.38 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Reduction in diastolic BP (treatment duration was between 6 and 156 weeks)												
29	randomized trials	serious [b]	serious [k]	not serious	not serious	none	–	–	–	MD 0.62 mmHg higher (0.06 lower to 1.3 higher)	⊕⊕◯◯ LOW	IMPORTANT
Adverse events (treatment duration was between 6 and 156 weeks)												
13	randomized trials	serious [l]	not serious	not serious	very serious [i]	none	238/9188 (2.6%)	280/9139 (3.1%)	OR 1.53 (0.91 to 2.58)	15 more per 1000 (from 3 fewer to 45 more)	⊕◯◯◯ VERY LOW	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												

–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference; OR: Odds ratio

Explanations

a. These results are from a network meta-analysis that included one trial directly comparing ARB to placebo, three trials comparing ACEi to placebo and two trials comparing ACEi to ARB with a total of six trials in the network.
b. Included trials were judged to have an unclear risk selection (random sequence generation, allocation concealment) bias and attrition bias.
c. The Q decomposition indicated heterogeneity within designs with Q: 6.76; df:3; p:0.08.
d. Adequate data to assess inconsistency and incoherence was not provided in this manuscript. We reached out to the authors for clarification/additional data, the authors have not responded.
e. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be important benefit and harm.
f. This review did not provide baseline risk or Forest plots; baseline risk is imputed based on the rate in control arms of some of the other antihypertensive trials.
g. These results are from a network meta-analysis that included two trials directly comparing ARB to placebo, two trials comparing ACEi to placebo and one trial comparing ACEi to ARB with a total of five trials in the network.
h. The Q decomposition indicated inconsistency between designs Q: 5.83, df: 1, p:0.02.
i. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
j. These results are from a network meta-analysis that included one trial directly comparing ARB to placebo, three trials comparing ACEi to placebo and one trial comparing ACEi to ARB with a total of five trials in the network.
k. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (64%).
l. The authors do not provide detailed risk of bias judgment. However, some of the included studies was judged to have low Jadad score.

Table 44 Evidence profile 5e: Beta-blocker (BB) compared to diuretic for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BB	Diuretic	Relative (95% CI)	Absolute (95% CI)		
Source												
Wiysonge 2017*(62)*												
Mortality (follow up of at least 1 year)												
5	randomized trials	serious [a]	not serious	not serious	not serious	none	389/9195 (4.2%)	368/9046 (4.1%)	RR 1.04 (0.91 to 1.19)	2 more per 1000 (from 4 fewer to 8 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Stroke (follow up of at least 1 year)b												
4	randomized trials	serious [c]	serious [d]	not serious	serious [e]	none	130/9142 (1.4%)	108/8993 (1.2%)	RR 1.17 (0.65 to 2.09)	2 more per 1000 (from 4 fewer to 13 more)	⊕◯◯◯ VERY LOW	CRITICAL
Coronary heart disease (follow up of at least 1 year)f												
4	randomized trials	serious [c]	serious [g]	not serious	serious [e]	none	323/9142 (3.5%)	294/8993 (3.3%)	RR 1.12 (0.82 to 1.54)	4 more per 1000 (from 6 fewer to 18 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Cardiovascular death (follow up of at least 1 year)												
3	randomized trials	serious [a]	not serious	not serious	serious [h]	none	217/8802 (2.5%)	195/8650 (2.3%)	RR 1.09 (0.90 to 1.32)	2 more per 1000 (from 2 fewer to 7 more)	⊕⊕◯◯ LOW	CRITICAL
Total cardiovascular disease (follow up of at least 1 year)												
4	randomized trials	serious [c]	not serious	not serious	serious [e]	none	469/9142 (5.1%)	409/8993 (4.5%)	RR 1.13 (0.99 to 1.28)	6 more per 1000 (from 0 fewer to 13 more)	⊕⊕◯◯ LOW	IMPORTANT
Withdrawal due to adverse effects (follow up of at least 1 year)												
3	randomized trials	serious [a]	serious [i]	not serious	very serious [e]	none	862/5845 (14.7%)	625/5721 (10.9%)	RR 1.69 (0.95 to 3.00)	75 more per 1000 (from 5 fewer to 218 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. Included studies were judged to be at high risk of bias in the domains of incomplete outcome data and unclear risk of bias in other domains.
b. Subgroup analysis based on the type of beta-blocker showed a RR of 0.92 with CI [0.55,1.54] in Cardio-selective beta-blocker and RR of 2.28 with CI of [1.31,3.95] for non-selective beta-blocker for the outcome of stroke.
c. Included studies were judged to be at high risk of bias in the domains of incomplete outcome data, blinding of participants and personnel and unclear risk of bias in other domains.
d. The point estimates vary importantly with regards to direction and magnitude of effect. There is high statistical heterogeneity, as reflected by the I-squared (72.9%).
e. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
f. Subgroup analysis based on age reported RR of 0.97 with CI of [0.81,1.17] in patients less than 65 years of age and 1.63 with CI of [1.15,2.32] in patients with more than 65 years of age for the outcome of total coronary heart disease.
g. The point estimates vary with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (66.2%).
h. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more. The extremes of the confidence interval will lead to different decisions.
i. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (94.68%).

Table 45 Evidence profile 5f: Beta-blocker (BB) compared to calcium channel blocker (CCB) for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BB	CCB	Relative (95% CI)	Absolute (95% CI)		
Source												
Wiysonge 2017*(62)*												
Mortality (follow up of at least 1 year)												
4	randomized trials	serious [a]	not serious	not serious	serious [b]	none	1768/22 525 (7.8%)	1637/22 300 (7.3%)	RR 1.07 (1.00 to 1.14)	5 more per 1000 (from 0 fewer to 10 more)	⊕⊕◯◯ LOW	CRITICAL
Stroke (follow up of at least 1 year)												
3	randomized trials	serious [c]	not serious	not serious	not serious	none	637/22 084 (2.9%)	512/22 083 (2.3%)	RR 1.24 (1.11 to 1.40)	6 more per 1000 (from 3 more to 9 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Coronary heart disease (follow up of at least 1 year)												
3	randomized trials	serious [c]	not serious	not serious	not serious	none	902/22 084 (4.1%)	860/22 083 (3.9%)	RR 1.05 (0.96 to 1.15)	2 more per 1000 (from 2 fewer to 6 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Cardiovascular death (follow up of at least 1 year)												
4	randomized trials	serious [a]	not serious	not serious	serious [b]	none	785/22 525 (3.5%)	700/22 300 (3.1%)	RR 1.15 (0.92 to 1.46)	5 more per 1000 (from 3 fewer to 14 more)	⊕⊕◯◯ LOW	CRITICAL
Total cardiovascular disease (follow up of at least 1 year)												
2	randomized trials	serious [d]	not serious	not serious	not serious	none	950/10 059 (9.4%)	800/9856 (8.1%)	RR 1.18 (1.08 to 1.29)	15 more per 1000 (from 6 more to 24 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Withdrawal due to adverse events (follow up of at least 1 year)												
2	randomized trials	serious [e]	serious [f]	not serious	serious [b]	none	427/10 775 (4.0%)	354/10 816 (3.3%)	RR 1.20 (0.71 to 2.04)	7 more per 1000 (from 9 fewer to 34 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. The two trials that have most of the weight of the pooled estimate (>90%) were judged at unclear risk of bias in the domain of incomplete outcome data.
b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
c. The two trials that have most of the weight of the pooled estimate (>90%) were judged at high risk of bias in the domain of blinding of participants and personnel and unclear risk of bias in the domain of incomplete outcome data.
d. The trial that has most of the weight of the pooled estimate (99.33%) was judged at unclear risk of bias at the domain of blinding of participants and personnel and unclear risk of bias in the domain of incomplete outcome data.
e. The two included trials were judged to have high risk of bias in the domain of blinding of participants and personnel and unclear risk of bias in the domains of incomplete outcome data and allocation concealment.
f. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (93.45%).

Table 46 Evidence profile 5g: Beta-blocker (BB) compared to renin-angiotensin-aldosterone system inhibitor (RAASi) for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BB	RAASi	Relative (95% CI)	Absolute (95% CI)		
Source												
Wiysonge 2017*(62)*												
Mortality (follow up of at least 1 year)												
3	randomized trials	serious [a]	not serious	not serious	serious [b]	none	496/5387 (9.2%)	455/5441 (8.4%)	RR 1.10 (0.98 to 1.24)	8 more per 1000 (from 2 fewer to 20 more)	⊕⊕◯◯ LOW	–
Stroke (follow up of at least 1 year)												
2	randomized trials	serious [c]	not serious	not serious	not serious	none	326/4946 (6.6%)	253/5005 (5.1%)	RR 1.30 (1.11 to 1.53)	15 more per 1000 (from 6 more to 27 more)	⊕⊕⊕◯ MODERATE	–
Coronary heart disease (follow up of at least 1 year)												
2	randomized trials	serious [c]	not serious	not serious	serious [d]	none	236/4946 (4.8%)	271/5005 (5.4%)	RR 0.90 (0.76 to 1.06)	5 fewer per 1000 (from 13 fewer to 3 more)	⊕⊕◯◯ LOW	–
Cardiovascular death (follow up of at least 1 year)												
3	randomized trials	serious [a]	not serious	not serious	serious [b]	none	270/5387 (5.0%)	253/5441 (4.6%)	RR 1.09 (0.92 to 1.29)	4 more per 1000 (from 4 fewer to 13 more)	⊕⊕◯◯ LOW	–
Cardiovascular disease (follow up of at least 1 year)												
3	randomized trials	serious [e]	not serious [f]	not serious	very serious [g]	none	675/5387 (12.5%)	625/5441 (11.5%)	RR 1.00 (0.72 to 1.38)	0 fewer per 1000 (from 32 fewer to 44 more)	⊕◯◯◯ VERY LOW	–
Withdrawal due to adverse effects (follow up of at least 1 year)												
2	randomized trials	serious [e]	not serious	not serious	not serious	none	951/4946 (19.2%)	687/5005 (13.7%)	RR 1.41 (1.29 to 1.54)	56 more per 1000 (from 40 more to 74 more)	⊕⊕⊕◯ MODERATE	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												

–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. The trial that has most of the weight of the pooled estimate (>80%) was judged at unclear risk of bias in the domain of allocation concealment.

b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

c. The trial that has most of the weight of the pooled estimate (>70%) was judged at unclear risk of bias in the domain of allocation concealment. The other study was judged to have high risk of bias in the domain of blinding of participants and personnel and unclear risk of bias in the domain of incomplete outcome data.

d. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.

e. The two trials that have most of the weight of pooled estimate (>80%) were judged at high risk of bias in the domain of blinding of participants and personnel and at unclear risk of bias in the domains of allocation concealment and incomplete outcome data.

f. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (73.82%).

g. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be an important benefit and harm.

Table 47 Evidence profile 5h: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to calcium channel blocker (CCB) for hypertensive patients with type 2 diabetes mellitus

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi	CCB	Relative (95% CI)	Absolute (95% CI)		
Sources												
Wang, 2018*(63)*, Bangalore, 2016*(64)*												
All-cause mortality (follow up of at least 6 months)												
4	randomized trials	serious [a]	not serious	not serious	serious [b]	none	778/4625 (16.8%)	786/4702 (16.7%)	RR 1.03 (0.91 to 1.16)	5 more per 1000 (from 15 fewer to 27 more)	⊕⊕◯◯ LOW	–
Major cardiovascular events (follow up of at least 6 months)												
2	randomized trials	serious [c]	not serious	not serious	not serious	none	-/814	337/802 (42.0%)	RR 0.78 (0.66 to 0.91)	92 fewer per 1000 (from 143 fewer to 38 fewer)	⊕⊕⊕◯ MODERATE	–
Heart failure (follow up of at least 6 months)												
4	randomized trials	serious [d]	not serious	not serious	not serious	none	433/4413 (9.8%)	563/4490 (12.5%)	RR 0.72 (0.61 to 0.83)	35 fewer per 1000 (from 49 fewer to 21 fewer)	⊕⊕⊕◯ MODERATE	–
Stroke (follow up of at least 6 months)												
4	randomized trials	serious [d]	not serious	not serious	serious [e]	none	296/4413 (6.7%)	256/4490 (5.7%)	RR 1.21 (0.97 to 1.51)	12 more per 1000 (from 2 fewer to 29 more)	⊕⊕◯◯ LOW	–
Myocardial infarction (follow up of at least 6 months)												
4	randomized trials	serious [d]	serious [f]	not serious	serious [g,h]	none	-/4364	27/567 (4.8%) [i]	RR 1.01 (0.86 to 1.18)	0 fewer per 1000 (from 7 fewer to 9 more)	⊕◯◯◯ VERY LOW	–
End-stage kidney disease (follow up of at least 6 months)												
2	randomized trials	serious [j]	not serious	not serious	serious [k]	none	187/4089 (4.6%)	230/4164 (5.5%)	RR 0.80 (0.64 to 1.00)	11 fewer per 1000 (from 20 fewer to 0 fewer)	⊕⊕◯◯ LOW	–
Systolic BP change (follow up of at least 6 months)												
11	randomized trials	serious [l]	not serious	not serious	not serious	none	2578	2703	–	MD 0.07 mmHg lower (1.11 lower to 0.97 higher)	⊕⊕⊕◯ MODERATE	–
Diastolic BP change (follow up of at least 6 months)												
11	randomized trials	serious [l]	not serious	not serious	not serious	none	2578	2703	–	MD 0.12 mmHg higher (0.49 lower to 0.72 higher)	⊕⊕⊕◯ MODERATE	–
Cardiovascular mortality (follow up of at least 1 year)												

10	randomized trials	serious [m]	not serious	not serious [n]	serious [e]	none	132/2770 (4.8%)	112/3103 (3.6%)	RR 1.17 (0.90 to 1.50)	6 more per 1000 (from 4 fewer to 18 more)	⊕⊕◯◯ LOW	–
Withdrawal due to adverse events (follow up of at least 1 year)												
5	randomized trials	serious [o]	not serious	not serious	very serious [b]	none	138/1225 (11.3%)	158/1241 (12.7%)	RR 0.89 (0.65 to 1.22)	14 fewer per 1000 (from 45 fewer to 28 more)	⊕◯◯◯ VERY LOW	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The two trials that comprise 23% weight of the pooled estimates were judged to be at high risk of bias because of inappropriate administration of co-intervention and unclear risk of bias in the domains of random sequence generation and allocation concealment.

b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be important benefit and harm.

c. The two included trials were judged to be at high risk of bias because of inappropriate administration of co-intervention and unclear risk of bias in the domains of random sequence generation, allocation concealment and blinding of participants and personnel.

d. The two trials that have most of the weight of the pooled estimate (>80%) were judged at unclear risk of bias in the domains of random sequence generation, allocation concealment, blinding of participants and personnel and blinding of outcome assessment.

e. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

f. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (78%).

g. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more. The extremes of the confidence interval will lead to different decisions.

h. The events rate was not provided by the review.

i. The SR doesn't provide event rates so it was extracted from IDNT, 2003.

j. The two included studies were judged at unclear risk of bias in the domains of random sequence generation, allocation concealment, blinding of participants and personnel and blinding of outcome assessment.

k. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or no effect.

l. The two trials that have most weight of the pooled effect estimates (>55%) were judged to be at unclear risk of bias in the domains of random sequence generation, allocation concealment and blinding of outcome assessment.

m. The two trials that have most weight of the effect estimates (39%) were judged at unclear risk of bias in the domain of random sequence generation.

n. We did not downgrade indirectness because only one included studies (ABCD normotensive) included patients with DM and normotensive and it contributed to 5.3% of the weight of pooled effect estimates.

o. The trials that have most weight of the effect estimates (47%) were judged at unclear risk of bias in the domains of random sequence generation, allocation concealment and blinding.

Table 48 Evidence profile 5i: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to beta-blocker (BB) for hypertensive patients with type 2 diabetes mellitus

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi	BB	Relative (95% CI)	Absolute (95% CI)		
Source												
Wang 2018*(63)*												
Systolic blood pressure (follow up of at least 6 months)												
4	randomized trials	serious [a]	not serious	not serious	not serious	none	678	712	-	MD 3.25 mmHg lower (5.36 lower to 1.14 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Diastolic blood pressure (follow up of at least 6 months)												
4	randomized trials	serious [a]	not serious	not serious	not serious	none	678	712	-	MD 0.76 mmHg higher (0.35 lower to 1.87 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
All-cause mortality (follow up of at least 1 year)												
2	randomized trials	serious [b]	not serious	not serious	very serious [c]	none	138/986 (14.0%)	163/967 (16.9%)	RR 0.84 (0.47 to 1.51)	27 fewer per 1,000 (from 89 fewer to 86 more)	⊕◯◯◯ VERY LOW	–
Cardiovascular mortality (follow up of at least 1 year)												
2	randomized trials	serious [b]	not serious	not serious	very serious [c]	none	77/986 (7.8%)	90/967 (9.3%)	RR 0.87 (0.47 to 1.60)	12 fewer per 1,000 (from 49 fewer to 56 more)	⊕◯◯◯ VERY LOW	–
Stroke (follow up of at least 1 year)												
2	randomized trials	serious [b]	not serious	not serious	very serious [c]	none	72/986 (7.3%)	82/967 (8.5%)	RR 0.88 (0.64 to 1.21)	10 fewer per 1,000 (from 31 fewer to 18 more)	⊕◯◯◯ VERY LOW	–
Myocardial infarction (follow up of at least 1 year)												
2	randomized trials	serious [b]	not serious	not serious	very serious [c]	none	102/986 (10.3%)	96/967 (9.9%)	RR 1.02 (0.73 to 1.40)	2 more per 1,000 (from 27 fewer to 40 more)	⊕◯◯◯ VERY LOW	–
End-stage kidney disease (follow up of at least 1 year)												
1	randomized trials	not serious	not serious	not serious	very serious [d]	none	4/400 (1.0%)	4/358 (1.1%)	RR 0.90 (0.22 to 3.58)	1 fewer per 1,000 (from 9 fewer to 29 more)	⊕⊕◯◯ LOW	–
Heart failure (follow up of at least 1 year)												
1	randomized trials	not serious	not serious	not serious	very serious [c]	none	12/400 (3.0%)	9/358 (2.5%)	RR 1.19 (0.50 to 2.83)	5 more per 1,000 (from 13 fewer to 46 more)	⊕⊕◯◯ LOW	–
Withdrawal due to adverse events (follow up of at least 1 year)												

2	randomized trials	serious [b]	not serious	not serious	very serious [c]	none	90/986 (9.1%)	134/967 (13.9%)	RR 0.51 (0.23 to 1.14)	68 fewer per 1,000 (from 107 fewer to 19 more)	⊕◯◯◯ VERY LOW	–
Cognitive impairment/dementia - not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. The trial that has most of the weight of the pooled estimate (>75%) was judged at high risk of bias in the domain of allocation concealment.

b. One of the two included studies was judged at high risk of bias in the domain of allocation concealment.

c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be important benefit and harm.

d. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

Table 49 Evidence profile 5j: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to diuretic for hypertensive patients with type 2 diabetes mellitus

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi	Diuretics	Relative (95% CI)	Absolute (95% CI)		
Sources												
Wang, 2018*(63)*, Bangalore, 2016*(64)*												
All-cause mortality (follow up of at least 6 months)												
2	randomized trials	not serious	not serious	not serious	serious [a]	none	675/3796 (17.8%)	1147/6277 (18.3%)	RR 0.99 (0.89 to 1.10)	2 fewer per 1000 (from 20 fewer to 18 more)	⊕⊕⊕◯ MODERATE	–
Heart failure (follow up of at least 6 months)												
1	randomized trials	serious [b]	not serious	not serious	serious [c]	none	365/3510 (10.4%)	581/5994 (9.7%)	RR 1.15 (1.00 to 1.32)	15 more per 1000 (from 0 fewer to 31 more)	⊕⊕◯◯ LOW	–
Stroke (follow up of at least 6 months)												
1	randomized trials	serious [b]	not serious	not serious	serious [c]	none	260/3510 (7.4%)	414/5994 (6.9%)	RR 1.06 (0.89 to 1.26)	4 more per 1000 (from 8 fewer to 18 more)	⊕⊕◯◯ LOW	–
Myocardial infarction (follow up of at least 6 months)												
3	randomized trials	serious [d]	not serious	not serious	serious [e,f]	none		3/283 (1.1%) [g]	RR 0.96 (0.84 to 1.10)	0 fewer per 1000 (from 2 fewer to 1 more)	⊕⊕◯◯ LOW	–
End-stage kidney disease (follow up of at least 6 months)												
1	randomized trials	serious [b]	not serious	not serious	serious [c]	none	105/3510 (3.0%)	156/5994 (2.6%)	RR 1.09 (0.82 to 1.45)	2 more per 1000 (from 5 fewer to 12 more)	⊕⊕◯◯ LOW	–
Systolic BP (follow up of at least 6 months)												
3	randomized trials	serious [h]	not serious	not serious	not serious	none	1424	2289	–	MD 2.54 mmHg higher (1.29 higher to 3.79 higher)	⊕⊕⊕◯ MODERATE	–
Diastolic BP (follow up of at least 6 months)												
3	randomized trials	serious [h]	not serious	not serious	not serious	none	1424	2289	–	MD 0.88 mmHg higher (0.09 higher to 1.66 higher)	⊕⊕⊕◯ MODERATE	–
Cardiovascular death (follow up of at least 1 year)												
1	randomized trials	serious [i]	not serious	not serious	very serious [c,j]	none	1/286 (0.3%)	2/283 (0.7%)	RR 0.50 (0.05 to 5.46)	4 fewer per 1000 (from 7 fewer to 32 more)	⊕◯◯◯ VERY LOW	–
Withdrawal due to adverse events (follow up of at least 1 year)												

1	randomized trials	serious [i]	not serious	not serious	very serious [a,j]	none	15/286 (5.2%)	14/283 (4.9%)	RR 1.06 (0.51 to 2.20)	3 more per 1000 (from 24 fewer to 59 more)	⨁◯◯◯ VERY LOW	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be important benefit and harm.
b. The included trial was judged at unclear risk of bias in the domain of blinding of outcome assessment.
c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
d. The trial that has most of the weight of the pooled estimate (99%) was judged at unclear risk in the domain of blinding of outcome assessment.
e. The extremes of the confidence interval will lead to different decision. The confidence interval suggests the possibility of a small benefit and a small harm.
f. The events rate was not reported in the review.
g. The systematic review does not provide events rate and total number of patients per arm so we extracted baseline risk from NESTOR trial even though the weight of this trial is 0.2%.
h. The two trials that have most of the weight of the pooled estimate (>90%) were judged at unclear risk of bias in the domains of random sequence generation, allocation concealment and blinding of outcome assessment.
i. The included trial was judged at unclear risk of allocation concealment.
j. There is a very low events rate.

Table 50 Evidence profile 5k: Calcium channel blocker (CCB) use compared to non-calcium channel blocker use for elderly patients with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB use	Non-CCB use	Relative (95% CI)	Absolute (95% CI)		
Source												
Hussain 2018*(56)*:												
Risk of developing dementia (follow up duration was between 3 and 13 years)[a]												
10 [b]	observational studies	not serious [c]	serious [d]	serious [e]	not serious	none	–	–	**RR 0.70** (0.58 to 0.85)	**1 fewer per 1000** (from 1 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	–
Risk of developing dementia in subgroup with Alzheimer's disease (follow up duration was between 3 and 13 years)												
5 [f]	observational studies	not serious [g]	serious [h]	serious [e]	not serious	none	1511/16 205 (9.3%)	1024/11 672 (8.8%)	**RR 0.87** (0.90 to 0.94)	**11 fewer per 1000** (from 9 fewer to 5 fewer)	⨁◯◯◯ VERY LOW	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. No event rates provided

b. Seven out of the 10 included studies were observational.

c. Two of the included studies were open label extension of trials. However, they only contribute to 16% of the weight of pooled estimates. The review states that all included studies are of high quality using Newcastle Ottawa scale without any further details.

d. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (88%).

e. The review includes comparators of placebo and active treatment in one analysis.

f. Four out of the five included studies were observational.

g. One of the included studies was open label extension of trial but it only contributes to 2.9% of the weight of pooled estimates. The review states that all included studies are of high quality using Newcastle Ottawa scale without any further details.

h. The point estimates vary with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (50%). This is borderline judgement.

Table 51 Evidence profile 5l: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to diuretic for black patients with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASis	Diuretics	Relative (95% CI)	Absolute (95% CI)		
Source												
Palla 2017*(65)*												
All-cause mortality (mean follow-up of 4 years)												
2 [a,b]	observational studies	not serious	not serious	not serious	very serious [c]	none	641/8547 (7.5%)	911/10 706 (8.5%)	**OR 1.16** (0.93 to 1.45)	**12 more per 1000** (from 5 fewer to 34 more)	⨁◯◯◯ VERY LOW	–
Myocardial infarction (mean follow-up of 4 years)												
2 [a,d]	observational studies	serious [e]	serious [f]	not serious	very serious [g]	none	276/8547 (3.2%)	404/10 706 (3.8%)[h]	**OR 1.86** (0.53 to 6.52)	**30 more per 1000** (from 17 fewer to 166 more)	⨁◯◯◯ VERY LOW	–
Stroke (mean follow-up of 4 years)												
2 [a,h]	observational studies	serious [e]	not serious	not serious	not serious	none	288/8547 (3.4%)	296/10 706 (2.8%)	**OR 1.59** (1.16 to 2.17)	**16 more per 1000** (from 4 more to 30 more)	⨁◯◯◯ VERY LOW	–
Heart failure (mean follow-up of 4 years)												
2 [a,i]	observational studies	serious [e]	serious [j]	not serious	very serious [c]	none	310/8547 (3.6%)	313/10 706 (2.9%)	**OR 1.96** (0.87 to 4.43)	**27 more per 1000** (from 4 fewer to 88 more)	⨁◯◯◯ VERY LOW	–
Composite outcome of All-cause mortality, myocardial infarction, stroke, heart failure (mean follow-up of 4 years)												
2 [a,k]	observational studies	serious [e]	serious [l]	not serious	not serious	none	1515/8547 (17.7%)	1924/10 706 (18.0%)	**OR 1.35** (1.24 to 1.46)	**49 more per 1000** (from 34 more to 63 more)	⨁◯◯◯ VERY LOW	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End–stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; OR: Odds ratio

Explanations

a. One of the included studies with higher weight is RCT (ALLHAT) and the other is propensity match cohort (Bangalore).
b. The odds ratio of mortality for RAASi vs diuretics in the included RCT (ALLHAT trial) was 1.07 with CI of [0.95, 1.21].
c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
d. The odds ratio of myocardial infarction for RAASi vs diuretics in the included RCT (ALLHAT trial) was 1.09 with CI [0.93, 1.29].
e. The review reports that all included studies are at low risk of bias however it does not give details about different RoB domains. However, the ALLHAT 2005 study that has most of the weight of the pooled estimate (>50%) was judged at unclear risk of bias in the domain of blinding of outcome assessment in another review.
f. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (81%).
g. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be important benefit and harm.
h. Baseline risk abstracted from Nestor, 2004.
i. The odds ratio of stroke for RAASi vs diuretics in the included RCT (ALLHAT trial) was 1.41 with CI [1.17, 1.7].
j. The odds ratio of heart failure for RAASi vs diuretics in the included RCT (ALLHAT trial) was 1.32 with [1.1, 1.59].
k. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (92%).
l. The odds ratio of composite outcomes for RAASi vs diuretics in the included RCT (ALLHAT trial) was 1.24 with CI [1.13, 1.36].
m. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (94%).

Table 52 Evidence profile 5m: Renin-angiotensin-aldosterone system inhibitor (RAASi) compared to beta-blocker (BB) for black patients with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi	Beta-blocker	Relative (95% CI)	Absolute (95% CI)		
Source												
Palla 2017*(65)*												
All-cause mortality (mean follow-up of 4 years)												
2 [a,b]	observational studies	not serious	not serious	not serious	serious [c]	none	166/3377 (4.9%)	186/3376 (5.5%)	OR 0.84 (0.60 to 1.19)	8 fewer per 1000 (from 21 fewer to 10 more)	⨁◯◯◯ VERY LOW	–
Myocardial infarction (mean follow-up of 4 years)												
3 [d,e]	observational studies	not serious	not serious	not serious	serious [f]	none	44/3647 (1.2%)	28/3639 (0.8%)	OR 1.67 (0.88 to 3.18)	5 more per 1000 (from 1 fewer to 16 more)	⨁◯◯◯ VERY LOW	
Stroke (mean follow-up of 4 years)												
3 [d,g]	observational studies	not serious	not serious	not serious	serious [f]	none	77/3647 (2.1%)	60/3639 (1.6%)	OR 1.29 (0.91 to 1.81)	5 more per 1000 (from 1 fewer to 13 more)	⨁◯◯◯ VERY LOW	–
Heart failure (mean follow-up of 4 years)												
2 [a,h]	observational studies	not serious	not serious	not serious	very serious [f]	none	94/3377 (2.8%)	53/3376 (1.6%)	OR 1.52 (0.58 to 4.00)	8 more per 1000 (from 7 fewer to 44 more)	⨁◯◯◯ VERY LOW	–
Composite outcomes (All-cause mortality, myocardial infarction, stroke, heart failure) (mean follow-up of 4 years)												
3 [a]	observational studies	not serious	serious [i]	not serious	not serious	none	403/3647 (11.1%)	342/3639 (9.4%)	OR 1.20 (1.03 to 1.40)	17 more per 1000 (from 3 more to 33 more)	⨁◯◯◯ VERY LOW	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End–stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; OR: Odds ratio

Explanations

a. The study with higher weight is observational (Bangalore) and the other studies are RCTs.

b. The odds ratio of mortality for RAASi vs BB in the included RCT (AASK trial) was 0.67 with CI [0.42, 1.05].

c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be important benefit and harm.
d. One of the three included studies is observational.
e. The odds ratio of myocardial infarction for RAASi vs BBs in the included RCT (AASK trial) was 1.06 with CI [0.55, 2.04]. The odds ratio of myocardial infarction for RAASi vs BBs in the included RCT (LIFE trial) was 2.17 with CI [0.81, 5.79].
f. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
g. The odds ratio of stroke for RAASi vs BBs in the included RCT (AASK trial) was 1.00 with CI [0.55, 1.81]. The odds ratio of stroke for RAASi vs BBs in the included RCT (LIFE trial) was 2.04 with CI [1, 4.17].
h. The odds ratio of heart failure for RAASi vs BBs in the included RCT (AASK trial) was 0.9 with CI [0.49, 1.68].
i. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (81%).

Table 53 Evidence profile 5n: Renin-angiotensin-aldosterone-system inhibitor (RAASi) compared to calcium channel blocker (CCB) for black patients with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi	CCB	Relative (95% CI)	Absolute (95% CI)		
Source												
Palla 2017*(65)*												
All-cause mortality (mean follow-up of 4 years)												
3 [a]	observational studies	not serious	not serious	not serious	serious [b]	none	694/8154 (8.5%)	623/7938 (7.8%)	OR 1.10 (0.98 to 1.23)	7 more per 1000 (from 1 fewer to 16 more)	⊕◯◯◯ VERY LOW	–
Myocardial infarction (mean follow-up of 4 years)												
3 [a]	observational studies	serious [c]	not serious	not serious	very serious [b]	none	296/8154 (3.6%)	253/7938 (3.2%)	OR 1.69 (0.81 to 3.51)	21 more per 1000 (from 6 fewer to 72 more)	⊕◯◯◯ VERY LOW	–
Stroke (mean follow-up of 4 years)												
3 [a]	observational studies	serious [c]	not serious	not serious	not serious	none	325/8154 (4.0%)	204/7938 (2.6%)	OR 1.56 (1.31 to 1.87)	14 more per 1000 (from 8 more to 21 more)	⊕◯◯◯ VERY LOW	–
Heart failure (mean follow-up of 4 years)												
3 [a]	observational studies	serious [c]	serious [d]	not serious	very serious [e]	none	350/8154 (4.3%)	318/7938 (4.0%)	OR 1.24 (0.71 to 2.18)	9 more per 1000 (from 11 fewer to 43 more)	⊕◯◯◯ VERY LOW	–
Composite outcome (All-cause mortality, myocardial infarction, stroke, heart failure (mean follow-up of 4 years)												
3 [a]	observational studies	serious [c]	serious [f]	not serious	not serious	none	1665/8154 (20.4%)	1398/7938 (17.6%)	OR 1.23 (1.13 to 1.34)	32 more per 1000 (from 18 more to 47 more)	⊕◯◯◯ VERY LOW	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End–stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; OR: Odds ratio

Explanations

a. One of the three included studies was observational (Bangalore).

b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

c. The review reports that all included studies are at low risk of bias, however it does not give details about different RoB domains. The ALLHAT 2005 study that has most of the weight of the pooled estimate (>50%) was judged at unclear risk of bias in the domain of blinding of outcome assessment in another review.
d. The point estimates vary importantly with regards to magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (86%).
e. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be important benefit and harm.
f. The point estimates vary importantly with regards to magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (94%).

Table 54 Evidence profile 5o: Calcium channel blocker (CCB) compared to non-calcium channel blocker antihypertensives for Asian populations with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	non-CCB antihypertensives	Relative (95% CI)	Absolute (95% CI)		
Source												
Tran 2017*(66)*												
Cardiovascular mortality (follow-up of at least 1 year)												
7	randomized trials	serious [a]	not serious	serious [b]	serious [c,d]	publication bias strongly suspected [e]	48/9377 (0.5%)	43/9391 (0.5%)	RR 1.10 (0.72 to 1.67)	0 fewer per 1000 (from 1 fewer to 3 more)	⨁◯◯◯ VERY LOW	–
Major adverse cardiac events (follow-up of at least 1 year)												
9	randomized trials	serious [a]	not serious	serious [b]	not serious	none	498/9963 (5.0%)	489/9969 (4.9%)	RR 1.02 (0.90 to 1.15)	1 more per 1000 (from 5 fewer to 7 more)	⨁⨁◯◯ LOW	–
Stroke (follow-up of at least 1 year)												
9	randomized trials	serious [a]	not serious	serious [b]	not serious	none	211/9963 (2.1%)	217/9969 (2.2%)	RR 0.97 (0.80 to 1.17)	1 fewer per 1000 (from 4 fewer to 4 more)	⨁⨁◯◯ LOW	–
Heart failure (follow-up of at least 1 year)												
6	randomized trials	serious [a]	not serious	serious [b]	serious [c,d]	none	52/5053 (1.0%)	50/5049 (1.0%)	RR 1.01 (0.51 to 2.00)	0 fewer per 1000 (from 5 fewer to 10 more)	⨁◯◯◯ VERY LOW	–
All-cause mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End–stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. The trials were judged at high risk of bias in the domains of randomization and blinding. However, the authors did not report the risk of bias assessment in details for each of the included trials.

b. We downgraded one level because the meta-analysis included two studies comparing CCB monotherapy or combination to non-CCB monotherapy or combination i.e. not all included studies examined head to head antihypertensive monotherapy.

c. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more.

d. There is a very low events rate.

e. There was evidence of publication bias based on Egger analysis.

Table 55 Evidence profile 5p: Calcium channel blocker (CCB) compared to angiotensin receptor blocker (ARB) for Asian populations with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	ARB	Relative (95% CI)	Absolute (95% CI)		
Source												
Tran 2017*(66)*												
Cardiovascular mortality (follow-up of at least 1 year)												
3	randomized trials	serious [a]	not serious	serious [b]	serious [c,d]	none	23/4606 (0.5%)	17/4614 (0.4%)	RR 1.35 (0.72 to 2.53)	1 more per 1000 (from 1 fewer to 6 more)	⊕◯◯◯ VERY LOW	–
Major adverse cardiac events (follow-up of at least 1 year)												
5	randomized trials	serious [a]	not serious	serious [b]	not serious	none	270/5192 (5.2%)	271/5192 (5.2%)	RR 0.99 (0.83 to 1.18)	1 fewer per 1000 (from 9 fewer to 9 more)	⊕⊕◯◯ LOW	–
Stroke (follow-up of at least 1 year)												
5	randomized trials	serious [a]	not serious	serious [b]	serious [c]	none	104/5192 (2.0%)	116/5192 (2.2%)	RR 0.93 (0.67 to 1.29)	2 fewer per 1000 (from 7 fewer to 6 more)	⊕◯◯◯ VERY LOW	–
Heart failure (follow-up of at least 1 year)												
4	randomized trials	serious [a]	not serious	serious [b]	serious [e]	none	40/4021 (1.0%)	39/4017 (1.0%)	RR 1.05 (0.41 to 2.67)	0 fewer per 1000 (from 6 fewer to 16 more)	⊕◯◯◯ VERY LOW	–
All-cause mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. The trials were judged at high risk of bias in the domains of randomization and blinding. However, the authors did not report the risk of bias assessment in details for each of the included trials.

b. We downgraded one level because the meta-analysis included two studies comparing CCB monotherapy or combination to non-CCB monotherapy or combination i.e. not all included studies compared head to head antihypertensive monotherapy.

c. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more. The extremes of the confidence interval will lead to different decisions.

d. There is a very low events rate.

e. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

Table 56 Evidence profile 5q: Angiotensin-converting enzyme inhibitor compared to angiotensin receptor blocker for hypertensive patients with myocardial infarction or heart failure

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE	ARB	Relative (95% CI)	Absolute (95% CI)		
Source												
Ohtsubo 2019*(67)*												
Recurrence or new onset myocardial infarction (follow up between 6 and 54 months)												
5	randomized trials	not serious [a]	not serious	serious [b]	not serious	publication bias strongly suspected	836/13 374 (6.3%)	866/13 336 (6.5%)	RR 0.97 (0.88 to 1.06)	2 fewer per 1000 (from 8 fewer to 4 more)	⨁⨁◯◯ LOW	–
Hospitalization for heart failure (follow up between 6 and 54 months)												
4	randomized trials	not serious [a]	not serious	serious [b]	serious [c]	publication bias strongly suspected [d]	583/4798 (12.2%)	599/4794 (12.5%)	RR 0.98 (0.84 to 1.14)	2 fewer per 1000 (from 20 fewer to 17 more)	⨁◯◯◯ VERY LOW	–
Cardiovascular or total mortality (follow up between 6 and 54 months)												
6	randomized trials	not serious [a]	not serious	serious [b]	serious [c]	none	3783/18 283 (20.7%)	3831/18 245 (21.0%)	RR 0.98 (0.91 to 1.05)	4 fewer per 1000 (from 19 fewer to 10 more)	⨁⨁◯◯ LOW	–
Cardiovascular events or stroke (follow up between 6 and 54 months)												
5	randomized trials	not serious [a]	not serious	serious [b]	serious [c]	none	2579/13 374 (19.3%)	2590/13 336 (19.4%)	RR 1.02 (0.94 to 1.11)	4 more per 1000 (from 12 fewer to 21 more)	⨁⨁◯◯ LOW	–
Adverse events (follow up between 6 and 54 months)[e]												
6	randomized trials	not serious [a]	serious [f]	serious [b]	not serious	publication bias strongly suspected [d]	4977/18 253 (27.3%)	4303/18 221 (23.6%)	RR 1.40 (1.11 to 1.77)	94 more per 1000 (from 26 more to 182 more)	⨁◯◯◯ VERY LOW	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. Even though T-VENTURE 2009 trial was judged to be at high risk of bias in the domains of allocation concealment and blinding, we did not downgrade risk of bias because this trial has the lowest weight of the pooled effect estimate (weight <4%).

b. The review states that "Among the six RCTs, the proportion of hypertensive patients ranged from 36 to 68.8%".

c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be an important benefit and harm.

d. The funnel plot suggests possibility of publication bias.

e. The review states "ACEis caused many adverse events, such as cough, taste disturbance, rash, angioedema, and other such issues, while ARBs frequently caused hypotension and renal dysfunction.

f. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (96%).

Table 57 Evidence profile 5r: Angiotensin-converting enzyme inhibitors (ACEi) compared to diuretics for non-dialysis chronic kidney disease stages 3–5

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE	Diuretics	Relative (95% CI)	Absolute (95% CI)		
Sources												
Zhang 2020 (Network meta-analysis*(59)*); ALLHAT 2006*(68)*												
Kidney events (defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in GFR, or ESKD) (follow up >6 months)												
1 [a]	randomized trials	serious [b]	not serious [c]	not serious [d]	serious [e,f]	none		259/5662 (4.6%) [g]	OR 0.76 (0.46 to 1.25)	11 fewer per 1000 (from 24 fewer to 11 more)	⨁⨁◯◯ LOW	–
Cardiovascular events (follow up >6 months)												
1 [a]	randomized trials	serious [b]	not serious [c]	not serious	serious [e,f]	none		870/2613 (33.3%)	OR 0.96 (0.73 to 1.25)	9 fewer per 1000 (from 66 fewer to 51 more)	⨁⨁◯◯ LOW	–
All-cause mortality (follow up >6 months)												
1 [a]	randomized trials	serious [b]	not serious [c]	not serious	very serious [e,f]	none		9/264 (3.4%) [h]	OR 0.52 (0.21 to 1.30)	16 fewer per 1000 (from 27 fewer to 10 more)	⨁◯◯◯ VERY LOW	
Hyperkalaemia (follow up >6 months)												
1 [a]	randomized trials	serious [b]	not serious [c]	not serious	very serious [e,f]	none		1/264 (0.4%)	OR 2.76 (0.70 to 10.89)	7 more per 1000 (from 1 fewer to 36 more)	⨁◯◯◯ VERY LOW	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke (follow up >6 months)[i]												
1 [j]	randomized trials	serious [b]	not serious	not serious	serious [k]	none	99/1533 (6.5%)	157/2613 (6.0%)	HR 1.10 (0.86 to 1.42)	6 more per 1000 (from 8 fewer to 24 more)	⨁⨁◯◯ LOW	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure (follow up >6 months)[l]												
1 [j]	randomized trials	serious [b]	not serious	not serious	not serious	none	191/1533 (12.5%)	259/2613 (9.9%)	OR 1.29 (1.06 to 1.58)	25 more per 1000 (from 5 more to 49 more)	⨁⨁⨁◯ MODERATE	–
Nonfatal myocardial infarction and fatal coronary heart disease (follow up >6 months)[m]												
1 [j]	randomized trials	serious [b]	not serious	not serious	serious [n]	none	184/1533 (12.0%)	318/2613 (12.2%)	HR 1.00 (0.84 to 1.20)	0 fewer per 1000 (from 18 fewer to 23 more)	⨁⨁◯◯ LOW	–
BP reduction and control – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Combined cardiovascular disease (follow up >6 months)[o]												
1 [j]	randomized trials	serious [b]	not serious	not serious	not serious	none	547/1533 (35.7%)	870/2613 (33.3%) [g]	HR 1.12 (1.01 to 1.25)	32 more per 1000 (from 3 more to 64 more)	⨁⨁⨁◯ MODERATE	–

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

Explanations

a. This outcome is informed by the network indirect comparison.

b. The included study was judged by another review (Lin, 2017)*(134)* to be at high risk of bias in the domain of selective reporting.
c. The review does not provide I-squared or the confidence intervals of individual studies to assess heterogeneity. The review states "Loop-specific inconsistency approach was used to assess the disagreement between direct and indirect evidence in the loop, and the consistency results were considered not significant when 95% CIs of inconsistency factors included zero or RoR included one. RoR is defined as the difference that OR value of direct evidence minus OR value of indirect evidence."
d. We did not downgrade indirectness because 50% drop in eGFR and doubling in serum creatinine are validated surrogates for ESKD.
e. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more.
f. No direct comparison data is available for this outcome.
g. We extracted the events rate from the ALLHAT 2006 however this is the events from from all arms (thiazide, CCB and ACEi). The events rate for thiazide arm was not provided in the ALLHAT 2006.
h. There is no direct comparison between ACEi and diuretics for the outcome of mortality. We used the events rate from diuretics arm from COPE 2013 trial which has three arms: ARB, BB and thiazide.
i. In the subgroup of patients with GFR <60 ml/min per 1.73 m2 and diabetes, the HR for stroke is 0.94 (0.62–1.43).
j. The result of this outcome is informed by the direct comparison of ACEi vs diuretics in the post hoc subgroup analysis of ALLHAT 2006.
k. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
l. In the subgroup of patients with GFR <60 ml/min per 1.73 m2 and diabetes, the OR for heart failure is 1.44 (1.05–1.97).
m. In the subgroup of patients with GFR <60 ml/min per 1.73 m2 and diabetes, the HR for nonfatal MI and fatal CHD is 1.03 (0.78–1.37).
n. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower end of the 95% CI crossed this threshold, suggesting that there may be important harm and harm.
o. In the subgroup of patients with GFR <60 ml/min per 1.73 m2 and diabetes, the HR for combined CVD is 1.08 (0.90–1.29).

Table 58 Evidence profile 5s: Angiotensin-converting enzyme inhibitor (ACE) compared to calcium channel blocker (CCB) for non-dialysis chronic kidney disease stages 3–5

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE	CCB	Relative (95% CI)	Absolute (95% CI)		
Source												
Zhang 2020*(59)*												
Kidney events (defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in GFR, or ESKD) (follow up >6 months)												
10 [a]	randomized trials	serious [b]	not serious [c]	not serious [d]	not serious	none		22.7% [e]	OR 0.67 (0.50 to 0.89)	63 fewer per 1000 (from 99 fewer to 20 fewer)	⊕⊕⊕◯ MODERATE	–
Cardiovasuclar events (follow up >6 months)												
10 [a]	randomized trials	serious [b]	not serious [c]	not serious	serious [f]	none		35.4% [e]	OR 0.99 (0.80 to 1.23)	2 fewer per 1000 (from 49 fewer to 49 more)	⊕⊕◯◯ LOW	–
cardiovascular mortality (follow up >6 months)												
10 [a]	randomized trials	serious [b]	not serious [c]	not serious	very serious [f]	none		22.4% [e]	OR 0.78 (0.48 to 1.28)	40 fewer per 1000 (from 102 fewer to 46 more)	⊕◯◯◯ VERY LOW	–
All-cause mortality (follow up >6 months)												
10 [a]	randomized trials	serious [b]	not serious [c]	not serious	serious [g]	none		2.8% [e]	OR 0.78 (0.51 to 1.17)	6 fewer per 1000 (from 14 fewer to 5 more)	⊕⊕◯◯ LOW	–
Hyperkalaemia (follow up >6 months)												
10 [a]	randomized trials	serious [b]	not serious [c]	not serious	not serious	none		0.7% [e]	OR 3.81 (1.58 to 9.20)	19 more per 1000 (from 4 more to 52 more)	⊕⊕⊕◯ MODERATE	–
Cough (follow up >6 months)												
10 [a]	randomized trials	serious [b]	not serious [c]	not serious	not serious	none		0.5% [e]	OR 8.20 (3.13 to 21.54)	33 more per 1000 (from 10 more to 88 more)	⊕⊕⊕◯ MODERATE	–
Hypotension (follow up >6 months)												
10 [a]	randomized trials	serious [b]	not serious [c]	not serious	very serious [h,i]	none			OR 1.59 (0.59 to 4.33)	2 fewer per 1000 (from 4 fewer to 1 fewer)	⊕◯◯◯ VERY LOW	–
Oedema (follow up >6 months)												
10	randomized trials	serious [b]	not serious [c]	not serious	not serious	none		0.0% [e]	**OR 0.16** (0.06 to 0.38)	**0 fewer per 1000** (from 0 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

BP reduction and control – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; OR: Odds ratio

Explanations

a. 10 is the total number of trials informing direct pairwise comparisons.

b. The weight of each of the included studies was not provided however seven of the 10 included studies were judged to be at high risk of bias in the domains of blinding of participants, personnel, outcome assessors, incomplete outcome data and selective outcome reporting. Also 7 of the included studies were judged to be at unclear risk of bias in the domains of random sequence generation and allocation concealment.

c. The review does not provide I-squared or the confidence intervals of individual studies to assess heterogeneity. The review states "Loop-specific inconsistency approach was used to assess the disagreement between direct and indirect evidence in the loop, and the consistency results were considered not significant when 95% CIs of inconsistency factors included zero or RoR included one. RoR is defined as the difference that OR value of direct evidence minus OR value of indirect evidence."

d. We did not downgrade indirectness because 50 % drop in eGFR and doubling in serum creatinine are validated surrogates for ESKD.

e. The baseline risk wasn't reported in the network meta-analysis. The values were abstracted directly from the included studies.

f. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower end of the 95% CI crossed this threshold, suggesting that there may be important benefit and harm.

g. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.

h. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more.

i. No events rate is available.

Table 59 Evidence profile 5t: Angiotensin-converting enzyme inhibitor (ACE) compared to beta-blocker for non-dialysis chronic kidney disease stages 3–5

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE	Beta-blocker	Relative (95% CI)	Absolute (95% CI)		
Source												
Zhang 2020*(59)*												
Kidney events (defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in GFR, or ESKD) (follow up >6 months)												
3 [a]	randomized trials	serious [b]	not serious [c]	not serious [d]	not serious	none		169/505 (33.5%)	OR 0.60 (0.37 to 0.96)	103 fewer per 1000 (from 178 fewer to 9 fewer)	⊕⊕⊕◯ MODERATE	–
Cardiovascular events (follow up >6 months)												
1 [e]	randomized trials	serious [b]	not serious [c]	not serious	serious [f,g]	none		13/441 (2.9%)	OR 0.95 (0.64 to 1.42)	1 fewer per 1000 (from 10 fewer to 12 more)	⊕⊕◯◯ LOW	–
Cardiovascular mortality (follow up >6 months)												
1 [e]	randomized trials	not serious	not serious [c]	not serious	very serious [g,h]	none		3.5/441 (0.8%)	OR 1.01 (0.44 to 2.33)	0 fewer per 1000 (from 4 fewer to 10 more)	⊕⊕◯◯ LOW	–
All-cause mortality (follow up >6 months)												
2 [i]	randomized trials	serious [j]	not serious [c]	not serious	serious [g]	none		13/457 (2.8%)	OR 0.60 (0.38 to 0.96)	11 fewer per 1000 (from 17 fewer to 1 fewer)	⊕⊕◯◯ LOW	–
Hyperkalaemia (follow up >6 months)												
3 [a]	randomized trials	serious [b]	not serious [c]	not serious	very serious [g,h]	none		2/505 (0.4%)	OR 1.86 (0.64 to 5.41)	3 more per 1000 (from 1 fewer to 17 more)	⊕◯◯◯ VERY LOW	–
Cough (follow up >6 months)												
2 [i]	randomized trials	serious [b]	not serious [c]	not serious	not serious	none		180/457 (39.4%)	OR 1.80 (1.08 to 3.00)	145 more per 1000 (from 19 more to 267 more)	⊕⊕⊕◯ MODERATE	–
Oedema (follow up >6 months)												
2 [i]	randomized trials	serious [b]	not serious [c]	not serious	very serious [f]	none		226/457 (49.5%)	OR 0.65 (0.22 to 1.91)	106 fewer per 1000 (from 317 fewer to 157 more)	⊕◯◯◯ VERY LOW	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction and control – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; OR: Odds ratio

Explanations

a. 3 is the total number of trials informing direct comparisons.
b. The weight of each of the included studies was not provided however all included studies were judged to be at high risk of bias in the domains of blinding of participants, personnel and outcome assessors.
c. The review does not provide I-squared or the confidence intervals of individual studies to assess heterogeneity. The review states "Loop-specific inconsistency approach was used to assess the disagreement between direct and indirect evidence in the loop, and the consistency results were considered not significant when 95% CIs of inconsistency factors included zero or RoR included one. RoR is defined as the difference that OR value of direct evidence minus OR value of indirect evidence."
d. We did not downgrade indirectness because 50 % drop in eGFR and doubling in serum creatinine are validated surrogates for ESKD.
e. 1 is the total number of trials informing direct comparisons.
f. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end and lower of the 95% CI crossed this threshold, suggesting that there may be important harm and benefit.
g. There is a low number of events.
h. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
i. 2 is the total number of trials informing direct comparisons.
j. The weight of each of the included studies was not provided however one of the included studies was at unclear risk of bias in the domains of random sequence generation and allocation concealment.

Table 60 Evidence profile 5u: Angiotensin-converting enzyme inhibitor (ACE) compared to Angiotensin II receptor blocker (ARB) for non-dialysis chronic kidney disease stages 3–5

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE	ARB	Relative (95% CI)	Absolute (95% CI)		
Source												
Zhang 2020*(59)*												
Kidney events (defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in GFR, or ESKD) (follow up >6 months)												
3 [a]	randomized trials	serious [b]	not serious [c]	not serious [d]	serious [e,f]	none		72/240 (30.0%)	OR 0.70 (0.52 to 0.97)	69 fewer per 1000 (from 118 fewer to 6 fewer)	⊕⊕◯◯ LOW	–
Cardiovascular events (follow up >6 months)												
2 [g]	randomized trials	serious [b]	not serious [c]	not serious	serious [h]	none		34/212 (16.0%)	OR 0.88 (0.73 to 1.07)	16 fewer per 1000 (from 38 fewer to 9 more)	⊕⊕◯◯ LOW	–
Cardiovascular death (follow up >6 months)												
2 [g]	randomized trials	not serious	not serious [c]	not serious	very serious [i]	none		88/729 (12.1%) [j]	OR 0.63 (0.46 to 0.86)	41 fewer per 1000 (from 61 fewer to 15 fewer)	⊕⊕◯◯ LOW	–
All-cause mortality (follow up >6 months)												
3 [a]	randomized trials	not serious	not serious [c]	not serious	very serious [i]	none		1/240 (0.4%)	OR 0.76 (0.59 to 0.98)	1 fewer per 1000 (from 2 fewer to 0 fewer)	⊕⊕◯◯ LOW	–
Hyperkalaemia (follow up >6 months)												
3 [a]	randomized trials	serious [b]	not serious [c]	not serious	very serious [i,k]	none		19/240 (7.9%)	OR 0.75 (0.45 to 1.23)	19 fewer per 1000 (from 42 fewer to 16 more)	⊕◯◯◯ VERY LOW	
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction and control – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; OR: Odds ratio

Explanations

a. The total number of trials informing direct comparisons is three.

b. The weight of each of the included studies was not provided, however all included studies were judged to be at high risk of bias in the domains of blinding of participants, personnel and outcome assessors.

c. The review does not provide I-squared or the confidence intervals of individual studies to assess heterogeneity. The review states "Loop-specific inconsistency approach was used to assess the disagreement between direct and indirect evidence in the loop, and the consistency results were considered not significant when 95% CIs of inconsistency factors included zero or RoR included one. RoR is defined as the difference that OR value of direct evidence minus OR value of indirect evidence."

d. We did not downgrade indirectness because 50% drop in eGFR and doubling in serum creatinine are validated surrogates for ESKD.

e. The upper value of the confidence interval is very close to the line of no effect. The CI suggests almost no effect or important benefit.
f. There is a low number of events.
g. 2 is the total number of trials informing direct comparisons.
h. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.
i. We downgraded imprecision two levels because of very low events rate.
j. The SR doesn't provide absolute values so we abstracted it from Post hoc ONTARGET.
k. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower end of the 95% CI crossed this threshold, suggesting that there may be an important harm and benefit.

Table 61 Evidence profile 5v: Angiotensin II receptor blocker (ARB) compared to diuretics for non-dialysis chronic kidney disease stages 3–5

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	Diuretics	Relative (95% CI)	Absolute (95% CI)		
Source												
Zhang 2020*(59)*; COPE 2013*(69)*												
Kidney events (defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in GFR, or ESKD) (follow up >6 months)												
1 [a]	randomized trials	serious [b]	not serious	not serious [c]	very serious [d]	none			OR 1.07 (0.61 to 1.87)	1 fewer per 1000 (from 2 fewer to 1 fewer)	⊕◯◯◯ VERY LOW	–
Hard composite cardiovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke excluding transient ischemic attack) (follow up of at least 3 years)												
1 [e]	randomized trials	serious [b]	not serious	not serious	very serious [f,g]	none	9/287 (3.1%)	7/264 (2.7%)	HR 1.19 (0.44 to 3.20)	5 more per 1000 (from 15 fewer to 56 more)	⊕◯◯◯ VERY LOW	–
All-cause mortality (follow up of at least 3 years)												
1 [e]	randomized trials	not serious	not serious	not serious	very serious [f,g]	none	7/287 (2.4%)	9/264 (3.4%)	HR 0.72 (0.27 to 1.93)	9 fewer per 1000 (from 25 fewer to 31 more)	⊕⊕◯◯ LOW	–
Hyperkalaemia (follow up >6 months)												
1 [a]	randomized trials	serious [b]	not serious	not serious	very serious [g,h,j]	none	8/287 (2.8%)	1/264 (0.4%)	OR 3.70 (1.03 to 13.28)	10 more per 1000 (from 0 fewer to 44 more)	⊕◯◯◯ VERY LOW	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Fatal and nonfatal stroke (follow up of at least 3 years)												
1 [e]	randomized trials	serious [b]	not serious	not serious	very serious [g,j]	none	7/287 (2.4%)	3/264 (1.1%)	HR 2.15 (0.56 to 8.33)	13 more per 1000 (from 5 fewer to 79 more)	⊕◯◯◯ VERY LOW	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction and control – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

The co-primary endpoints were defined as a composite of cardiovascular events and achievement of target BP. Cardiovascular events consisted of the following groups: sudden death, fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, hospitalization due to unstable angina, new onset of heart failure (New York Heart Association class II-IV), new onset or worsening of peripheral arterial disease, and renal events (defined as serum creatinine level doubled to over 2 mg/dl, serum creatinine >=4.0 mg/dl, or renal dialysis). (follow up of at least 3 years)

1 [e]	randomized trials	serious [b]	not serious	not serious	very serious [f]	none	15/287 (5.2%)	13/264 (4.9%)	HR 1.08 (0.51 to 2.26)	4 more per 1000 (from 24 fewer to 59 more)	⊕◯◯◯ VERY LOW	–

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio

Explanations

a. This outcome is informed by the indirect comparison only of the network meta-analysis.
b. The included trial was judged to be at high risk of bias in the domains of blinding of participants and personnel.
c. We did not downgrade indirectness because 50% drop in eGFR and doubling in serum creatinine are validated surrogates for ESKD.
d. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more.
e. When the direct comparison of network meta-analysis is informed by one trial we used the data of the trial. This outcome is informed by the direct comparison of ARB vs diuretics in the COPE 2013*(69)* trial.
f. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower ends of the 95% CI crossed this threshold, suggesting that there may be important harm and benefit.
g. There is a low number of events.
h. The baseline risk was extracted from the COPE*(69)* trial.
i. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
j. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

Table 62 Evidence profile 5w: Angiotensin II receptor blocker (ARB) compared to calcium channel blocker (CCB) for non-dialysis chronic kidney disease stages 3–5

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	CCB	Relative (95% CI)	Absolute (95% CI)		
Source												
Zhang 2020*(59)*												
Kidney events (defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in GFR, or ESKD) (follow up >6 months)												
1 [a,b]	randomized trials	serious [c]	not serious [d]	not serious [e]	serious [f,g]	none		23/1186 (1.9%)	OR 0.94 (0.67 to 1.32)	1 fewer per 1000 (from 6 fewer to 6 more)	⊕⊕◯◯ LOW	–
Cardiovascular events (follow up >6 months)												
2 [h]	randomized trials	serious [c]	not serious [d]	not serious	very serious [i]	none		376/1753 (21.4%)	OR 1.13 (0.91 to 1.39)	21 more per 1000 (from 15 fewer to 61 more)	⊕◯◯◯ VERY LOW	–
Cardiovascular mortality (follow up >6 months)												
1 [a]	randomized trials	not serious	not serious [d]	not serious	very serious [i]	none		37/567 (6.5%)	OR 1.24 (0.83 to 1.86)	14 more per 1000 (from 10 fewer to 50 more)	⊕⊕◯◯ LOW	–
All-cause mortality (follow up >6 months)												
2 [j]	randomized trials	not serious	not serious [d]	not serious	serious [f]	none			OR 1.02 (0.71 to 1.46)	1 fewer per 1000 (from 1 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	–
Hyperkalaemia (follow up >6 months)												
2 [j]	randomized trials	serious [c]	not serious [d]	not serious	not serious	none			OR 5.10 (2.08 to 12.50)	5 fewer per 1000 (from 13 fewer to 2 fewer)	⊕⊕⊕◯ MODERATE	–
Cough (follow up >6 months)												
2 [j]	randomized trials	serious [c]	not serious [d]	not serious	very serious [f]	none			OR 1.69 (0.24 to 12.03)	2 fewer per 1000 (from 12 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	–
Hypotension (follow up >6 months)												
2 [a]	randomized trials	serious [c]	not serious [d]	not serious	very serious [f]	none			OR 1.68 (0.20 to 14.38)	2 fewer per 1000 (from 14 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction and control – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; OR: Odds ratio

Explanations

a. 1 is the total number of trials informing direct comparisons.
b. Since the CASE-J study provides the hazard ratio for each subgroup of CKD separately, we used the network meta-analysis OR for CKD 3-5.
c. The weight of each of the included studies was not provided, however the included study was judged to be at high risk of bias in the domains of blinding of participants and personnel.
d. The review does not provide I-squared or the confidence intervals of individual studies to assess heterogeneity. The review states "Loop-specific inconsistency approach was used to assess the disagreement between direct and indirect evidence in the loop, and the consistency results were considered not significant when 95% CIs of inconsistency factors included zero or RoR included one. RoR is defined as the difference that OR value of direct evidence minus OR value of indirect evidence."
e. We did not downgrade indirectness because 50 % drop in eGFR and doubling in serum creatinine are validated surrogates for ESKD.
f. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more.
g. We downgraded imprecision one level because of low number of events.
h. 2 (CASE-J and IDNT) is the total number of trials informing direct comparisons.
i. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower end of the 95% CI crossed this threshold, suggesting that there may be important harm and benefit.
j. None of the two studies provides direct comparison for this outcome of interest. We used the network OR is based on indirect comparison.

Table 63 Evidence profile 5x: Angiotensin II receptor blocker (ARB) compared to beta-blocker (BB) for non-dialysis chronic kidney disease stages 3–5

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	BB	Relative (95% CI)	Absolute (95% CI)		
Source												
Zhang 2020*(59)*												
Kidney events (defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in GFR, or ESKD) (follow up >6 months)												
1 [a]	randomized trials	serious [b]	not serious [c]	not serious [d]	serious [e]	none	–	–	OR 0.84 (0.48 to 1.47)	1 fewer per 1000 (from 1 fewer to 0 fewer)	⨁⨁◯◯ LOW	–
Cardiovascular mortality (follow up >6 months)												
1 [a]	randomized trials	not serious	not serious [c]	not serious	very serious [e]	none	–	–	OR 1.60 (0.66 to 3.91)	2 fewer per 1000 (from 4 fewer to 1 fewer)	⨁⨁◯◯ LOW	–
Hyperkalaemia (follow up >6 months)												
1 [a]	randomized trials	serious [b]	not serious [c]	not serious	serious [f,g]	none	8/287 (2.8%)	1/283 (0.4%)	OR 2.49 (0.83 to 7.50)	5 more per 1000 (from 1 fewer to 22 more)	⨁⨁◯◯ LOW	–
Cough (follow up >6 months)												
1 [a]	randomized trials	serious [b]	not serious [c]	not serious	very serious [e]	none	–	–	OR 0.37 (0.06 to 2.18)	0 fewer per 1000 (from 2 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction and control – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; OR: Odds ratio

Explanations

a. This outcome is only informed by the indirect comparison of the network meta-analysis. b. The included study was judged to be at high risk of bias in the domains of blinding of the participants and personnel.

c. The review states "Loop-specific inconsistency approach was used to assess the disagreement between direct and indirect evidence in the loop, and the consistency results were considered not significant when 95% CIs of inconsistency factors included zero or RoR included one. RoR is defined as the difference that OR value of direct evidence minus OR value of indirect evidence."

d. We did not downgrade indirectness because 50 % drop in eGFR and doubling in serum creatinine are validated surrogates for ESKD.

e. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more.

f. The baseline risk was extracted from COPE 2013*(69)* trial.

g. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

Table 64 Evidence profile 5y: Beta-blocker (BB) compared to angiotensin receptor blocker (ARB) for individuals with hypertension and non-dialysis chronic kidney disease 3-5

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BB	ARB	Relative (95% CI)	Absolute (95% CI)		
Source												
COPE 2013*(69)*												
Coprimary end points: composite of cardiovascular morbidity and mortality (sudden death, fatal or non-fatal stroke, fatal or non-fatal myocardial infarction, hospitalization due to unstable angina, new onset of heart failure (New York Heart Association class II–IV), new onset or worsening of peripheral arterial disease and renal events defined as serum creatinine level doubled to over 2mgdl1, serum creatinine X4.0mg dl1, or renal dialysis), and achievement of target BP (o140/90mmHg). (follow up of at least 3 years)												
1 [a]	randomized trials	serious [b]	not serious	not serious	very serious [c]	none	13/283 (4.6%)	15/287 (5.2%)	HR 0.90 (0.43 to 1.89)	5 fewer per 1000 (from 29 fewer to 44 more)	⊕◯◯◯ VERY LOW	–
Hard composite cardiovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke excluding transient ischemic attack) (follow up of at least 3 years)												
1 [a]	randomized trials	serious [b]	not serious	not serious	very serious [c]	none	8/283 (2.8%)	9/287 (3.1%)	HR 0.92 (0.36 to 2.40)	2 fewer per 1000 (from 20 fewer to 42 more)	⊕◯◯◯ VERY LOW	–
Fatal and non-fatal stroke												
1 [a]	randomized trials	serious [b]	not serious	not serious	very serious [c]	none	8/283 (2.8%)	7/287 (2.4%)	HR 1.19 (0.43 to 3.29)	5 more per 1000 (from 14 fewer to 54 more)	⊕◯◯◯ VERY LOW	–
All-cause mortality												
1 [a]	randomized trials	serious [b]	not serious	not serious	very serious [c]	none	8/283 (2.8%)	7/287 (2.4%)	HR 1.23 (0.45 to 3.39)	6 more per 1000 (from 13 fewer to 56 more)	⊕◯◯◯ VERY LOW	–

CI: Confidence interval; HR: Hazard Ratio

Explanations

a. When the outcome is informed by 1 study in the network meta-analysis, we decided to use the data of the direct comparison of this study (COPE 2013*(69)*).

b. The study was judged to be at high risk of bias in the domain of blinding of participants and personnel.

c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower end of the 95% CI crossed this threshold, suggesting that there may be important harm and benefit.

Table 65 Evidence profile 5z: Calcium channel blocker (CCB) compared to non-calcium channel blocker for individuals with hypertension and established cardiovascular disease (defined through patient history or investigations)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	non-CCB	Relative (95% CI)	Absolute (95% CI)		
Source												
Jeffers 2017*(70)*												
All-cause mortality (follow up >6 months)												
5	randomized trials	very serious [a]	not serious	not serious	serious [b,c]	none	2403/21 668 (11.1%)	3127/25 207 (12.4%)	RR 0.95 (0.90 to 1.01)	6 fewer per 1000 (from 12 fewer to 1 more)	⊕◯◯◯ VERY LOW	CRITICAL
Cardiovascular mortality (follow up >6 months)												
5	randomized trials	very serious [a]	not serious	not serious	not serious [c]	none	1194/21 668 (5.5%)	1519/27 207 (5.6%)	RR 0.97 (0.89 to 1.06)	2 fewer per 1000 (from 6 fewer to 3 more)	⊕⊕◯◯ LOW	CRITICAL
Major cardiovascular events (myocardial infarction, congestive heart failure, stroke, cardiovascular mortality) (follow up >6 months)												
4	randomized trials	very serious [d]	not serious	not serious	serious [c,e]	none	2173/10 461 (20.8%)	2805/13 898 (20.2%)	RR 1.04 (0.98 to 1.10)	8 more per 1000 (from 4 fewer to 20 more)	⊕◯◯◯ VERY LOW	CRITICAL
Myocardial infarction (follow up >6 months)												
4	randomized trials	very serious [d]	not serious	not serious	not serious [c]	none	1229/21 533 (5.7%)	1427/25 019 (5.7%)	RR 1.05 (0.97 to 1.15)	3 more per 1000 (from 2 fewer to 9 more)	⊕⊕◯◯ LOW	IMPORTANT
Stroke (follow up >6 months)												
4	randomized trials	very serious [a]	not serious	not serious	not serious [c]	none	642/21 533 (3.0%)	911/25 019 (3.6%)	RR 0.89 (0.79 to 1.00)	4 fewer per 1000 (from 8 fewer to 0 fewer)	⊕⊕◯◯ LOW	IMPORTANT
Congestive heart failure (follow up >6 months)												
2	randomized trials	serious [f]	serious [g]	not serious	not serious [c]	none	898/9438 (9.5%)	1008/12 888 (7.8%)	RR 1.22 (1.09 to 1.35)	17 more per 1000 (from 7 more to 27 more)	⊕⊕◯◯ LOW	IMPORTANT
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Systolic BP												
4	randomized trials	very serious [h]	not serious	not serious	not serious	none			–	MD 0.32 mmHg higher (0.13 lower to 0.76 higher)	⊕⊕◯◯ LOW	–
Diastolic BP												
4	randomized trials	very serious [h]	not serious	not serious	not serious	none			–	MD 0.12 mmHg lower (0.38 lower to 0.13 higher)	⊕⊕◯◯ LOW	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. Two of the five trials were open labeled; three had missing data. The review was of low quality, did not perform a risk of bias assessment. Post hoc analysis of data.
b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.
c. The patients in the amlodipine arm of the ALLHAT trial were double counted by the review when calculating the effect estimate. The 95% CI would have been wider if the review had not counted ALLHAT amlodipine arm twice.
d. Two of the four trials were open labeled; had missing data. The review was of low quality, did not perform a risk of bias assessment. Post hoc analysis of data.
e. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.
f. The dominant trial had missing data. The review was of low quality, did not perform a risk of bias assessment. Post hoc analysis of data.
g. The point estimates vary importantly with regards to direction and magnitude of effect, statistical test for heterogeneity was not reported.
h. The review did not provide risk of bias assessment however some of the included studies were high/unclear risk of bias in the domain of blinding and incomplete outcome data.

Table 66 Evidence profile 5aa: Calcium channel blocker (CCB) compared to non-calcium channel blocker for individuals with hypertension and previous stroke

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	non-CCB	Relative (95% CI)	Absolute (95% CI)		
Source												
Jeffers 2017*(70)*												
All-cause death (follow up >6 months)												
3	randomized trials	serious [a]	not serious	not serious	serious [b,c]	none	505/3377 (15.0%)	630/3826 (16.5%)	RR 0.93 (0.82 to 1.05)	12 fewer per 1000 (from 30 fewer to 8 more)	⊕⊕◯◯ LOW	–
Cardiovascular death (follow up >6 months)												
2	randomized trials	serious [a]	not serious	not serious	serious [c,d]	none	212/2682 (7.9%)	270/3116 (8.7%)	RR 0.91 (0.74 to 1.11)	8 fewer per 1000 (from 23 fewer to 10 more)	⊕⊕◯◯ LOW	–
Major cardiovascular events (follow up >6 months)												
3	randomized trials	serious [e]	serious [f]	not serious	serious [c,d]	none	670/3377 (19.8%)	773/3826 (20.2%)	RR 1.00 (0.90 to 1.11)	0 fewer per 1000 (from 20 fewer to 22 more)	⊕◯◯◯ VERY LOW	–
Myocardial infarction (follow up >6 months)												
2	randomized trials	serious [e]	not serious	not serious	serious [c,d]	none	164/2682 (6.1%)	208/3116 (6.7%)	RR 0.92 (0.73 to 1.15)	5 fewer per 1000 (from 18 fewer to 10 more)	⊕⊕◯◯ LOW	–
Stroke (follow up >6 months)												
4	randomized trials	serious [g]	not serious	not serious	serious [b,c]	none	441/4878 (9.0%)	519/5339 (9.7%)	RR 0.94 (0.82 to 1.07)	6 fewer per 1000 (from 17 fewer to 7 more)	⊕⊕◯◯ LOW	–
Congestive heart failure (follow up >6 months)												
2	randomized trials	serious [e]	not serious	not serious	serious [c,h]	none	188/2682 (7.0%)	191/3116 (6.1%)	RR 1.18 (0.94 to 1.49)	11 more per 1000 (from 4 fewer to 30 more)	⊕⊕◯◯ LOW	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse effects – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Systolic BP (follow up >6 months)												
3	randomized trials	serious [g]	not serious	not serious	not serious	none	3377	3826	–	MD 0.95 mmHg lower (2.03 lower to 0.13 higher)	⊕⊕⊕◯ MODERATE	–
Diastolic BP (follow up more than 6 months)												
3	randomized trials	serious [g]	not serious	not serious	not serious	none	3377	3826	-	MD 1.1 mmHg lower (1.7 lower to 0.51 lower)	⊕⊕⊕◯ MODERATE	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The review does not provide weight of the included studies and does not perform risk of bias assessment. However ASCOT 2005 was judged by another review (Wiysonge 2017*(62)*) to be at unclear risk of bias in the domain of incomplete outcome data..

b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.

c. The patients in the amlodipine arm of the ALLHAT trial were double counted by the review when calculating the effect estimate. The 95% CI would have been wider if the review had not counted ALLHAT amlodipine arm twice.

d. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower end of the 95% CI crossed this threshold, suggesting that there may be important harm and benefit.

e. The review does not provide weight of the included studies and does not perform risk of bias assessment. However ASCOT 2005 was judged by another review (Wiysonge 2017*(62)*) to be at unclear risk of bias in the domain of incomplete outcome data. In addition, 2 of the included studies are at high or unclear risk of bias in the domain of blinding.

f. One of the point estimates vary importantly with regards to direction and magnitude of effect, statistical test for heterogeneity was not reported. The weight of the included studies was not reported.

g. The review does not provide weight of the included studies and does not perform risk of bias assessment. However ASCOT 2005 was judged by another review (Wiysonge 2017*(62)*) to be at unclear risk of bias in the domain of incomplete outcome data. In addition, 3 of the included studies are at high or unclear risk of bias in the domain of blinding.

h. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

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?

Systematic review for desirable and undesirable effects

Evidence was considered in respect of the following components (Table 67) to determine 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 in adults with hypertension requiring pharmacological treatment (Table 68–Table 71).

Table 67 Components for PICO question 6

Population	Intervention	Comparison	Outcome	Subgroup
Adult men and women >18 years old with primary HTN requiring pharmacological treatment	Monotherapy of BB, CCB, diuretics, ACEi, or ARB	Combinations of BB, CCB, diuretics, ACEi, or ARB	- death (all-cause mortality) - cardiovascular death (death from mi, sudden cardiac death or stroke) - stroke - myocardial infarction - end-stage renal disease - cognitive impairment/ dementia - heart failure events - adverse effects - BP reduction and control (if data on CVD events are absent)	Based on different effect modifiers such as: - estimated cardiovascular risk - pre-existing CAD - stroke - diabetes - age - sex - chronic kidney disease - race/ethnicity - level of baseline BP

Table 68 Evidence profile 6a: Combination therapy compared to monotherapy for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination therapy	Monotherapy	Relative (95% CI)	Absolute (95% CI)		
Source												
Garjon 2020*(71)*; NICE evidence review*(72)*												
Total mortality (follow up of at least 1 year)												
3	randomized trials	serious [a]	not serious	serious [b]	very serious [c]	none	1/233 (0.4%)	1/335 (0.3%)	RR 1.35 (0.08 to 21.72)	1 more per 1000 (from 3 fewer to 62 more)	⊕◯◯◯ VERY LOW	–
Serious adverse events (follow up of at least 1 year)[de]												
3	randomized trials	serious [a]	not serious	serious [b]	very serious [f]	none	28/233 (12.0%)	59/335 (17.6%)	RR 0.77 (0.31 to 1.92)	41 fewer per 1000 (from 122 fewer to 162 more)	⊕◯◯◯ VERY LOW	–
Cardiovascular events (follow up of at least 1 year)[g]												
3	randomized trials	serious [a]	not serious	serious [b]	very serious [c]	none	2/233 (0.9%)	3/335 (0.9%)	RR 0.98 (0.22 to 4.41)	0 fewer per 1000 (from 7 fewer to 31 more)	⊕◯◯◯ VERY LOW	–
Cardiovascular mortality (follow up of at least 1 year)												
3	randomized trials	serious [a]	not serious	serious [b]	very serious [h]	none	0/233 (0.0%)	0/335 (0.0%)	NE		⊕◯◯◯ VERY LOW	–
Withdrawal due to adverse events (follow up of at least 1 year)[ij]												
3	randomized trials	serious [a]	not serious	serious [b]	very serious [f]	none	24/233 (10.3%)	43/335 (12.8%)	RR 0.85 (0.53 to 1.35)	19 fewer per 1000 (from 60 fewer to 45 more)	⊕◯◯◯ VERY LOW	–
Systolic BP change from baseline at end of 1 year[kl]												
3	randomized trials	serious [a]	not serious	serious [b]	serious [m]	none	224	324	–	MD 2.06 mmHg lower (5.39 lower to 1.27 higher)	⊕◯◯◯ VERY LOW	–
Diastolic BP change from baseline at end of 1 year[no]												
2	randomized trials	serious [a]	not serious	serious [b]	not serious	none	169	274	–	MD **0.12 mmHg lower** (1.21 lower to 0.96 higher)	⊕⊕◯◯ LOW	–
Change in creatinine clearance at 12 months												
1	randomized trials	serious [p]	not serious	serious [q]	not serious	none	237	244	–	MD **0.7 ml/min higher** (1.19 lower to 2.59 higher)	⊕⊕◯◯ LOW	–
Change in serum creatinine at 12 months												
1	randomized trials	not serious	not serious	serious [q]	not serious	none	232	225	–	MD **2.3 µmol/L higher** (0.7 higher to 3.9 higher)	⊕⊕⊕◯ MODERATE	–
Dizziness (hypotension) (follow up of at least 1 year)												
1	randomized trials	serious [p]	not serious	serious [r]	very serious [f]	none	3/244 (1.2%)	5/237 (2.1%)	**RR 0.58** (0.14 to 2.41)	**9 fewer per 1000** (from 18 fewer to 30 more)	⊕◯◯◯ VERY LOW	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End–stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The review made the judgment of high risk of bias and downgraded risk of bias one level because all data came from a subgroup of participants not predefined in the original study. PREMIER study which has significant weight of the pooled effect estimates (between 23 and 50% of the weight) was judged at high risk of bias in the domain of incomplete outcome data.

b. The two trials that have most of the weight of the pooled estimate (>70%) were in patients with diabetes. We downgraded indirectness one level as this population is not representative of the general population with HTN.

c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

d. No statistically significant difference in the RR of adverse events between men and women. The RR is 1.25 with CI of [0.52,3] in women. The RR is 0.75 with CI of [0.45,1.24] in men.

e. Subgroup analysis showed that RR for adverse events in patients with diabetes is 0.62 with CI of [0.24, 1.64]. The RR of adverse events in patients without diabetes is 3.14 with CI of [0.34, 29.4].

f. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be important benefit and harm.

g. Subgroup analysis showed that the RR for cardiovascular events in patients with diabetes is 0.62 with CI [0.1,3.95]. The RR for cardiovascular events in patients without diabetes is 3.14 with CI [0.13, 75.69].

h. There was no events rate and it did not meet the optimal information size.

i. No statistically significant difference in the RR of withdrawal due to adverse events between men and women. The RR is 1.27 in women with CI of [0.43,3.73]. The RR is 0.83 in men with CI of [0.42,1.66].

j. Subgroup analysis showed RR for the outcome of withdrawal due to adverse events in patients with diabetes of 0.81 with CI [0.49,1.35] and RR for the outcome of withdrawal due to adverse events in patients without diabetes of 1.05 with CI [0.32, 3.45].

k. Subgroup analysis based on gender showed mean difference in SBP from baseline at end of 1 year was 1.74 with CI [-2.1, 5.58] in women and mean difference in SBP from baseline at end of 1 year was -1.03 with CI of [-3.25, 1.19] in men.

l. Subgroup analysis showed that the mean difference in systolic BP in patients with diabetes is -2.54 with CI of [-8.27,3.19] and the mean difference in systolic BP in patients without diabetes is -2.33 with CI of [-7.28,2.62].

m. The confidence interval crossed the lower limit of 5 mmHg. Judgment to be reviewed with the panel.

n. Subgroup analysis base on gender showed mean difference in DBP from baseline at end of 1 year was 0.47 with CI [-1.96, 2.9] in women and mean difference in DBP from baseline at end of 1 year was -0.77 with CI [-2.08, 0.54] in men.

o. Subgroup analysis showed that the mean difference in diastolic BP in patients with diabetes is -0.39 with CI of [-1.56,0.78] and the mean difference in diastolic BP in patients without diabetes is 1.45 with CI of [-1.4,4.3].

p. The included PREMIER study was judged to be at high risk of bias in the domain of incomplete outcome data.

q. Serum creatinine and creatinine clearance are surrogate markers for ESKD. We downgraded one level for indirectness.

r. The included trial was in patients with diabetes. We downgraded indirectness one level as this population is not representative of the general population with HTN.

Table 69 Evidence profile 6b: Dual agents (ACEi/ARB and CCB) compared to single agent (ACEi/ARB only) for patients with hypertension and chronic kidney disease

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	dual agents (ACEi/ARB and CCB)	single agent (ACEi/ARB only)	Relative (95% CI)	Absolute (95% CI)		
Source												
Huang 2016*(73)*												
End-stage kidney disease (follow up of 21 to 48 months)												
3	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	15/88 (17.0%)	25/101 (24.8%)	RR 0.84 (0.52 to 1.33)	40 fewer per 1000 (from 119 fewer to 82 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Cardiovascular events (follow up of 24 to 66 months)[c]												
3	randomized trials	serious [d]	not serious	not serious	very serious [b]	none	5/194 (2.6%)	10/208 (4.8%)	RR 0.58 (0.21 to 1.63)	20 fewer per 1000 (from 38 fewer to 30 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Changes in SBP (follow up of 3 to 66 months)[c]												
6	randomized trials	serious [e]	not serious	not serious	not serious	none	283	290	–	MD 4.46 mmHg lower (6.95 lower to 1.97 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Changes in DBP (follow up of 3 to 66 months)[c]												
6	randomized trials	serious [e]	serious [f]	not serious	not serious	none	283	290	–	MD 1.28 mmHg lower (3.18 lower to 0.62 higher)	⊕⊕◯◯ LOW	IMPORTANT
Adverse events (follow up of 12 to 66 months)[c]												
4	randomized trials	serious [g]	not serious	not serious	very serious [b]	none	39/210 (18.6%)	44/222 (19.8%)	RR 1.05 (0.72 to 1.53)	10 more per 1000 (from 55 fewer to 105 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Glomerular filtration rate (follow up of 3 to 48 months)[c]												
8	randomized trials	serious [h]	serious [i]	serious [j]	not serious	none	172	188	–	MD 0.32 ml/min lower (1.53 lower to 0.89 higher)	⊕◯◯◯ VERY LOW	–
All-cause mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												

–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The two trials that have most of the weight of the pooled estimate (>90% of the weight) were judged to be at high risk of bias in the domains of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be important benefit and harm.

c. The review states: "Three trials recruited only diabetes patients. Our findings for cardiovascular events and all secondary outcomes except SBP were consistent with the overall results."

d. The two trials that have most of the weight of the pooled estimate (>85% of the weight) were judged to be at high risk of bias in the domains of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

e. The three trials that have most of the weight of the pooled estimate (>80% of the weight) were judged to be at high risk of bias in the domains of allocation concealment, blinding of participants and personnel, blinding of outcome assessment and selective reporting.

f. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (81%).

g. The three trials that have most of the weight of the pooled estimate (>80% of the weight) were judged to be at high risk of bias in the domains of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

h. The four trials that have most of the weight of the pooled estimate (>70% of the weight) were judged to be at high risk of bias in the domains of allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.

i. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (61%).

j. The outcome of interest is end-stage kidney disease. The change in GFR is surrogate marker. We downgraded indirectness one level.

Table 70 Evidence profile 6c: Calcium channel blocker (CCB) + angiotensin receptor blocker (ARB) at standard-dose compared to high-dose calcium channel blocker (CCB) for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CCB + ARB at standard-dose	High-dose CCB	Relative (95% CI)	Absolute (95% CI)		
Source												
He 2017*(74)*												
Total adverse events (duration of 6 to 48 weeks)[ab]												
5	randomized trials	serious [c]	not serious	not serious	not serious [d]	none	–	582/1122 (51.9%) [e]	RR 0.84 (0.74 to 0.95)	83 fewer per 1000 (from 135 fewer to 26 fewer)	⊕⊕⊕◯ MODERATE	–
Discontinuation due to adverse events (duration of 6 to 48 weeks)[ab]												
4	randomized trials	serious [c]	not serious	not serious	very serious [f]	none	–	114/1122 (10.2%) [e]	RR 0.32 (0.15 to 0.60)	69 fewer per 1000 (from 86 fewer to 41 fewer)	⊕◯◯◯ VERY LOW	–
Cough [ab]												
2	randomized trials	serious [c]	not serious	not serious	very serious [g]	none	–	–	RR 1.45 (0.24 to 8.63)	1 fewer per 1000 (from 9 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	–
Dizziness[ab]												
4	randomized trials	serious [c]	not serious	not serious	very serious [g]	none	–	5/255 (2.0%) [e]	RR 0.99 (0.33 to 2.99)	0 fewer per 1000 (from 13 fewer to 39 more)	⊕◯◯◯ VERY LOW	–
Hyperkalaemia[ab]												
2	randomized trials	serious [c]	not serious	not serious	very serious [g]	none	–	–	RR 2.14 (0.71 to 6.45)	2 fewer per 1000 (from 6 fewer to 1 fewer)	⊕◯◯◯ VERY LOW	–
Dyspnea[ab]												
3	randomized trials	serious [c]	not serious	not serious	very serious [g]	none	–	–	RR 2.99 (0.48 to 18.79)	3 fewer per 1000 (from 19 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	–
Systolic BP (duration of 6 to 48 weeks)[h]												
12	randomized trials	serious [c]	not serious	not serious	not serious	none	–	–	–	MD 2.52 mmHg lower (3.76 lower to 1.28 lower)	⊕⊕⊕◯ MODERATE	–
Diastolic BP (duration of 6 to 48 weeks)[h]												
12	randomized trials	serious [c]	serious [i]	not serious	not serious	none	–	–	–	MD 2.07 mmHg lower (3.73 lower to 0.42 lower)	⊕⊕◯◯ LOW	–

BP control rate (duration of 6 to 48 weeks)[j]												
7	randomized trials	serious [c]	not serious	not serious	not serious	none	–	–	RR 1.17 (1.08 to 1.26)	1 fewer per 1000 (from 1 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	–
All-cause mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The total number of events and the total number of patients was not reported in the review.
b. The review reports that the duration of trials was between 6-8 weeks but one study was 48 weeks.
c. All included studies were judged at high risk of bias.
d. Decision to be checked with the panel if the CI crosses the MID.
e. SR doesn't provide baseline risk so it was abstracted from the largest primary studies reported in the systematic review.
f. The extreme of CI will lead to different decisions.
g. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more.
h. Total number of participants is 2823.
i. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (89.8%).
j. Total number of participants is 2527.

Table 71 Evidence profile 6d: Dual renin-angiotensin-aldosterone inhibitor (RAASi) compared to RAASi monotherapy for non-dialysis chronic kidney disease stages 3–5

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dual RAASi inhibitor	RAASi monotherapy	Relative (95% CI)	Absolute (95% CI)		
Source												
post hoc Ontarget*(75)* (Tobe 2011)												
Chronic dialysis or doubling of creatinine (followed until a primary event occurred or until the end of the study (median, 56 months))												
1 [a]	randomized trials	not serious	not serious	not serious	serious [b]	none	64/1871 (3.4%)	92/3752 (2.5%)	HR 1.40 (1.02 to 1.93)	10 more per 1000 (from 0 fewer to 22 more)	⊕⊕⊕◯ MODERATE	–
Chronic dialysis (followed until a primary event occurred or until the end of the study (median, 56 months))												
1 [a]	randomized trials	not serious	not serious	not serious	serious [b]	none	28/1871 (1.5%)	44/3752 (1.2%)	HR 1.28 (0.80 to 2.06)	3 more per 1000 (from 2 fewer to 12 more)	⊕⊕⊕◯ MODERATE	–
Doubling of creatinine (followed until a primary event occurred or until the end of the study (median, 56 months))												
1 [a]	randomized trials	not serious	not serious	not serious	serious [b]	none	47/1871 (2.5%)	63/3752 (1.7%)	HR 1.50 (1.03 to 2.19)	8 more per 1000 (from 0 fewer to 20 more)	⊕⊕⊕◯ MODERATE	–
Primary cardiovascular outcome (followed until a primary event occurred or until the end of the study (median, 56 months))												
1 [a]	randomized trials	not serious	not serious	not serious	serious [c]	none	423/1871 (22.6%)	858/3752 (22.9%)	HR 0.99 (0.88 to 1.12)	2 fewer per 1000 (from 24 fewer to 24 more)	⊕⊕⊕◯ MODERATE	–
Cardiovascular death (followed until a primary event occurred or until the end of the study (median, 56 months))												
1 [a]	randomized trials	not serious	not serious	not serious	serious [c]	none	216/1871 (11.5%)	431/3752 (11.5%)	HR 1.01 (0.86 to 1.19)	1 more per 1000 (from 15 fewer to 20 more)	⊕⊕⊕◯ MODERATE	–
All-cause death (followed until a primary event occurred or until the end of the study (median, 56 months))												
1 [a]	randomized trials	not serious	not serious	not serious	serious [c]	none	345/1871 (18.4%)	662/3752 (17.6%)	HR 1.05 (0.93 to 1.20)	8 more per 1000 (from 11 fewer to 31 more)	⊕⊕⊕◯ MODERATE	–
Acute dialysis (followed until a primary event occurred or until the end of the study (median, 56 months))												
1 [a]	randomized trials	not serious	not serious	not serious	serious [b]	none	17/1871 (0.9%)	19/3752 (0.5%)	HR 1.81 (0.94 to 3.49)	4 more per 1000 (from 0 fewer to 12 more)	⊕⊕⊕◯ MODERATE	–
Hyperkalaemia >5.5 mmol/L (followed until a primary event occurred or until the end of the study (median, 56 months))												
1 [a]	randomized trials	not serious	not serious	not serious	not serious	none	169/1871 (9.0%)	1211/3752 (32.3%)	HR 1.64 (1.34 to 2.01)	150 more per 1000 (from 84 more to 220 more)	⊕⊕⊕⊕ HIGH	–
Hyperkalaemia >6.5 mmol/L (followed until a primary event occurred or until the end of the study (median, 56 months))												
1 [a]	randomized trials	not serious	not serious	not serious	serious [b]	none	10/1871 (0.5%)	7/3752 (0.2%)	HR 2.87 (1.09 to 7.53)	3 more per 1000 (from 0 fewer to 12 more)	⊕⊕⊕◯ MODERATE	–
Syncope												
1 [a]	randomized trials	not serious	not serious	not serious	serious [d,e]	none	5/1871 (0.3%)	4/3752 (0.1%)	HR 2.51 (0.67 to 9.32)	2 more per 1000 (from 0 fewer to 9 more)	⊕⊕⊕◯ MODERATE	–

Hypotension												
1 [a]	randomized trials	not serious	not serious	not serious	not serious	none	83/1871 (4.4%)	99/3752 (2.6%)	HR 1.68 (1.26 to 2.24)	18 more per 1000 (from 7 more to 32 more)	⊕⊕⊕⊕ HIGH	–
Cough												
1 [a]	randomized trials	not serious	not serious	not serious	not serious	none	83/1871 (4.4%)	90/3752 (2.4%)	HR 1.85 (1.38 to 2.48)	20 more per 1000 (from 9 more to 34 more)	⊕⊕⊕⊕ HIGH	–
Diarrhoea												
1 [a]	randomized trials	not serious	not serious	not serious	very serious [e]	none	16/1871 (0.9%)	6/3752 (0.2%)	HR 5.35 (2.10 to 13.60)	7 more per 1000 (from 2 more to 20 more)	⊕⊕◯◯ LOW	–
Total discontinuations												
1 [a]	randomized trials	not serious	not serious	not serious	not serious	none	626/1871 (33.5%)	1043/3752 (27.8%)	HR 1.20 (1.11 to 1.31)	46 more per 1000 (from 25 more to 69 more)	⊕⊕⊕⊕ HIGH	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction and control – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; HR: Hazard Ratio

Explanations

a. When the number of studies providing direct comparison in the network meta-analysis (Zhang 2020) is 1, we use the data of the study rather than NMA.

b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

c. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower end of the 95% CI crossed this threshold, suggesting that there may be important harm and harm.

d. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more.

e. There is a low events rate.

PICO question 7: In adults with hypertension requiring pharmacological treatment, which 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?

Systematic review for desirable and undesirable effects

Evidence was considered in respect of the following components (Table 72) to determine which 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 in adults with hypertension requiring pharmacological treatment (Table 73–Table 77).

Table 72 Components for PICO question 7

Population	Intervention	Comparison	Outcome	Subgroup
Adult men and women >18 years old with primary HTN requiring pharmacological treatment	Combination therapy of two or more drugs (BB, CCB, diuretics, ACEi, or ARB)	Different combinations of two or more drugs (BB, CCB, diuretics, ACEi, or ARB)	Death (all-cause mortality) - CVD death (death from MI, sudden cardiac death or stroke) - stroke - myocardial infarction - end-stage renal disease - cognitive impairment/ dementia - heart failure events - adverse effects - BP reduction and control (if data on CVD events are absent)	Based on different effect modifiers such as: - estimated cardiovascular risk - pre-existing CAD - stroke - diabetes - age - sex - chronic kidney disease - race/ethnicity - level of baseline BP

Table 73 Evidence profile 7a: Renin-angiotensin-aldosterone system inhibitor (RAASi) + calcium channel blocker (CCB) compared to RAASi + diuretic for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi + CCB	RAASi + diuretic	Relative (95% CI)	Absolute (95% CI)		
Source												
Lu 2017*(76)*												
All-cause mortality (mean follow-up of 2.9 years)												
2	randomized trials	serious [a]	not serious	not serious	serious [b]	none	300/8312 (3.6%)	338/8335 (4.1%)	RR 0.89 (0.76 to 1.04)	4 fewer per 1000 (from 10 fewer to 2 more)	⊕⊕◯◯ LOW	CRITICAL
Cardiovascular events (mean follow-up of 2.9 years)												
2	randomized trials	serious [c]	not serious	not serious	not serious	none	668/8312 (8.0%)	814/8335 (9.8%)	RR 0.82 (0.75 to 0.91)	18 fewer per 1000 (from 24 fewer to 9 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Stroke (mean follow-up of 2.9 years)												
2	randomized trials	serious [d]	not serious	not serious	not serious	none	175/8312 (2.1%)	199/8335 (2.4%)	RR 0.88 (0.72 to 1.08)	3 fewer per 1000 (from 7 fewer to 2 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Withdrawal due to adverse events (mean follow-up of 2.9 years)												
15	randomized trials	serious [e]	not serious	not serious	not serious	none	917/10 433 (8.8%)	1062/10 489 (10.1%)	RR 0.87 (0.80 to 0.94)	13 fewer per 1000 (from 20 fewer to 6 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Systolic BP (mean follow-up of 2.9 years)												
26	randomized trials	serious [f]	serious [g]	not serious	not serious	none	10 922	11 001	–	MD 0.45 mmhg lower (0.87 lower to 0.03 lower)	⊕⊕◯◯ LOW	IMPORTANT
Diastolic BP (mean follow–up of 2.9 years)												
26	randomized trials	serious [h]	serious [i]	not serious	not serious	none	10 922	11 001	–	MD 0.43 mmHg lower (0.7 lower to 0.16 lower)	⊕⊕◯◯ LOW	IMPORTANT
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The trial that has most of the weight of the pooled estimate (77.5%) was judged at unclear risk of bias in the domain of random sequence generation.

b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.

c. We downgraded one level because the ACCOMPLISH 2008 trial that has most of the weight of the pooled estimate (83.4%) was judged at unclear risk of bias in the domain of random sequence generation. In addition, the COLM 2014 trial was judged at high risk of Blinding of participants and personnel (performance bias), Open-label, however with blinded end point. The weight of the COLM 2014 of the pooled effect estimate is 16.6%.

d. We downgraded one level because the ACCOMPLISH 2008 trial that has most of the weight of the pooled estimate (66.8%) was judged at unclear risk of bias in the domain of random sequence generation. In addition, the COLM 2014 trial was judged at high risk of Blinding of participants and personnel (performance bias), Open-label, however with blinded end point. The weight of the COLM 2014 of the pooled effect estimates is 33.2%.

e. The trial that has most of the weight of the pooled estimate (77.6%) was judged at unclear risk of bias in the domain of random sequence generation. In addition, the COLM 2014 trial was judged at high risk of Blinding of participants and personnel (performance bias), Open-label, however with blinded end point. The weight of the COLM 2014 of the pooled effect estimates is 12.3%.

f. We downgraded one level because the ACCOMPLISH 2008 trial that has most of the weight of the pooled estimate (40.5%) was judged at unclear risk of bias in the domain of random sequence generation. In addition, the COLM 2014 trial was judged at high risk of Blinding of participants and personnel (performance bias), Open-label, however with blinded end point. The weight of the COLM 2014 of the pooled effect estimates is 21%.

g. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (74%).

h. We downgraded one level because the ACCOMPLISH 2008 trial that has most of the weight of the pooled estimate (47.5%) was judged at unclear risk of bias in the domain of random sequence generation. In addition, the COLM 2014 trial was judged at high risk of Blinding of participants and personnel (performance bias), Open-label, however with blinded end point. The weight of the COLM 2014 of the pooled effect estimates is 16.6%.

i. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (76%).

Table 74 Evidence profile 7b: Renin-angiotensin-aldosterone system inhibitor (RAASi) + calcium channel blocker (CCB) compared to CCB + diuretic for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi + CCB	CCB + diuretic	Relative (95% CI)	Absolute (95% CI)		
Source												
Lu 2017*(76)*												
All-cause mortality (mean follow-up of 2.9 years)												
2	randomized trials	serious [a]	not serious	not serious	serious [b]	none	105/7876 (1.3%)	120/7870 (1.5%)	RR 0.87 (0.67 to 1.13)	2 fewer per 1000 (from 5 fewer to 2 more)	⊕⊕◯◯ LOW	CRITICAL
Stroke (mean follow-up of 2.9 years)												
2	randomized trials	serious [a]	not serious	not serious	serious [c]	none	158/7876 (2.0%)	129/7870 (1.6%)	RR 1.22 (0.97 to 1.54)	4 more per 1000 (from 0 fewer to 9 more)	⊕⊕◯◯ LOW	IMPORTANT
Withdrawal due to adverse events (mean follow-up of 2.9 years)												
4	randomized trials	serious [d]	not serious	not serious	not serious	none	49/2468 (2.0%)	75/2414 (3.1%)	RR 0.63 (0.45 to 0.90)	11 fewer per 1000 (from 17 fewer to 3 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Systolic BP (mean follow-up of 2.9 years)												
6	randomized trials	serious [a]	serious [e]	not serious	not serious	none	9319	9207	–	MD 0.12 mmHg lower (0.45 lower to 0.21 higher)	⊕⊕◯◯ LOW	IMPORTANT
Diastolic BP (mean follow-up of 2.9 years)												
6	randomized trials	serious [a]	serious [f]	not serious	not serious	none	9319	9207	–	MD 0.03 mmHg lower (0.27 lower to 0.22 higher)	⊕⊕◯◯ LOW	IMPORTANT
Cardiovascular mortality – not reported												
-	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
-	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
-	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
-	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
-	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The trial that has most of the weight of the pooled estimate (>75%) was judged at unclear risk of bias in the domains of allocation concealment and incomplete outcome data.

b. The confidence interval crosses the line of no effect, and suggests the possibility of an important benefit and a small harm. The extremes of the confidence interval will lead to different decisions.

c. The confidence interval crosses the line of no effect, and suggests the possibility of a small benefit and an important harm. The extremes of the confidence interval will lead to different decisions.

d. The trial that has a significant weight of the pooled estimate (26.4%) was judged at unclear risk of bias in the domains of random sequence generation, allocation concealment, and blinding of outcome assessment. In addition the COPE 2011 trial which has the weight of 14.6% was judged at high risk of bias in the domain of blinding of participants and personnel.
e. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (81%).
f. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (90%).

Table 75 Evidence profile 7c: Renin-angiotensin-aldosterone system inhibitor (RAASi) + calcium channel blocker (CCB) compared to CCB + beta-blocker (BB) for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi + CCB	CCB + BB	Relative (95% CI)	Absolute (95% CI)		
Source												
Lu 2017*(76)*												
Withdrawal due to adverse events (mean follow-up of 2.9 years)												
3	randomized trials	serious [a]	not serious	not serious	serious [b]	none	33/1451 (2.3%)	45/1437 (3.1%)	RR 0.74 (0.48 to 1.15)	8 fewer per 1000 (from 16 fewer to 5 more)	⊕⊕◯◯ LOW	IMPORTANT
Systolic BP (mean follow-up of 2.9 years)												
5	randomized trials	serious [c]	not serious	not serious [d]	not serious	none	1614	1537	-	MD 0.24 mmHg higher (0.61 lower to 1.08 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
Diastolic BP (mean follow-up of 2.9 years)												
5	randomized trials	serious [c]	not serious	not serious [d]	not serious	none	1614	1537	-	MD 0.06 mmHg higher (0.48 lower to 0.6 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
All-cause mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The trial that has most of the weight of the pooled estimate (61.7%) was judged at high risk of bias in the domain of blinding of participants and personnel and unclear risk of bias in the domains random sequence generation, allocation concealment and selective reporting.

b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit

c. The two trials that have most of the weight of the pooled estimate (>80%) were judged at high risk of bias in the domain of blinding of participants and personnel and unclear risk of bias in the domains random sequence generation and allocation concealment.

d. Studies used different doses for CCB and some were individualized per patient which may affect the generalizability of the results on other patients.

Table 76 Evidence profile 7d: Renin-angiotensin-aldosterone system inhibitor (RAASi) + calcium channel blocker (CCB) compared to beta-blocker (BB) + diuretic for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi + CCB	BB + diuretic	Relative (95% CI)	Absolute (95% CI)		
Source												
Lu 2017*(76)*												
Withdrawal due to adverse events (mean follow-up of 2.9 years)												
3	randomized trials	serious [a]	not serious	not serious	serious [b]	none	11/348 (3.2%)	15/348 (4.3%)	RR 0.74 (0.35 to 1.58)	11 fewer per 1000 (from 28 fewer to 25 more)	⊕⊕◯◯ LOW	–
Systolic BP (mean follow-up of 2.9 years)												
3	randomized trials	serious [a]	serious [c]	not serious	not serious [d]	none	333	324	–	MD 1.5 mmHg higher (0.81 lower to 3.82 higher)	⊕⊕◯◯ LOW	–
Diastolic BP (mean follow–up of 2.9 years)												
3	randomized trials	serious [a]	not serious	not serious	not serious [d]	none	333	324	–	MD 1.17 mmHg higher (0.22 lower to 2.56 higher)	⊕⊕⊕◯ MODERATE	–
All–cause mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. The trial that has most of the weight of the pooled estimate (>65%) was judged at unclear risk of bias in the domains of allocation concealment and blinding of outcome assessment.

b. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower and upper ends of the 95% CI crossed this threshold, suggesting that there may be an important benefit and harm.

c. The point estimates vary importantly with regards to direction and magnitude of effect, and some of the CIs do not overlap. There is high statistical heterogeneity, as reflected by the I-squared (86%).

d. The CI does not cross the MID threshold for individual patients (judgment to be checked with the panel).

Table 77 Evidence profile 7e: Renin-angiotensin-aldosterone system inhibitor (RAASi) + calcium channel blocker (CCB) compared to renin angiotensin system (RAASi) inhibitor + diuretics for individuals with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAASi + CCB	RAASi + diuretics	Relative (95% CI)	Absolute (95% CI)		
Source												
Cheng 2016*(77)*												
eGFR/creatinine clearance[ab]												
9	randomized trials	serious [c]	not serious [d]	serious [e]	not serious	none	6329	6370	–	SMD 0.36 SD higher (0.2 higher to 0.53 higher)	⨁⨁◯◯ LOW	–
Serum creatinine												
9	randomized trials	serious [f]	not serious	serious [g]	not serious	none	2932	2942	–	MD 0.05 mg/dL lower (0.07 lower to 0.03 lower)	⨁⨁◯◯ LOW	–
All-cause mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP reduction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; SMD: Standardised mean difference; MD: Mean difference

Explanations

a. Subgroup analysis based on ethnicity showed consistent evidence in both Asian and non-Asian populations. For Asian patients std mean difference was 0.4, CI (0.24, 0.56). For non-Asian population std mean difference was 0.33, CI (0.04, 0.62).

b. The authors used std mean difference because some studies used mL/min and the others used mL/min/1.73m2 as the unit of measurement.

c. The four trials that have significant weight of the pooled estimate (>45%) were judged at high risk of bias in the domains of allocation concealment and randomization.

d. Even though there is statistical inconsistency, all estimates suggest the same direction of effect and only one of the CIs does not overlap with the others.
e. We downgraded indirectness because the change in eGFR/creatinine clearance is a surrogate marker for ESKD.
f. The trials that have significant weight of the pooled estimate (29%) were judged at high risk of bias in the domains of allocation concealment and randomization.
g. We downgraded indirectness because the change in serum creatinine is a surrogate marker for ESKD.

Evidence to decision for PICO questions 4–7

Values and preferences

Shahaj, 2019*(12)*: 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) were identified 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).

Fragasso, 2012*(6)*: 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.

Resources required

Luthy, 2008*(78)*: Norvasc (amlodipine), which is a CCB), is one of the most commonly prescribed medications in the treatment of HTN. Even though amlodipine is now available as a generic, the cost is still significant. When taken every day as prescribed, patients without prescription benefits must pay, on average, USD 64.00 for a 30-day supply of the 10-mg dose (Drugs.com). The cost of amlodipine per pill equals about USD 2.13 (Drugstore.com, 2007). Coupled with the fact that patients with HTN commonly take many prescription drugs for other comorbidities, such as diabetes and hyperlipidemia, consideration of a patient's economic situation while paying for many prescription drugs can be a major factor in determining patient compliance with the prescribed regimen.

Luthy, 2008*(78)*: Thiazide: Hydrochlorothiazide (HCTZ), a thiazide diuretic, is a cost-efficient, first-line option when initiating treatment for HTN. For the commonly prescribed dose of 12.5–50 mg per day, patients can expect to pay about USD 12.00 for a 30-day supply, approximately USD 0.40 per pill.

Luthy, 2008*(78)*: Captopril, an ACEi, is the most cost-efficient option for the adjunct treatment of HTN, costing USD 12.00 for a one-month supply of 50 mg tablets. The cost per pill equals about USD 0.22. While a captopril–HCTZ combination pill is available, the economic burden is similar to Norvasc at USD 2.00 per tablet. However, when administered separately, HCTZ and captopril are an effective and cost-efficient alternative to the popularly prescribed Norvasc.

Gu, 2015*(8)*: Because medication costs are usually paid out-of-pocket by patients with HTN, local and national governments do not directly feel the impact of high drug costs. However, high drug costs likely have a big impact at the level of individual households and therefore indirectly on the national economy. Additionally, Chinese patients are reluctant to pay out of pocket for antihypertensive medications, and studies of Chinese patients have shown that out-of-pocket drug costs reduce medication adherence among patients with HTN and CVD.

Bramlage, 2009*(79)*: Drug costs were highest for patients being treated and being persistent with ARB therapy (EUR 326.16), closely followed by patients persistent with CCB treatment (EUR 234.63) and patients switching between classes (up to EUR 268.07)

Chrysant, 2008*(80)*: The primary endpoint was the cost of therapy, which declined by 33% and in this study resulted in a saving of USD 19.00 per patient/month after switching from a multiple-pill combination to a single-pill combination.

Cost effectiveness

Modelling studies were assessed for their overall quality by evaluating the structure of the model, appropriateness of the assumptions, sources of model inputs and sensitivity analyses. A formal quality assessment tool was not used. Most studies used a state transition model (Markov) model with variable cycle lengths (1 month to 1 year, variable time horizons (1 year to lifetime/95 years of age), almost all were from a payer/health system perspective. The majority did not use a systematic review to identify most appropriate model inputs; the method for choosing studies for utility inputs was seldom described. Most studies included one-way sensitivity analyses, some performed multi-way and probabilistic sensitivity analyses. An assumption that significantly influenced outcomes for Q 6–8 were that single-pill combinations increase compliance, resulting in lower BP.*(14, 16)* Costs due to adverse events were included by some,*(20)* not others. Although model and assumptions were extensively described in some studies,*(8)* inputs were not based on a systematic review, leading to the possibility of bias in choosing inputs. The generalizability of these studies is very limited due to contextual differences.

The cost effectiveness of low-cost essential antihypertensive medicines for HTN control in China was assessed in a modelling study by Gu and colleagues.*(8)* Based on a state transition model, cost effectiveness of treatment for stage 1 (BP 140–159/90–99 mmHg) and stage 2 (BP ≥160/100 mmHg) were calculated. One-way and probabilistic sensitivity analyses were used. Treating hypertensive adults with prior cardiovascular disease for secondary prevention was found to be cost saving in the main simulation and 100% of probabilistic simulation results. Treatment of all other patient cohorts, including sensitivity analyses, was found to be cost effective at a willingness to pay threshold of USD 50 000.

Data from 4500 US adults with HTN from the community quality index study were modelled to estimate cost and cost-effectiveness to payers of consistently providing the basic elements of BP management (visits and medications associated with recommended care)*(81)*. They compared "usual care" with "improved care" (100% provision of recommended care processes). Some inputs were obtained from systematic review/meta-analysis of RCTs from the literature. Improved care cost USD 170 per person with mild HTN, USD 801 for moderate HTN and USD 850 for severe HTN annually.

Park and colleagues*(82)* conducted a systematic review of cost-effectiveness analyses of antihypertensive medicines. They included 76 studies in their review. These included 14 studies comparing medicines with no treatment, 16 studies comparing medicines with conventional treatment, 28 studies comparing medicines between medicine classes, 13 studies comparing medicines within medicine class and 11 studies comparing different combination therapies. Quality assessment was performed using the Quality of Health Economic Studies scale. Twenty-one studies scored >91, 10 studies scored <70 on a 100-point scale. 80% of reported funding was from industry, these studies provided positive evidence for the companies that sponsored them. The majority (41) of the studies were from Europe, 16 were from North America and 19 were from other countries. ARBs were the most frequently evaluated drug class (62 times either as intervention or comparator in 42 studies); the most frequently included ARB were losartan (20 studies) and irbesartan (15 studies). CCBs were the next most frequent class evaluated (32 times in 31 studies); amlodipine was the most common drug in this class (19 studies). Next in frequency were ACEi (28 studies) and beta-blockers (BBs) (25 times in 23 studies) (most common atenolol in 16 studies). Thiazide diuretics were evaluated 17 times, hydrochlorothiazide was most frequent (10 studies).

All antihypertensives were cost effective compared with no treatment (dominant USD 19 945/QALY). ARBs were more cost effective than CCBs in nine comparisons, whereas CCBs were more cost effective than ARBs in two comparisons. As previously noted, most of these were funded by industry and the results favoured the sponsor. ARBs were more cost effective than ACEis or BBs in all comparisons. Variations in study results are likely due to variations in study settings, analytic models, variations in cost and publication bias.

Using a state transition model, Tajeu and colleagues*(83)* study cost effectiveness of antihypertensive medications in white and black men and women in the United States. The simulation study population was modelled using demographic and clinical data from an ongoing observational study of risk factors associated with stroke (REGARDS study). Health states considered included stroke, coronary heart disease, heart failure, chronic kidney disease and end-stage kidney disease. The model included white and black adults with HTN and ≥45 years of age. Antihypertensive treatment was found to be cost effective with ICER/QALY of more than USD 10 000 for all groups.

In an economic analysis funded by Novartis of patients with chronic kidney disease treated with benazepril, the authors used data from the AIPRI study for transition probabilities in model inputs.*(84)* The rationale for selecting the other input sources was unclear. Benazepril was found to be dominant in the long run (7-year time horizon)

For low- and middle-income countries, Gad and colleagues conducted a cost-effectiveness analysis in the Ghanaian setting. Using a state transition model with six health states, one-year cycle length and a lifetime time horizon, they compared cost effectiveness of different classes of medications (ACEi, ARB, BB, CCB, thiazide-like diuretics, no intervention). All classes were found to be more effective than no intervention, thiazide diuretics were the most cost effective (GHS 276/DALY). CCBs were more effective and more expensive. ACEis, ARBs and BBs were less effective than thiazide diuretics. The results were maintained in sensitivity analyses.

Ekwunife and colleagues conducted a cost-utility analysis of antihypertensive medications in Nigeria.*(85)* They constructed a Markov model, with six health states, a cycle length of one year and a time horizon of 30 years, of patients stratified by cardiovascular risk. Probabilistic sensitivity analysis was conducted and results presented as cost-effectiveness acceptability frontiers. They found thiazide diuretics to be the most cost-effective option across cardiovascular risk groups, followed by CCBs, at a willingness to pay of at least USD 2000/QALY. The results were robust and insensitive to parameter alterations.

An industry-sponsored (Solvay Pharmaceuticals) cost utility analysis*(86)* comparing eprosartan with enalapril and nitrendipine found eprosartan to be cost effective at a willingness to pay threshold of EUR 30 000. Another industry-funded study (Pfizer)*(87)* from Taiwan comparing amlodipine and valsartan in a Markov model with a five-year time horizon and one-year cycle length did not include a systematic literature review for its inputs. This study found amlodipine to be dominant; the results were robust in sensitivity analyses.

A non-industry funded study in the Polish setting comparing ACEis and ARBs*(88)* found ACEis to provide improved outcomes compared to ARBs; the annual gain from change in treatment from ARB to ACEi for the Polish population was 830 QALY and 1018 life-years gained.

An economic evaluation sponsored by Daiichi-Sankyo in China*(14)* was very well designed. Model inputs for drug efficacy and other outcomes were based on a systematic review and MA/NMA. However, the process for selecting references for utilities was not clear, leaving the possibility of bias in choosing inputs for utilities. They constructed a Markov model with five health states, analysed from a payer perspective over a 20-year time horizon. Olmesartan/amlodipine single-pill combination was dominant, compared with Olmesartan and amlodipine multiple-pill combination and Valsartan/amlodipine single-pill combination.

Similarly, a single-pill combination of indapamide and amlodipine compared with multiple-pill combination therapy*(16)* was found to be cost saving in a Polish setting. The authors used a Markov model with eight health states, cycle length of one month, over a lifetime time horizon. These results were consistent in sensitivity analyses.

Lung et al compared cost effectiveness of a triple-pill strategy (consisting of amlodipine, telmisartan and chlorthalidone) with usual care based on data from a trial (TRIUMPH) incorporated into a discrete-time simulation model (10-year time horizon). They extrapolated the data for the proportion of individuals reaching BP target to disability adjusted life years (DALYs) averted. Modelling inputs were from the literature – no systematic review, no rational for the references chosen. Their results indicated a cost of USD 2842.79 per DALY averted over a 10-year period. Findings were robust to variations in all key-parameters.

Equity

Meiqari, 2019*(11)*: Although beta-blockers (BBs), loop diuretics, and statins might be available in some community health systems (CHSs) in low-income countries, health insurance does not cover them at commune level. Patients seeking medication in the public sector face two problems. First, there is fragmentation and lack of consistency in prescribing medication between different levels. For example, doctors at higher levels may prescribe newer-generation medication that is not covered by health insurance at CHSs; if the patients want to keep using the same medication, they have to return to the higher-level facilities or purchase them at their own expense. While most basic HTN medication is cheap, newer generations may be less affordable. Second, current regulations, according to JAHR 2014,*(89)* allow provincial facilities to dispense HTN medication for short periods. These short periods of prescribed medication require more visits to health facilities, which increases the treatment cost for patients, reduces their compliance, and decreases the odds of HTN control.

Helmer, 2018*(44)*: Much research has been done to assess the best hypertensive treatment approaches in black patients; however, there is a paucity of high-quality data. Although there are no published data assessing clinical outcomes specifically in black patients using ACEi or ARB monotherapy, evidence from subgroup analyses and cohort studies suggests that these patients may have higher rates of cardiovascular and cerebrovascular outcomes compared with those taking other antihypertensives

Tajeu, 2017*(83)*: Increasing treatment rates and adherence among black adults may allow third-party payers and healthcare providers to align themselves with the National Academies of the Sciences – Health and Medicine Division's commitment to address racial disparities in care.

Indirect evidence, Buckley, 2016*(90)*: A unique and complex array of factors may influence African American beliefs about HTN. First, African Americans may have impaired access to health care and education, although one study suggested this gap has significantly decreased due to public health initiatives. Many African American participants expressed a distrust of the health care system and the belief that they received different or worse care than patients of other ethnicities. These beliefs may lead African Americans to choose alternative views on HTN. Alternatively, African Americans may have chosen to entrust friends, family, and community members with their medical care independently of their views on the medical system. Prior research has suggested that the immediate community significantly influences the beliefs and behaviours of African Americans.

Alsabbagh, 2014*(91)*: Higher socioeconomic status (SES) was associated with a lower risk of nonadherence in 31 of 40 cohorts (77.5%), with no difference in one cohort, and with a higher risk of nonadherence in eight cohorts. Overall, the pooled adjusted risk estimate indicated a lower risk of nonadherence among individuals with a higher SES: 0.89 (95% CI 0.87–0.92; P 0.001). In health care research, low SES has proven to be a strong predictor of health care utilization, morbidity, and premature death. Nonadherence to chronic medications, such as antihypertensives (AHTs), can also be determined by low SES.

Lewis, 2012*(92)*: Patients who experience fewer logistic barriers (i.e. difficulty obtaining clinic appointments and health insurance) have better medication adherence rates.

Acceptability

Shahaj, 2019*(12)*: Deliberately choosing to avoid or reduce medication (intentional nonadherence), rather than forgetfulness, was a theme in some studies. For some patients, symptoms acted as a guide for the seriousness of their HTN and guided their medication use; for example, they stopped treatment if symptoms disappeared. Some were guided by stress, using medication to manage worry or anxiety rather than HTN. Fear of dependency affected the amount of medication they took.

Gwadry, 2013*(93)*: A significant improvement in medication adherence was found with increasing age and provider visits, and reductions in multiple-dosing regimens and medication class.

Alghurair, 2012*(94)*: Twelve surveys studied poor adherence caused by therapy-related barriers. The most commonly identified barriers from this dimension were occurrence of side-effects, complexity of drug regimens, and interference of medication taking with daily routines.

Wetzel, 2004*(95)*: An inverse association between dose regimen and compliance is shown, with mean compliance percentages being higher on a once-daily regimen (85– 94%) compared to a twice-daily regimen (75–88%).

Feasibility

Angeli, 2012*(96)*: 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.

Outcome utilities

Please refer to Table 78 below.

Table 78 Utilities per outcome for PICO questions 4–7

Outcomes	Utility	Systematic review (SR)	Primary studies reported in the SR
Hypertension	0.96	Ren 2020*(14)*	Li 2015*(15)*
	0.98 (range: 1–0.95)	Kawalec 2015*(16)*	Burstrom 2001*(17)*, Sullivan 2008*(18)*, Wang 2008*(19)*
Type 2 diabetes mellitus	0.985	Gad 2020*(20)*	Salomon 2012*(21)*
MACE	Time NR: All CVD excluding stroke: 0.73 (95%CI: 0.69–0.76)	Kawalec 2015*(16)*	Lunde, 2013*(22)*
Stroke	First month after onset: 0.55	Ren 2020*(14)*	Li 2015*(15)*
	Days 1–3: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4–28: 0.88	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.65	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.70 (95%CI: 0.67-0.73)	Kawalec 2015*(16)*	Golicki 2010*(24)*
MI	First month after onset: 0.60	Ren 2020*(14)*	Li 2015*(15)*
	Days 1–3: 0.58	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4–28: 0.94	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.70	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: Disability weight 0.124	Gad 2020*(20)*	Salomon 2012*(21)*
ESRD	ESRD pre-dialysis: 0.73 (95% CI: 0.62–1)	Cooper 2020*(25)*	Jesky 2016*(26)*
	Hemodialysis: 0.75 (SD: 0.25)	Cooper 2020*(25)*	Briggs 2016*(27)*
Cognitive impairment/dementia	Patient rating: 0.85 (SD: 0.19)	NA	Rowen 2015*(28)*
	Patient rating: mild dementia 0.79 (SD: 0.22) moderate dementia: 0.72 (0.23)	NA	Orgeta 2015*(29)*
	Carer rating: mild dementia 0.63 (SD: 0.27) moderate dementia: 0.52 (0.27)	NA	Orgeta 2015*(29)*
HF events	First month after onset: 0.63	Ren 2020*(14)*	Li 2015*(15)*
	Chronic state: 0.73	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.79	Gad 2020*(20)*	Salomon 2012*(21)*
Adverse events	Common: 0.88	Gu 2015*(8)*	Clinical Judgement
	Infrequent: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*

PICO question 8: In adults with hypertension requiring pharmacological intervention, is the use of a single-pill combination of antihypertensive drugs associated with improved outcomes?

Systematic review for desirable and undesirable effects

Evidence was considered in respect of the following components (Table 79) to determine whether the use of a single-pill combination of antihypertensive drugs is associated with improved outcomes in adults with hypertension requiring pharmacological intervention (Table 80).

Table 79 Components for PICO question 8

Population	Intervention	Comparison	Outcomes	Subgroup
Adult men and women with hypertension requiring pharmacological intervention	Single-pill combination of antihypertensive drugs – five classes (any two or more from the five)	Pharmacological interventions that do not involve use of single-pill combinations	- death (all-cause mortality) - cardiovascular death (death from MI sudden cardiac death or stroke) - stroke - myocardial infarction - end-stage kidney disease - heart failure events. - adverse effects - patient satisfaction - adherence - BP level/change - number of antihypertensive medications	Based on different effect modifiers such as: - estimated cardiovascular risk (pre-existing CAD) - stroke - diabetes - age - sex - chronic kidney disease - race/ethnicity - level of baseline BP

Table 80 Evidence profile 8a: Single-pill combination compared to no single-pill combination in patients with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single-pill combination	No single-pill combination	Relative (95% CI)	Absolute (95% CI)		
Adverse events (follow up: range 4 weeks to 4 months; assessed with: Mallat, 2016*(97)*)												
4	randomized trials	serious [a]	not serious	not serious	serious [b]	none	56/124 (45.2%)	51/125 (40.8%)	RR 1.13 (0.85 to 1.50)	53 more per 1000 (from 61 fewer to 204 more)	⊕⊕◯◯ LOW	–
Blood pressure control (number of patients achieving BP target at the end of the trial) (follow up: range 4 weeks to 12 weeks; assessed with: Mallat, 2016*(97)*)												
3	randomized trials	serious [a]	not serious	not serious	serious [b]	none	42/51 (82.4%)	38/52 (73.1%)	RR 1.11 (0.92 to 1.33)	80 more per 1000 (from 58 fewer to 241 more)	⊕⊕◯◯ LOW	–
Mean systolic BP (follow up: range 4 weeks to 4 months; assessed with: Mallat, 2016*(97)*)												
3	randomized trials	serious [a]	not serious	not serious	not serious [c]	none	62	62	-	MD 0.81 mmHg lower (3.25 lower to 1.64 higher)	⊕⊕⊕◯ MODERATE	–
Adherence (medicine possession ratio (MPR): the number of days of medication supply within the prescription refill interval. A patient is adherent if MPR >0.8) (follow up: range 6 months to 13 months; assessed with: Kawalec, 2018*(98)*)												
2	observational studies	not serious [d]	not serious	not serious	not serious	none	1073/1840 (58.3%)	376/927 (40.6%)	OR 1.47 (1.23 to 1.74)	95 more per 1000 (from 51 more to 137 more)	⊕⊕◯◯ LOW	–
Adherence (proportion of days covered (PDC): the percentage of days during which a medication was taken by patients, on the basis of the proportion of days covered. A patient is adherent if PDC>0.80) (follow up: median 12 months; assessed with: Kawalec, 2018*(98)*)												
2	observational studies	not serious [d]	not serious [e]	not serious	not serious	none	3162/7077 (44.7%)	2329/10 060 (23.2%)	OR 2.25 (1.09 to 4.64)	172 more per 1000 (from 16 more to 351 more)	⊕⊕◯◯ LOW	–
Adherence (medicine possession ratio (MPR): the number of days of medication supply within the prescription refill interval). (follow up: range 6 months to 5 years; assessed with: Kawalec, 2018*(98)*)												
4	observational studies	not serious [d]	not serious [f]	not serious	not serious	none	386 723	203 571	-	MD 13.2 days higher (8.9 higher to 17.2 higher)	⊕⊕◯◯ LOW	
Adherence (Proportion of days covered (PDC): the percentage of days during which a medication was taken by patients, on the basis of the proportion of days covered. (follow up: mean 12 months; assessed with: Kawalec, 2018*(98)*)												
1	observational studies	not serious [d]	not serious	not serious	not serious	none	4864	7748	–	MD 29 days higher (27.8 higher to 30.2 higher)	⊕⊕◯◯ LOW	–
Medication persistence (based on prescription refill interval) (follow up: 6 months; assessed with: Kawalec, 2018*(98)*)												

2	observational studies	not serious [d]	not serious [e]	not serious	not serious	none	227 996/384 104 (59.4%)	80 489/197 936 (40.7%)	OR 3.82 (1.20 to 12.21) [g]	317 more per 1000 (from 45 more to 487 more)	⊕⊕◯◯ LOW	–
Medication persistence (based on prescription refill interval) (follow up: 12 months; assessed with: Kawalec, 2018*(98)*)												
4	observational studies	not serious [d]	not serious	not serious	not serious	none	6898/11 465 (60.2%)	1950/9115 (21.4%)	OR 3.24 (1.30 to 8.08) [g]	255 more per 1000 (from 47 more to 473 more)	⊕⊕◯◯ LOW	–
All-cause mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Patient satisfaction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Number of antihypertensive medications – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; MD: Mean difference; OR: Odds ratio

Explanations

a. All included trials had unclear or high risk of bias.

b. The confidence interval suggests the possibility of important benefit and important harm.

c. The confidence interval is precise around the line of no effect, suggesting the possibility of trivial benefit and trivial harm.

d. According to the authors' analysis, risk of bias was not associated with study results.

e. The CIs of the studies do not overlap; however, this is due to the very precise estimates, which are not qualitatively different.

f. Although there is statistical heterogeneity, all studies are consistent with regards to the direction of the effect and thus we decided to not rate down further.

g. Another systematic review (Du, 2018[(99)]) also reports this outcome, but without providing a specific time point. The RR was 1.84 (95% CI, 1.00 to 3.39).

Evidence to decision for PICO question 8

Values and preferences

Krousel, 2005*(100)*: Simplification of dosing regimens as an approach to increased medication adherence has been examined in several studies. This approach draws on the principle that adherence relies on patients remembering to take medication rather than an unwillingness to tolerate side-effects or a lack of motivation for compliance. Two out of three systematic reviews reported that simplifying dosing regimens results in significant improvements in medication adherence, ranging from 6–20%.

Resources required

Indirect evidence in PICOs 4–7 Resources section.

Cost effectiveness

An economic evaluation sponsored by Daiichi-Sankyo in China*(14)* was very well designed Model inputs for drug efficacy and other outcomes were based on a systematic review and MA/NMA. However, the process for selecting references for utilities was not clear, leaving the possibility of bias in choosing inputs for utilities. They constructed a Markov model with five health states, analysed from a payer perspective over a 20-year time horizon. Olmesartan/amlodipine single-pill combination was dominant compared with olmesartan and amlodipine multiple-pill combination and valsartan/amlodipine single-pill combination.

Equity

No research evidence.

Acceptability

Angeli, 2012*(96)*: compliance with medications was modestly higher with single-pill combinations compared with multiple-pill combinations (odds ratio [OR] 1.21; 95% CI 1.03, 1.43). However, single-pill combinations did not result in a significantly longer persistence with treatment when compared with multiple-pill combinations (OR 1.54; 95% CI 0.95, 2.49).

Feasibility

No research evidence.

Outcome utilities

Please refer to Table 81 below.

Table 81 Utilities per outcome for PICO question 8

Outcomes	Utility	Systematic review	Primary studies reported in the SR
Hypertension	0.96	Ren 2020*(14)*	Li 2015*(15)*
	0.98 (range: 1 – 0.95)	Kawalec 2015*(16)*	Burstrom 2001*(17)*, Sullivan 2008*(18)*, Wang 2008*(19)*
Type 2 diabetes mellitus	0.985	Gad 2020*(20)*	Salomon 2012*(21)*
MACE	Time NR: All CVD excluding stroke: 0.73 (95%CI: 0.69–0.76)	Kawalec 2015*(16)*	Lunde, 2013*(22)*
Stroke	First month after onset: 0.55	Ren 2020*(14)*	Li 2015*(15)*
	Days 1-3: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4-28: 0.88	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.65	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.70 (95%CI: 0.67-0.73)	Kawalec 2015*(16)*	Golicki 2010*(24)*
MI	First month after onset: 0.60	Ren 2020*(14)*	Li 2015*(15)*
	Days 1-3: 0.58	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4-28: 0.94	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.70	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: Disability weight 0.124	Gad 2020*(20)*	Salomon 2012*(21)*
ESRD	ESRD pre-dialysis: 0.73 (95% CI: 0.62–1)	Cooper 2020*(25)*	Jesky 2016*(26)*
	Hemodialysis: 0.75 (SD: 0.25)	Cooper 2020*(25)*	Briggs 2016*(27)*
Cognitive impairment/dementia	Patient rating: 0.85 (SD: 0.19)	NA	Rowen 2015*(28)*
	Patient rating:. mild dementia 0.79 (SD: 0.22) moderate dementia: 0.72 (0.23)	NA	Orgeta 2015*(29)*
	Carer rating: mild dementia 0.63 (SD: 0.27) moderate dementia: 0.52 (0.27)	NA	Orgeta 2015*(29)*
HF events	First month after onset: 0.63	Ren 2020*(14)*	Li 2015*(15)*
	Chronic state: 0.73	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.79	Gad 2020*(20)*	Salomon 2012*(21)*
Adverse events	Common: 0.88	Gu 2015*(8)*	Clinical Judgement
	Infrequent: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*

PICO question 9: What target blood pressure should pharmacological treatment aim to achieve?

Systematic review for desirable and undesirable effects

Evidence was considered in respect of the following components (Table 82) to determine that target blood pressure (BP) pharmacologic treatment should aim to achieve (Table 83–Table 90).

Table 82 Components for PICO question 9

Population	Intervention	Comparison	Outcome	Subgroup

Adult men and women (>18 years old) with primary hypertension requiring pharmacological treatment	Specific systolic and diastolic BP targets:
	- Systolic (mm Hg):
	  - <120, <130, <140, <150
	- Diastolic (mm Hg):
	  - <70, <80`, <90
		Systolic or diastolic BP targets that are higher than the intervention targets	- death (all-cause mortality)
			- cardiovascular death (death from MI, sudden cardiac death or stroke)
			- stroke
			- myocardial infarction
			- end-stage kidney disease
			- cognitive impairment/ dementia
			- heart failure events
			- adverse effects
				Based on different effect modifiers such as:
				- estimated cardiovascular risk
				- pre-existing CAD
				- stroke
				- diabetes
				- age
				- sex
				- chronic kidney disease
				- race/ethnicity
				- level of baseline BP

Table 83 Evidence profile 9a: A systolic blood pressure target <130 mm/Hg compared to a systolic blood pressure target <140 mm/Hg in patients with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SBP target <130 mm/Hg	SBP target <140 mm/Hg	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: mean 3.5 years; assessed with: Arguedas, 2020*(101)*)												
3	randomized trials	serious [a]	not serious	not serious	serious [b]	none	111/2151 (5.2%)	106/2164 (4.9%)	RR 1.06 (0.82 to 1.37)	3 more per 1000 (from 9 fewer to 18 more)	⨁⨁◯◯ LOW	–
Cardiovascular mortality (follow up: mean 3.5 years; assessed with: Arguedas, 2020*(101)*)												
2	randomized trials	serious [a]	not serious	not serious	serious [c]	none	36/1593 (2.3%)	41/1611 (2.5%)	RR 0.87 (0.56 to 1.34)	3 fewer per 1000 (from 11 fewer to 9 more)	⨁⨁◯◯ LOW	–
Total serious adverse events (Total serious morbidity and mortality) (assessed with: Arguedas, 2020*(101)*)												
2	randomized trials	serious [a]	not serious	not serious	serious [d]	none	46/1593 (2.9%)	341/1611 (21.2%)	RR 1.05 (0.92 to 1.20)	11 more per 1000 (from 17 fewer to 42 more)	⨁⨁◯◯ LOW	–
Myocardial infarction (follow up: mean 3.5 years; assessed with: Arguedas, 2020*(101)*)												
3	randomized trials	serious [a]	not serious	not serious	not serious [e]	none	40/2151 (1.9%)	46/2164 (2.1%)	RR 0.88 (0.58 to 1.33)	3 fewer per 1000 (from 9 fewer to 7 more)	⨁⨁⨁◯ MODERATE	–
Stroke (follow up: mean 3.5 years; assessed with: Arguedas, 2020*(101)*)												
2	randomized trials	serious [a]	not serious	not serious	serious [f]	none	126/1593 (7.9%)	153/1611 (9.5%)	RR 0.82 (0.65 to 1.02)	17 fewer per 1000 (from 33 fewer to 2 more)	⨁⨁◯◯ LOW	–
Heart failure (follow up: mean 3.5 years; assessed with: Arguedas, 2020*(101)*)												
2	randomized trials	serious [a]	not serious	not serious	serious [d]	none	3/650 (0.5%)	7/245 (2.9%)	RR 0.42 (0.11 to 1.63)	17 fewer per 1000 (from 25 fewer to 18 more)	⨁⨁◯◯ LOW	–
Serious adverse events (follow up: mean 3.5 years; assessed with: Arguedas, 2020*(101)*)												
3	randomized trials	serious [a]	not serious	not serious	not serious [g]	none	81/2151 (3.8%)	49/2164 (2.3%)	RR 1.87 (1.34 to 2.61)	20 more per 1000 (from 8 more to 36 more)	⨁⨁⨁◯ MODERATE	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. All included studies were judged at high risk of bias in at least 1 domain.
b. Using a threshold of 10 per 1000 patients as an important difference, the confidence interval suggests the possibility of a trivial benefit and an important harm.
c. Using a threshold of 10 per 1000 patients as an important difference, the confidence interval suggests the possibility of an important benefit and a trivial harm.
d. The confidence interval crosses the line of no effect and suggests the possibility of important benefit and important harm.
e. Using a threshold of 10 per 1000 patients as an important difference, the confidence interval does not suggest the possibility of an important benefit or an important harm (i.e. the confidence interval is precise around the line of no effect).
f. The confidence interval crosses the line of no effect and suggests the possibility of important benefit and trivial harm.
g. The total number of events is small, but we were unsure of whether to rate down for optimal information size given that the total sample size is >4000 patients.

Table 84 Evidence Profile 9b: A systolic blood pressure target <120 mm/Hg compared to a systolic blood pressure target 130-139 mm/Hg in patients with hypertension who are >65 years old

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SBP target <120 mm/Hg	SBP target 130-139 mm/Hg	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
1	randomized trials	not serious	not serious	not serious	serious [a]	none	73/1317 (5.5%)	107/1319 (8.1%)	RR 0.67 (0.49 to 0.91)	27 fewer per 1000 (from 41 fewer to 7 fewer) [b]	⊕⊕⊕◯ MODERATE	–
Cardiovascular mortality (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
1	randomized trials	not serious	not serious	not serious	serious [c]	none	18/1317 (1.4%)	29/1319 (2.2%)	RR 0.60 (0.33 to 1.09)	9 fewer per 1000 (from 14 fewer to 2 more) [d]	⊕⊕⊕◯ MODERATE	–
Chronic kidney disease (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
1	randomized trials	not serious	not serious	not serious	serious [c]	none	5/1627 (0.3%)	2/1633 (0.1%)	RR 2.45 (0.48 to 12.57)	1 more per 1000 (from 0 fewer to 12 more) [e]	⊕⊕⊕◯ MODERATE	–
Heart failure (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
2	randomized trials	not serious	not serious	not serious [f]	serious [g]	none	[h]	[h]	RR 0.62 (0.46 to 0.83)	16 fewer per 1000 (from 23 fewer to 2 more) [i]	⊕⊕⊕◯ MODERATE	–
Myocardial infarction (follow up: range 12 months to 24 months; assessed with: Murad, 2019*(102)*)												
1	randomized trials	not serious	not serious	not serious	serious [c]	none	37/1317 (2.8%)	53/1319 (4.0%)	RR 0.69 (0.45 to 1.05)	12 fewer per 1000 (from 22 fewer to 2 more) [j]	⊕⊕⊕◯ MODERATE	–
Stroke (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
1	randomized trials	not serious	not serious	not serious	serious [c]	none	18/1317 (1.4%)	29/1319 (2.2%)	RR 0.68 (0.40 to 1.15)	8 fewer per 1000 (from 15 fewer to 3 more) [k]	⊕⊕⊕◯ MODERATE	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. The authors of the SR rated down the certainty of the evidence due to imprecision. They do not provide an explanation but it seems that it is because the OIS is not met.

b. The baseline risk they used was 81 per 1000, based in the control arm of the trial included.

c. The authors rated down the certainty of the evidence two levels due to imprecision, but based on the absolute estimates of effect, we are rating down just once.

d. The baseline risk they used was 22 per 1000, based in the control arm of the trial included..

e. The baseline risk they used was one per 1000, based in the control arm of the trial included..

f. According to the ACC/AHA guidelines, in the description of their evidence regarding patients with heart failure: "In adults with hypertension (SBP 130 mm Hg or DBP 80 mm Hg) and a high risk of CVD, a strong body of evidence supports treatment with antihypertensive medications (see Section 8.1.2) and more intensive rather than less-intensive intervention . In SPRINT, a more intensive intervention that targeted an SBP <120 mm Hg significantly reduced the primary outcome (CVD composite) by about 25% . The incidence of HF, a component of the primary outcome, was also substantially decreased (hazard ratio: 0.62; 95% confidence interval: 0.45–0.84). Meta-analyses of clinical trials have identified a similar beneficial effect of more-intensive BP reduction on the incidence of HF, but the body of information from studies confined to trials that randomly assigned participants to different BP targets is more limited and less compelling".

g. The authors of the systematic review rated down the certainty of the evidence one level due to imprecision. The confidence interval suggests the possibility of a small benefit and a trivial harm.

h. The total number of participants per arm and study is only reported in one of the two studies providing information for this outcome. The total of participants is 2636.
i. They used a baseline risk of 42 per 1000, based on the result on the trial included that reported the information per arm.
j. The baseline risk they used was 40 per 1000, based in the control arm of the trial included.
k. The baseline risk they used was 25 per 1000, based in the control arm of the trial included.

Table 85 Evidence Profile 9c: A systolic blood pressure target <130 mm/Hg compared to a systolic blood pressure target 130-149 mm/Hg in patients with hypertension who are >65 years old

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SBP target <130 mm/Hg	SBP target 130–149 mm/Hg	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
1	randomized trials	not serious	not serious	not serious	very serious [a]	none	37/248 (14.9%)	40/246 (16.3%)	RR 0.83 (0.55 to 1.26)	28 fewer per 1000 (from 73 fewer to 42 more) [b]	⨁⨁◯◯ LOW	–
Cardiovascular mortality (follow up: range 12 months to 24 months; assessed with: Murad, 2019*(102)*)												
1	randomized trials	not serious	not serious	not serious	serious [c]	none	8/248 (3.2%)	17/246 (6.9%)	RR 0.42 (0.18 to 0.98)	40 fewer per 1000 (from 56 fewer to 1 fewer) [d]	⨁⨁⨁◯ MODERATE	–
Myocardial infarction (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
1	randomized trials	not serious	not serious	not serious	very serious [a]	none	5/248 (2.0%)	6/246 (2.4%)	RR 0.77 (0.23 to 2.55)	6 fewer per 1000 (from 18 fewer to 37 more) [e]	⨁⨁◯◯ LOW	–
Stroke (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
1	randomized trials	not serious	not serious	not serious	serious [f]	none	8/248 (3.2%)	17/246 (6.9%)	RR 0.89 (0.62 to 1.27)	7 fewer per 1000 (from 26 fewer to 18 more) [g]	⨁⨁⨁◯ MODERATE	–
Chronic kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Hear failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. The authors rated down the certainty of the evidence two levels due to imprecision. We agree with this judgment based on the absolute estimates of effect that suggest the possibility of an important benefit and an important harm.

b. They used as a baseline risk 163 per 1000 patients, based on the control arm of the included study.

c. The authors rated down for imprecision but did not provide an explanation. It is likely that the optimal information size is not met. In a partially or fully contextualized approach, the 95% CI suggest the possibility of trivial benefit in one extreme and important benefit in the other extreme.

d. They used a baseline risk of 69 per 1000 patients, based on the control arm of the included study.

e. They used a baseline risk of 24 per 1000 patients, based on the control arm of the included study.

f. The authors of the systematic review rated down the certainty of the evidence two levels due to imprecision. Based on the absolute estimates of effect suggesting the possibility of small benefit and small harm, we only rated down one level.

g. We used a baseline risk of 69 per 1000, based on the control arm of the included study.

Table 86 Evidence profile 9d: A systolic blood pressure target <140 mm/Hg compared to a systolic blood pressure target 140–160 mm/Hg in patients with hypertension who are >65 years old

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SBP target <140 mm/Hg	SBP target 140- 160 mm/Hg	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
2	randomized trials	not serious	not serious	not serious [a]	serious [b]	none	78/3260 (2.4%)	72/3839 (1.9%)	RR 1.03 (0.64 to 1.67)	1 more per 1000 (from 6 fewer to 12 more) [c]	⊕⊕⊕◯ MODERATE	–
Cardiovascular mortality (follow up: range 12 months to 24 months; assessed with: Murad, 2019*(102)*)												
2	randomized trials	not serious	not serious	not serious	not serious [d]	none	17/3839 (0.4%)	15/3839 (0.4%)	RR 1.11 (0.55 to 2.23)	0 fewer per 1000 (from 2 fewer to 5 more) [e]	⊕⊕⊕⊕ HIGH	–
Chronic kidney disease												
2	randomized trials	not serious	not serious	not serious	not serious [d]	none	15/2796 (0.5%)	13/2783 (0.5%)	RR 1.11 (0.51 to 2.39)	1 more per 1000 (from 2 fewer to 7 more) [f]	⊕⊕⊕⊕ HIGH	–
Heart failure (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
1	randomized trials	not serious	not serious	not serious	not serious [d]	none	8/2212 (0.4%)	7/2206 (0.3%)	RR 1.14 (0.41 to 3.14)	0 fewer per 1000 (from 2 fewer to 6 more) [g]	⊕⊕⊕⊕ HIGH	–
Myocardial infarction (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
2	randomized trials	not serious	not serious	not serious	not serious [d]	none	11/3839 (0.3%)	10/3839 (0.3%)	RR 1.09 (0.46 to 2.57)	0 fewer per 1000 (from 2 fewer to 6 more) [g]	⊕⊕⊕⊕ HIGH	–
Stroke (follow up: range 12 months to 96 months; assessed with: Murad, 2019*(102)*)												
2	randomized trials	not serious	not serious	not serious	not serious [d]	none	17/3839 (0.4%)	15/3839 (0.4%)	RR 0.90 (0.61 to 1.35)	2 fewer per 1000 (from 7 fewer to 6 more) [h]	⊕⊕⊕⊕ HIGH	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. The ACC/AHA guidelines describe as evidence, "In patients with increased cardiovascular risk [Stable Ischemic heart disease] , reduction of SBP to <130/80 mm Hg has been shown to reduce CVD complications by 25% and all-cause mortality by 27%."

b. The authors rated down the certainty of the evidence two levels. However, the CI suggests the possibility of a trivial benefit and a small harm, and therefore we rated down only one level.

c. They used a baseline risk of 19 per 1000 patients, based on the control arm of the two included studies.

d. The authors rated down the certainty of the evidence two levels. However, the CI is precise around the line of no effect and there is a large sample size included.

e. They used a baseline risk of 4 per 1000 patients, based on the control arm of the two included studies.

f. They used a baseline risk of 5 per 1000, based on the control arm of the two included studies.

g. They used a baseline risk of 3 per 1000 patients, based on the control arm of the included study.

h. We used the numbers reported by the authors of the systematic review. They used a baseline risk of 17 per 1000 patients.

Table 87 Evidence profile 9e: A blood pressure target <140/90 mmHg compared to a blood pressure target <150 to 160/ 95 to 105 mm/Hg in patients with hypertension who are >65 years old

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP target <140/90 mmHg	BP <150 to 160/ 95 to 105 mm/Hg	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 2 years to 4 years; assessed with: Garrison, 2017*(103)*)												
3	randomized trials	serious [a]	serious [b]	not serious	not serious [c]	none	129/4120 (3.1%)	159/4101 (3.9%)	RR 0.81 (0.65 to 1.01)	7 fewer per 1000 (from 14 fewer to 0 fewer)	⊕⊕◯◯ LOW	–
Cardiovascular mortality (follow up: range 2 years to 4 years; assessed with: Garrison, 2017*(103)*)												
3	randomized trials	serious [a]	not serious	not serious	not serious	none	45/4120 (1.1%)	68/4101 (1.7%)	RR 0.66 (0.46 to 0.94)	6 fewer per 1000 (from 9 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	–
Stroke (follow up: range 2 years to 4 years; assessed with: Garrison, 2017*(103)*)												
3	randomized trials	serious [a]	not serious	not serious	not serious [d]	none	81/4120 (2.0%)	101/4101 (2.5%)	RR 0.80 (0.60 to 1.06)	5 fewer per 1000 (from 10 fewer to 1 more)	⊕⊕⊕◯ MODERATE	–
Cardiovascular serious adverse events (follow up: range 2 years to 4 years; assessed with: Garrison, 2017*(103)*)												
3	randomized trials	serious [a]	not serious	not serious	not serious [d]	none	173/4120 (4.2%)	205/4101 (5.0%)	RR 0.84 (0.69 to 1.02)	8 fewer per 1000 (from 15 fewer to 1 more)	⊕⊕⊕◯ MODERATE	–
Serious adverse events (follow up: median 3 years; assessed with: Garrison, 2017*(103)*)												
1	randomized trials	serious [a]	not serious	not serious	not serious [e]	none	80/1534 (5.2%)	87/1545 (5.6%)	RR 1.08 (0.81 to 1.45)	5 more per 1000 (from 11 fewer to 25 more)	⊕⊕⊕◯ MODERATE	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. All included studies were judged at high risk of bias. b. Not all the confidence intervals overlap, the I-squared is 79%, and the p value of the statistical test of heterogeneity is statistically significant.
c. Although the upper bound of the confidence interval crosses the null effect, this is likely to be the result of inconsistency and thus we decided to not rate down further.
d. Although the upper bound of the confidence interval crosses the null effect, the absolute estimate is precise around this line.
e. Although the confidence interval crosses the null effect, the absolute estimate is precise around this line.

Table 88 Evidence profile 9f: A systolic blood pressure target <130 mm/Hg compared to a systolic blood pressure target <140 mm/Hg in patients with ischemic stroke, haemorrhagic stroke, or transient ischemic attack

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SBP target <130 mm/Hg	SBP target <140 mm/Hg	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow up: range 12 months to 44 months; assessed with: Zonneveld, 2018*(5)*)												
3	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	112/1808 (6.2%)	105/1824 (5.8%)	RR 1.08 (0.83 to 1.39)	5 more per 1000 (from 10 fewer to 22 more)	⊕⊕⊕◯ MODERATE	–
Stroke (fatal and non fatal) (follow up: range 12 months to 44 months; assessed with: Zonneveld, 2018*(5)*)												
3	randomized trials	serious [c]	not serious	not serious	not serious [b]	none	119/1808 (6.6%)	153/1824 (8.4%)	RR 0.80 (0.63 to 1.00)	17 fewer per 1000 (from 31 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	
Recurrent stroke over time (follow up: median 44 months; assessed with: Zonneveld, 2018*(5)*)												
1	randomized trials	serious [d]	not serious	not serious	not serious [b]	none	-/1501	-/1519	HR 0.81 (0.64 to 1.03)	-- per 1000 (from -- to --)	⊕⊕⊕◯ MODERATE	–
Major cardiovascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause) (follow up: range 12 months to 44 months; assessed with: Zonneveld, 2018*(5)*)												
3	randomized trials	serious [e]	not serious	not serious	serious [f]	none	162/1808 (9.0%)	197/1824 (10.8%)	RR 0.58 (0.23 to 1.46)	45 fewer per 1000 (from 83 fewer to 50 more)	⊕⊕◯◯ LOW	–
Ischemic stroke (follow up: range 24 months to 44 months; assessed with: Zonneveld, 2018*(5)*)												
2	randomized trials	serious [g]	not serious	not serious	not serious [b]	none	112/1542 (7.3%)	133/1561 (8.5%)	RR 0.86 (0.67 to 1.09)	12 fewer per 1000 (from 28 fewer to 8 more)	⊕⊕⊕◯ MODERATE	–
Hemorrhagic stroke (follow up: range 24 months to 44 months; assessed with: Zonneveld, 2018*(5)*)												
2	randomized trials	serious [h]	not serious	not serious	not serious [h]	none	7/1542 (0.5%)	17/1561 (1.1%)	RR 0.42 (0.17 to 1.02)	6 fewer per 1000 (from 9 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	
Myocardial infarction (follow up: range 12 months to 44 months; assessed with: Zonneveld, 2018*(5)*)												
3	randomized trials	serious [i]	not serious	not serious	not serious [b]	none	37/1808 (2.0%)	42/1824 (2.3%)	RR 0.90 (0.58 to 1.38)	2 fewer per 1000 (from 10 fewer to 9 more)	⊕⊕⊕◯ MODERATE	–
Vascular death (follow up: range 12 months to 44 months; assessed with: Zonneveld, 2018*(5)*)												
2	randomized trials	serious [j]	not serious	not serious	not serious [b]	none	36/1767 (2.0%)	42/1782 (2.4%)	RR 0.87 (0.56 to 1.35)	3 fewer per 1000 (from 10 fewer to 8 more)	⊕⊕⊕◯ MODERATE	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio; HR: Hazard Ratio

Explanations

a. The trial that has most of the weight of the pooled estimate (95.6%) was judged at unclear risk of bias. We rated down one level when also considering that the CI suggests the possibility of a small benefit and a small harm.
b. We did not rate down the certainty of the evidence further due to imprecision. See comment under risk of bias for this outcome.
c. The trial that has most of the weight of the pooled estimate (98.3%) was judged at unclear risk of bias. We rated down one level when also considering the potential imprecision reflected by the upper limit of the CI, which is suggesting that there could be no benefit..
d. The only trial providing information for this outcome was judged at unclear risk of bias. We rated down one level when also considering the potential imprecision reflected by the upper limit of the CI, which is suggesting that there could be no benefit or some harm.
e. The trial that has most of the weight of the pooled estimate (70.5%) was judged at unclear risk of bias..
f. The 95% CI suggests important benefit and important harm. We only rated down one level because we already rated down for risk of bias, although the risk of bias was unclear.
g. The trial that has most of the weight of the pooled estimate (99.4%) was judged at unclear risk of bias. We rated down one level when also considering the potential imprecision reflected by the upper limit of the CI, which is suggesting that there could be a small harm.
h. The trial that has most of the weight of the pooled estimate (89.5%) was judged at unclear risk of bias. We rated down one level when also considering the potential imprecision reflected by the upper limit of the CI, which is suggesting that there could be no benefit..
i. The trial that has most of the weight of the pooled estimate (95.7%) was judged at unclear risk of bias. We rated down one level when also considering the potential imprecision reflected by the upper limit of the CI, which is suggesting that there could be a small harm.
j. The trial that has most of the weight of the pooled estimate (98.1%) was judged at unclear risk of bias. We rated down one level when also considering the potential imprecision reflected by the upper limit of the CI, which is suggesting that there could be a small harm

Table 89 Evidence profile 9g: A blood pressure target <135/85 mm/Hg compared to a blood pressure target <140 to 160/90 to 100 mm/Hg in patients with hypertension and cardiovascular disease

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BP target <135/85 mm/Hg	BP target <140 to 160/90 to 100 mm/Hg	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: mean 3.7 years; assessed with: Saiz, 2017*(104)*)												
6	randomized trials	serious [a]	not serious	not serious	serious [b]	none	373/5456 (6.8%)	294/4339 (6.8%)	RR 1.05 (0.90 to 1.22)	3 more per 1000 (from 7 fewer to 15 more)	⊕⊕◯◯ LOW	–
Cardiovascular mortality (follow up: mean 3.7 years; assessed with: Saiz, 2017*(104)*)												
6	randomized trials	serious [a]	not serious	not serious	not serious [c]	none	169/5456 (3.1%)	137/4339 (3.2%)	RR 0.96 (0.77 to 1.21)	1 fewer per 1000 (from 7 fewer to 7 more)	⊕⊕⊕◯ MODERATE	–
Serious adverse events (follow up: median 3.7 years; assessed with: Saiz, 2017*(104)*)												
6	randomized trials	serious [a]	not serious [d]	not serious	serious [b]	none	966/5456 (17.7%)	805/4339 (18.6%)	RR 1.02 (0.95 to 1.11)	4 more per 1000 (from 9 fewer to 20 more)	⊕⊕◯◯ LOW	–
Cardiovascular events (follow up: mean 3.7 years; assessed with: Saiz, 2017*(104)*)												
6	randomized trials	serious [a]	not serious	not serious	not serious	none	555/5456 (10.2%)	535/4339 (12.3%)	RR 0.87 (0.78 to 0.98)	16 fewer per 1000 (from 27 fewer to 2 fewer)	⊕⊕⊕◯ MODERATE	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cognitive impairment – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. All included studies were judged at high risk of bias in at least 1 domain.
b. The CI suggests the possibility of trivial benefit and small but important harm.
c. Although the 95% CI crosses the line of no effect, the absolute effect is precise around this line.
d. The authors conducted a subgroup analysis based on the method of measurement of the outcome (total SAEs vs subset of total SAEs), but the results were not different between subgroups.

Table 90 Evidence profile 9h: A systolic blood pressure target < 120 (mmHg) compared to a systolic blood pressure target <140 (mmHg) for individuals with hypertension and chronic kidney disease and without diabetes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SBP target <120 (mmHg)	SBP target <140 (mmHg)	Relative (95% CI)	Absolute (95% CI)		
Source												
Cheung, 2017*(105)* (SPRINT-CKD)												
Primary cardiovascular outcome, defined as the composite of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, and death from cardiovascular causes (median follow up 3.3 years)												
1 [a,b,c,d]	randomized trials	serious [e]	not serious	not serious	serious [f]	none	112/1330 (8.4%)	131/1316 (10.0%)	HR 0.81 (0.63 to 1.05)	18 fewer per 1000 (from 36 fewer to 5 more)	⨁⨁◯◯ LOW	–
All-cause death (median follow up 3.3 years)												
1 [g,h,i,j]	randomized trials	not serious	not serious	not serious	serious [k]	none	70/1330 (5.3%)	95/1316 (7.2%)	HR 0.72 (0.53 to 0.99)	20 fewer per 1000 (from 33 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE	–
Main kidney outcome, defined as the composite of a decrease in eGFR of ≥50% from baseline (confirmed by repeat testing ≥90 days later) or the development of ESRD (median follow up 3.3 years)												
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	15/1330 (1.1%)	16/1316 (1.2%)	HR 0.90 (0.44 to 1.83)	1 fewer per 1000 (from 7 fewer to 10 more)	⨁⨁◯◯ LOW	–
Myocardial infarction												
1	randomized trials	serious [e]	not serious	not serious	serious [m]	none	44/1330 (3.3%)	45/1316 (3.4%)	HR 0.94 (0.62 to 1.44)	2 fewer per 1000 (from 13 fewer to 15 more)	⨁⨁◯◯ LOW	
Acute coronary syndrome												
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	15/1330 (1.1%)	11/1316 (0.8%)	HR 1.35 (0.60 to 3.08)	3 more per 1000 (from 3 fewer to 17 more)	⨁⨁◯◯ LOW	–
Stroke												
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	27/1330 (2.0%)	27/1316 (2.1%)	HR 0.99 (0.57 to 1.70)	0 fewer per 1000 (from 9 fewer to 14 more)	⨁⨁◯◯ LOW	–
Heart failure												
1	randomized trials	serious [e]	not serious	not serious	serious [f]	none	41/1330 (3.1%)	52/1316 (4.0%)	HR 0.72 (0.47 to 1.10)	11 fewer per 1000 (from 21 fewer to 4 more)	⨁⨁◯◯ LOW	–
CVD death												
1	randomized trials	not serious	not serious	not serious	serious [n]	none	18/1330 (1.4%)	30/1316 (2.3%)	HR 0.57 (0.31 to 1.02)	10 fewer per 1000 (from 16 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	–
Primary outcome or cardiovascular procedure												
1	randomized trials	serious [e]	not serious	not serious	serious [f]	none	127/1330 (9.5%)	161/1316 (12.2%)	HR 0.81 (0.63 to 1.05)	22 fewer per 1000 (from 43 fewer to 6 more)	⨁⨁◯◯ LOW	–
Incidence of 50% eGFR reduction from baseline												
1	randomized trials	serious [e]	not serious	not serious	serious [o]	none	10/1330 (0.8%)	12/1316 (0.9%)	HR 0.79 (0.34 to 1.83)	2 fewer per 1000 (from 6 fewer to 8 more)	⨁⨁◯◯ LOW	–

Incidence of 40% eGFR reduction from baseline											
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	30/1330 (2.3%)	19/1316 (1.4%)	HR 1.50 (0.85 to 2.68)	7 more per 1000 (from 2 fewer to 24 more)	⊕⊕◯◯ LOW	
Incidence of 30% eGFR reduction from baseline											
1	randomized trials	serious [e]	not serious	not serious	not serious	none	92/1330 (6.9%)	44/1316 (3.3%)	HR 2.03 (1.42 to 2.91)	33 more per 1000 (from 14 more to 61 more)	⊕⊕⊕◯ MODERATE	–
Incidence of 50% eGFR reduction from baseline at 6 months post-randomization											
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	7/1330 (0.5%)	4/1316 (0.3%)	HR 1.65 (0.48 to 5.62)	2 more per 1000 (from 2 fewer to 14 more)	⊕⊕◯◯ LOW	–
Incidence of 40% eGFR reduction from baseline at 6 months post-randomization											
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	15/1330 (1.1%)	14/1316 (1.1%)	HR 1.01 (0.49 to 2.10)	0 fewer per 1000 (from 5 fewer to 12 more)	⊕⊕◯◯ LOW	–
Incidence of 30% eGFR reduction from baseline at 6 months post-randomization											
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	44/1330 (3.3%)	35/1316 (2.7%)	HR 1.19 (0.76 to 1.85)	5 more per 1000 (from 6 fewer to 22 more)	⊕⊕◯◯ LOW	
Primary outcome or all cause death											
1	randomized trials	serious [e]	not serious	not serious	serious [f]	none	152/1330 (11.4%)	179/1316 (13.6%)	HR 0.82 (0.66 to 1.02)	23 fewer per 1000 (from 44 fewer to 3 more)	⊕⊕◯◯ LOW	–
Hypotension											
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	51/1330 (3.8%)	38/1316 (2.9%)	HR 1.34 (0.88 to 2.04)	10 more per 1000 (from 3 fewer to 29 more)	⊕⊕◯◯ LOW	–
Syncope											
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	54/1330 (4.1%)	42/1316 (3.2%)	HR 1.28 (0.86 to 1.92)	9 more per 1000 (from 4 fewer to 28 more)	⊕⊕◯◯ LOW	–
Bradycardia											
1	randomized trials	serious [e]	not serious	not serious	serious [m]	none	37/1330 (2.8%)	40/1316 (3.0%)	HR 0.92 (0.59 to 1.44)	2 fewer per 1000 (from 12 fewer to 13 more)	⊕⊕◯◯ LOW	–
Electrolytes abnormalities											
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	69/1330 (5.2%)	51/1316 (3.9%)	HR 1.35 (0.94 to 1.94)	13 more per 1000 (from 2 fewer to 35 more)	⊕⊕◯◯ LOW	–
Injurious fall											
1	randomized trials	serious [e]	not serious	not serious	serious [m]	none	125/1330 (9.4%)	138/1316 (10.5%)	HR 0.90 (0.71 to 1.15)	10 fewer per 1000 (from 29 fewer to 15 more)	⊕⊕◯◯ LOW	–
Acute kidney failure											
1	randomized trials	serious [e]	not serious	not serious	not serious	none	114/1330 (8.6%)	78/1316 (5.9%)	HR 1.46 (1.10 to 1.95)	26 more per 1000 (from 6 more to 53 more)	⊕⊕⊕◯ MODERATE	–
Serum sodium <130 mmol/l											

1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	49/1330 (3.7%)	35/1316 (2.7%)	HR 1.39 (0.90 to 2.15)	10 more per 1000 (from 3 fewer to 30 more)	⊕⊕◯◯ LOW	–
Serum potassium <3.0 mmol/l												
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	30/1330 (2.3%)	16/1316 (1.2%)	HR 1.87 (1.02 to 3.43)	10 more per 1000 (from 0 fewer to 29 more)	⊕⊕◯◯ LOW	
Serum potassium >5.5 mmol/l												
1	randomized trials	serious [e]	not serious	not serious	serious [p]	none	106/1330 (8.0%)	78/1316 (5.9%)	HR 1.36 (1.01 to 1.82)	20 more per 1000 (from 1 more to 46 more)	⊕⊕◯◯ LOW	–
Orthostatic hypotension without dizziness												
1	randomized trials	serious [e]	not serious	not serious	serious [m]	none	301/1330 (22.6%)	302/1316 (22.9%)	HR 0.99 (0.85 to 1.17)	2 fewer per 1000 (from 31 fewer to 33 more)	⊕⊕◯◯ LOW	–
Orthostatic hypotension with dizziness												
1	randomized trials	serious [e]	not serious	not serious	serious [l]	none	24/1330 (1.8%)	23/1316 (1.7%)	HR 1.04 (0.59 to 1.84)	1 more per 1000 (from 7 fewer to 14 more)	⊕⊕◯◯ LOW	–
Total serious adverse events over the entire duration of follow-up of 3.3 years												
1	randomized trials	serious [e]	not serious	not serious	very serious [m]	none	627/1330 (47.1%)	640/1316 (48.6%)	HR 0.98 (0.87 to 1.09)	7 fewer per 1000 (from 46 fewer to 30 more)	⊕◯◯◯ VERY LOW	–
Cognitive impairment/dementia – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; HR: Hazard Ratio

Explanations

a. Subgroup analysis based on age showed lower primary cardiovascular outcome in the subgroup of patients with age > or = 75 years with HR 0.64 (0.45-0.92) for intensive treatment vs standard treatment. The HR for patients age <75 years was 1.11 (0.74-1.66) for intensive treatment vs standard treatment. However, this analysis is a subgroup analysis of the SPRINT CKD which is a subgroup study of the SPRINT trial.

b. Subgroup analysis based on gender showed lower cardiovascular outcomes in both men and women. The HR for cardiovascular outcomes in women was 0.62 (0.39-0.99) and in men was 0.87 (0.64-1.20) for intensive treatment vs standard treatment. However, this analysis is a subgroup analysis of the SPRINT CKD which is a subgroup study of the SPRINT trial.

c. Subgroup analysis based on ethnicity showed HR for cardiovascular outcomes in black population of 1.02 (0.58-1.81) for intensive treatment vs standard treatment and in nonblack population of 0.77 (0.57-1.03) for intensive treatment vs standard treatment. However, this analysis is a subgroup analysis of the SPRINT CKD which is a subgroup study of the SPRINT trial.

d. Subgroup analysis based on albuminuria showed that in patients with ACR ≤ median, the HR of cardiovascular outcomes was 0.84 (0.51-1.36) for intensive treatment vs standard treatment and in patients with ACR > median, the HR of cardiovascular outcomes was 0.81 (0.59-1.11) for intensive treatment vs standard treatment. However, this analysis is a subgroup analysis of the SPRINT CKD which is a subgroup study of the SPRINT trial.

e. The SPRINT trial is at high risk of bias in the domain of blinding. SPRINT CKD is subgroup study.

f. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.

g. Subgroup analysis based on age showed lower All-cause mortality in both age groups with HR of cardiovascular outcomes in patients <75 years of 0.84 (0.49-1.44) for intensive treatment vs standard treatment and in patients ≥75 years of 0.64 (0.43-0.96) for intensive treatment vs standard treatment. However, this analysis is a subgroup analysis of the SPRINT CKD which is a subgroup study of the SPRINT trial.

h. Subgroup analysis based on gender showed lower All-cause mortality in both men and women with HR of cardiovascular events in women 0.73 (0.41-1.31) for intensive treatment vs standard treatment and in men 0.71 (0.48-1.03) for intensive treatment vs standard treatment. However, this analysis is a subgroup analysis of the SPRINT CKD which is a subgroup study of the SPRINT trial.

i. Subgroup analysis based on ethnicity showed HR of All-cause mortality in black patients of 1.26 (0.60-2.68) and in nonblack patients of 0.63 (0.44-0.90) for intensive treatment vs standard treatment. However, this analysis is a subgroup analysis of the SPRINT CKD which is a subgroup study of the SPRINT trial.

j. Subgroup analysis based on albuminuria showed that the HR of All-cause mortality in patients with ACR ≤ median was 0.98 (0.54-1.77) for intensive vs standard treatment and in patients with ACR > median the HR of All-cause mortality was 0.66 (0.45-0.97) for intensive vs standard treatment. However, this analysis is a subgroup analysis of the SPRINT CKD which is a subgroup study of the SPRINT trial..

k. The confidence interval almost crosses the line of no effect, and suggests that the difference could be importantly less, or no effect.

l. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper end of the 95% CI crossed this threshold, suggesting that there may be an important harm.

m. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the upper and lower end of the 95% CI crossed this threshold, suggesting that there may be an important harm and benefit.

n. Rating the certainty that there is no important effect (using a threshold of 10 per 1000 patients), the lower end of the 95% CI crossed this threshold, suggesting that there may be an important benefit.
o. The confidence interval crosses the line of no effect, and suggests that the difference could be importantly less, or importantly more.
p. The confidence interval almost crosses the line of no effect, and suggests that the difference could be importantly more, or no effect.

Evidence to decision for PICO question 9

Values and preferences

Risso, 2015*(7)*: From a patient perspective, HTN is often a silent disease and patients may not take antihypertensive medications as directed because their positive effects are not as obvious as potential side-effects from the medications.

Resources required

No research evidence.

Cost effectiveness

Richman and colleagues*(9)* conducted a trial-based economic evaluation incorporating the effect estimates for treatment effects and adverse event rates from the SPRINT trial in a Markov model. They compared intensive BP management (SBP <120 mmHg) with standard (SBP<140 mmHg) among 68-year-old high-risk adults with HTN but not diabetes. Model inputs were obtained from the Centers for Disease Control and Prevention Life Table: Projected age- and cause-specific mortality, calibrated to rates reported in SPRINT. Population-based observational data was used for heart failure, MI, stroke and subsequent mortality. Utilities were obtained based on EQ-5D scores from a nationally representative sample. Costs were based on published sources. The base case ICER was USD 23 777 per QALY. The results were robust, ICERs with sensitivity analyses changing parameter inputs several-fold were <USD 50 000.

Howard and colleagues*(10)* constructed a cost-effectiveness study of screening and optimal management of HTN and diabetes and chronic kidney disease in an Australian setting. They found that an intensive management of HTN of previously uncontrolled HTN compared with usual care resulted in an ICER of AUD 2588. They do not specify the target BP for the comparisons.

Equity

Meiqari, 2019*(11)*: Many barriers in access to HTN care in low-income settings are low patient health literacy; overburdened health care providers; the lack of an organizational structure to accommodate a nonphysician as a primary care provider; the lack of confidence and/or policy towards the nonphysician providers' ability to manage uncomplicated and stable patients; the lack of infrastructure for data collection and monitoring of clinical information on a periodic basis as a more intensive target seems to requires more data collection and monitoring; and finally, limited resources.

Acceptability

Shahaj, 2019*(12)*: Deliberately choosing to avoid or reduce medication (intentional nonadherence), rather than forgetfulness, was a theme in some studies. For some patients, symptoms acted as a guide to the seriousness of their HTN and guided their medication use; for example, they stopped treatment if symptoms disappeared. Some were guided by stress, using medication to manage worry or anxiety rather than HTN. Fear of dependency affected the amount of medication they took.

Feasibility

Risso, 2015*(7)*: The guidelines envisage that all clinics should manage patients with HTN, with staff undergoing specific training in screening and HTN management. BP is not routinely checked during attendance at primary care clinics for other problems, contrary to national guidelines; however some doctors do measure BP in all patients visiting the clinics.

Brook, 2011: Busy primary care physicians often fail to ask about adherence and frequently do not adjust medications for uncontrolled patients.

Outcome utilities

Please refer to Table 91 below.

Table 91 Utilities per outcome for PICO question 10

Outcomes	Utility	Systematic review	Primary studies reported in the SR
Hypertension	0.96	Ren 2020*(14)*	Li 2015*(15)*
	0.98 (range: 1 – 0.95)	Kawalec 2015*(16)*	Burstrom 2001*(17)*, Sullivan 2008*(18)*, Wang 2008*(19)*
Type 2 diabetes mellitus	0.985	Gad 2020*(20)*	Salomon 2012*(21)*
MACE	Time NR: All CVD excluding stroke: 0.73 (95%CI: 0.69–0.76)	Kawalec 2015*(16)*	Lunde, 2013*(22)*
Stroke	First month after onset: 0.55	Ren 2020*(14)*	Li 2015*(15)*
	Days 1-3: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4-28: 0.88	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.65	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.70 (95%CI: 0.67-0.73)	Kawalec 2015*(16)*	Golicki 2010*(24)*
MI	First month after onset: 0.60	Ren 2020*(14)*	Li 2015*(15)*
	Days 1-3: 0.58	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4-28: 0.94	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.70	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: Disability weight 0.124	Gad 2020*(20)*	Salomon 2012*(21)*
ESRD	ESRD pre-dialysis: 0.73 (95% CI: 0.62–1)	Cooper 2020*(25)*	Jesky 2016*(26)*
	Hemodialysis: 0.75 (SD: 0.25)	Cooper 2020*(25)*	Briggs 2016*(27)*
Cognitive impairment/dementia	Patient rating: 0.85 (SD: 0.19)	NA	Rowen 2015*(28)*
	Patient rating: mild dementia 0.79 (SD: 0.22) moderate dementia: 0.72 (0.23)	NA	Orgeta 2015*(29)*
	Carer rating: mild dementia 0.63 (SD: 0.27) moderate dementia: 0.52 (0.27)	NA	Orgeta 2015*(29)*
HF events	First month after onset: 0.63	Ren 2020*(14)*	Li 2015*(15)*
	Chronic state: 0.73	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.79	Gad 2020*(20)*	Salomon 2012*(21)*
Adverse events	Common: 0.88	Gu 2015*(8)*	Clinical Judgement
	Infrequent: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*

PICO question 10: In adults with hypertension given pharmacological treatment, when should blood pressure be reassessed?

Systematic review for desirable and undesirable effects

Evidence was considered in respect of the following components (Table 92) to determine when adults with hypertension given pharmacological treatment should have their blood pressure (BP) reassessed (Table 93, Table 94).

Table 92 Components for PICO question 10

Population	Intervention	Comparison	Outcome	Subgroup
Adult men and women with hypertension receiving a pharmacological intervention.	Specific interval	Alternative interval	- death (all-cause mortality) - cardiovascular death (death from MI, sudden cardiac death or stroke) - stroke - myocardial infarction - end stage kidney disease - heart failure events - adverse effects - blood pressure control - adherence - patient satisfaction	- titration phase vs controlled HTN follow up - level of initial blood pressure - other conditions - remote monitoring vs clinical visit

Table 93 Evidence profile 10a: A 3-month interval compared to a 6 month interval for reassessment of patients with hypertension receiving pharmacological treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month interval	6-month interval	Relative (95% CI)	Absolute (95% CI)		
Systolic BP measured by family doctors (follow up: 12 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	300	302	–	MD **0.05 mmHg lower** (2.04 lower to 1.94 higher)	⊕⊕⊕◯ MODERATE	–
Systolic BP measured by family doctors (follow up: 18 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	[c]	[c]	–	MD **0.74 mmHg lower** (2.54 lower to 1.05 higher) [d]	⊕⊕⊕◯ MODERATE	–
Systolic BP measured by family doctors (follow up: 24 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	298	297	–	MD **1.17 mmHg lower** (3.61 lower to 1.27 higher)	⊕⊕⊕◯ MODERATE	
Systolic BP measured by family doctors (follow up: 36 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	294	289	–	MD **0.98 mmHg lower** (3.5 lower to 1.55 higher) [e]	⊕⊕⊕◯ MODERATE	–
Diastolic BP measured by family doctors (follow up: 12 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	300	302	–	MD **0.01 mmHg higher** (1.21 lower to 1.29 higher)	⊕⊕⊕◯ MODERATE	–
Diastolic BP measured by family doctors (follow up: 18 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	[c]	[c]	–	MD **0.71 mmHg higher** (0.26 lower to 1.68 higher) [f]	⊕⊕⊕◯ MODERATE	–
Diastolic BP measured by family doctors (follow up: 24 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	298	297	–	MD **0.22 mmHg lower** (1.59 lower to 1.14 higher)	⊕⊕⊕◯ MODERATE	–
Diastolic BP measured by family doctors (follow up: 36 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	not serious [b]	none	294	289	–	MD **1.11 mmHg higher** (0.21 lower to 2.44 higher) [g]	⊕⊕⊕◯ MODERATE	–
BP out of control as judged by doctor (follow up: 12 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	serious [h]	none	63/302 (20.9%)	52/300 (17.3%)	**RR 1.20** (0.86 to 1.68)	**35 more per 1,000** (from 24 fewer to 118 more)	⊕⊕◯◯ LOW	–
BP out of control as judged by doctor (follow up: 24 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	serious [i]	none	59/299 (19.7%)	67/291 (23.0%)	**RR 0.83** (0.61 to 1.14)	**39 fewer per 1,000** (from 90 fewer to 32 more)	⊕⊕◯◯ LOW	–
BP out of control as judged by doctor (follow up: 36 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	serious [j]	none	50/275 (18.2%)	41/260 (15.8%)	**RR 1.15** (0.79 to 1.68)	**24 more per 1,000** (from 33 fewer to 107 more)	⊕⊕◯◯ LOW	–
Patient satisfaction (percentage of general satisfaction with clinical care (follow up: 36; assessed with: Birtwhistle, 2004*(106)*; Scale from: 0 to 100)												

1	randomized trials	serious [a]	not serious	not serious	serious [i]	none	260	257	-	MD **2.69 % lower** (5.76 lower to 0.38 higher) [k]	⊕⊕◯◯ LOW	–
Adherence (as reported by the patient: proportion who report forgetting to take their pills) (follow up: 36 months; assessed with: Birtwhistle, 2004*(106)*)												
1	randomized trials	serious [a]	not serious	not serious	serious [j]	none	78/263 (29.7%)	71/263 (27.0%)	**RR 1.10** (0.84 to 1.44)	**27 more per 1,000** (from 43 fewer to 119 more) [l]	⊕⊕◯◯ LOW	–
Mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. There is no description of allocation concealment. The trial could not be blinded due to the nature of the intervention. This may have increase the risk of performance bias.

b. Rating the certainty that there is no important difference, the CI does not suggest the possibility of important benefit or important harm. It is important to note that these are 90% CIs.

c. Not reported per group, 494 in total. d. Very similar results when measured by nurses, the MD was -1.64 (90% CI, -3.49 to 0.21).

e. Very similar results when measured by nurses, the MD was -2.35 (90% CI, -4.84 to 0.15). f. Very similar results when measured by nurses, the MD was 0.60 (90% CI, -0.61 to 1.82).

g. Very similar results when measured by nurses, the MD was 0.25 (90% CI, -1.61 to 2.11).

h. The 95% CI suggests the possibility of important benefit and important harm.

i. The 95% CI suggests the possibility of important benefit and trivial harm.

j. The 95% CI suggest the possibility of some benefit and important harm.

k. The researchers also measured different aspects of satisfaction with general care and with the doctor. Almost all CIs cross the threshold of null effect.

l. The researchers also measured adherence by asking the patients to answer whether they were "careless at times about taking your medicine", whether they "sometimes stop taking your medicine", and whether "if you feel worse when you take the medicine, do you stop taking it". The results were similar, with no important differences between the proportion of patients.

Table 94 Evidence profile 10b: An approximately 3-month interval compared to an approximately 1 month interval for reassessments of patients with hypertension receiving pharmacological treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Approximately 1 month-interval	Approximately 3-month interval	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: mean 37.4 months; assessed with: Xu, 2015*(107)*)												
1	observational studies	not serious	not serious	not serious	not serious	none	-/14 747 [a]	-/16 092	RR 1.21 (1.13 to 1.30) [b]	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	–
Cardiovascular event or death (not defined) (follow up: mean 37.4 months; assessed with: Xu, 2015*(107)*)												
1	observational studies	not serious	not serious	not serious	not serious	none	-/17 525 [a]	-/17 524 [a]	RR 1.18 (1.11 to 1.25) [b]	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
BP – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adherence – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Patient satisfaction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. The number of events in the group was not reported.

b. The CIs of the comparison between 1 month and less than 1 month, 1 to 1.5 month, and 1.5 to 2.7 months overlap. The CI of the comparison between 1.5 to 2.7 and > 2.7 month overlap.

Evidence to decision for PICO question 10

Values and preferences

No research evidence

Resources required

No research evidence

Cost effectiveness

No research evidence

Equity

Meiqari, 2019*(11)*: Many barriers to accessing HTN care in low-income settings are low patient health literacy; overburdened health care providers; the lack of an organizational structure to accommodate a nonphysician as a primary care provider; the lack of confidence and/or policy towards the nonphysician providers' ability to manage uncomplicated and stable patients; the lack of infrastructure for data collection and monitoring of clinical information on a periodic basis; and finally, limited resources.

Acceptability

Walker, 2019*(108)*: More frequent monitoring increased patients' sense of safety in remaining independent at home, particularly for those living alone and older adults. Patients became less fearful of being alone, or not picking up an important clinical sign that there condition may be deteriorating.

Risso, 2015*(7)*: Very few asymptomatic patients ask for their BP to be checked, with one Medical Officer noting: "Rarely people came in just to have their BP checked [without symptoms], because they think they are still young so why they need to have a health check-up?" At one clinic only half those scheduled to attend actually did so, most of whom had another condition, such as diabetes. Another factor, noted in many settings, is that "from a patient perspective, hypertension is often a silent disease and patients may not take antihypertensive medications as directed because their positive effects are not as obvious as potential side effects from the medications".

Gwadry, 2013*(93)*: One study found a decrease in adherence with an increase in time between intervention and follow-up, emphasizing the importance of interventions to promote sustainable behaviour change.

Feasibility

Russo, 2015: In the public sector, a nurse will take the patient's BP readings and any other tests required, which are then followed up by the Medical Officer as the nurse is not allowed to prescribe medications. However, physicians reported seeing 10 or more patients per hour, or 100 in a day, leaving inadequate time for meaningful interaction: "Many of healthcare providers [are] not able to sit down and have counselling session regarding their medications with their patients" (KI).

Risso, 2015*(7)*: Commonly, the Medical Officer will just "tell the patient to continue medication, sometimes without physical examination" (HP); they report having little time to talk with patients, and they simply "take their [the patient's] word" as to whether they are adhering to medication and modifying their lifestyle as the doctors have insufficient time to engage with them to ensure a shared understanding. In the public sector, a nurse will take the patient's BP readings and any other tests required, which are then followed up by the Medical Officer as the nurse is not allowed to prescribe medications. However, physicians reported seeing 10 or more patients per hour, or 100 in a day, leaving inadequate time for meaningful interaction: "Many of healthcare providers [are] not able to sit down and have counselling session regarding their medications with their patients".

Jaana, 2007*(109)*: Despite existing evidence on the effectiveness of telemonitoring for patients experiencing hypertension, there is no empirical evidence of its potential success over longer periods of time as well as its generalizability to patients with various backgrounds and educational levels who might react differently to this approach, though several studies identified potential savings and a reduction in the number of visits to healthcare providers.

Brook, 2011*(110)*: Busy primary care physicians often fail to ask about adherence and frequently do not adjust medications for uncontrolled patients.

Outcome utilities

Please refer to Table 95 below.

Table 95 Utilities per outcome for PICO question 10

Outcomes	Utility	Systematic review	Primary studies reported in the SR
Hypertension	0.96	Ren 2020*(14)*	Li 2015*(15)*
	0.98 (range: 1 – 0.95)	Kawalec 2015*(16)*	Burstrom 2001*(17)*, Sullivan 2008*(18)*, Wang 2008*(19)*
Type 2 diabetes mellitus	0.985	Gad 2020*(20)*	Salomon 2012*(21)*
MACE	Time NR: All CVD excluding stroke: 0.73 (95%CI: 0.69–0.76)	Kawalec 2015*(16)*	Lunde, 2013*(22)*
Stroke	First month after onset: 0.55	Ren 2020*(14)*	Li 2015*(15)*
	Days 1-3: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4-28: 0.88	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.65	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.70 (95%CI: 0.67-0.73)	Kawalec 2015*(16)*	Golicki 2010*(24)*
MI	First month after onset: 0.60	Ren 2020*(14)*	Li 2015*(15)*
	Days 1-3: 0.58	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4-28: 0.94	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.70	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: Disability weight 0.124	Gad 2020*(20)*	Salomon 2012*(21)*
ESRD	ESRD pre-dialysis: 0.73 (95% CI: 0.62–1)	Cooper 2020*(25)*	Jesky 2016*(26)*
	Hemodialysis: 0.75 (SD: 0.25)	Cooper 2020*(25)*	Briggs 2016*(27)*
Cognitive impairment/dementia	Patient rating: 0.85 (SD: 0.19)	NA	Rowen 2015*(28)*
	Patient rating: mild dementia 0.79 (SD: 0.22) moderate dementia: 0.72 (0.23)	NA	Orgeta 2015*(29)*
	Carer rating: mild dementia 0.63 (SD: 0.27) moderate dementia: 0.52 (0.27)	NA	Orgeta 2015*(29)*
HF events	First month after onset: 0.63	Ren 2020*(14)*	Li 2015*(15)*
	Chronic state: 0.73	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.79	Gad 2020*(20)*	Salomon 2012*(21)*
Adverse events	Common: 0.88	Gu 2015*(8)*	Clinical Judgement
	Infrequent: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*

PICO question 11: Can pharmacological management of hypertension be provided by nonphysician care providers?

Systematic review for desirable and undesirable effects

Evidence was considered in respect of the following components (Table 96) to determine whether pharmacological management of hypertension can be provided by nonphysician care providers (Table 97–Table 103).

Table 96 Components for PICO question 11

Population	Intervention	Comparison	Outcome	Subgroups
Adult men and women	Pharmacological management by non-physician care p	Pharmacological management by medically qualified practitioners (doctors)	- death (all-cause mortality) - cardiovascular death (death from MI, sudden cardiac death or stroke) - stroke - myocardial infarction - end stage kidney disease - heart failure events - blood pressure control - adherence - serious adverse effects - patient satisfaction	- initiation vs follow up - self-care vs community HCW vs nurse vs pharmacist vs physician assistants vs in or out of clinic - levels of care - rural vs urban settings - ethnicity

Table 97 Evidence profile 11a: Pharmacological management by a pharmacist compared to usual care in patients with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological management by pharmacist	Usual care	Relative (95% CI)	Absolute (95% CI)		
BP control (BP goal attainment 140/90 mmHg) (assessed with: Greer, 2016*(111)*)												
7	randomized trials	very serious [a]	not serious	not serious	not serious	none	532/973 (54.7%)	383/1014 (37.8%)	RR 1.45 (1.24 to 1.70) [b]	170 more per 1,000 (from 91 more to 264 more) [c]	⨁⨁◯◯ LOW	–
Clinical events (definition not provided) (assessed with: Greer, 2016*(111)*)												
6	randomized trials	very serious [d]	not serious [e]	not serious	not serious [e]	none	Based on 2236 participants, the authors report that pharmacist-led care led to similar numbers of clinical events than usual care. They do not report the numbers.				⨁⨁◯◯ LOW [f]	–
Health-related quality of life (assessed with: Greer, 2016*(111)*)												
7	randomized trials	very serious [g]	not serious [e]	not serious	not serious [e]	none	Based on 2031 participants, the authors report that pharmacist-led care led to similar health-related quality of life. They do not report the numbers.				⨁⨁◯◯ LOW [f]	–
Patient satisfaction (assessed with: Greer, 2016*(111)*)												
7	randomized trials	very serious [h]	serious [i]	serious [j]	not serious [e]	none	Based on 1519 participants, the authors say that there were "mixed results". They do not provide any more details.				⨁◯◯◯ VERY LOW [f]	–
Adherence (defined as poor or less than perfect adherence) (assessed with: Greer, 2016*(111)*)												
	randomized trials	very serious [h]	not serious	not serious	not serious [e]	none	The authors reported that poor or less than perfect adherence to the prescribed regimen was "generally similar between groups". They do not provide any other details, including the number of studies and patients providing information.				⨁⨁◯◯ LOW [f]	–
Adherence (defined as the extent to which medication taking behaviour is consistent with health care provider recommendations) (assessed with: Conn 2015*(112)*)												
	randomized trials	not serious	not serious [e]	very serious [k]	not serious [e]	none	The authors determined if the effect of interventions to imporve adherence differed when the intervention was delivered by a pharmacist (change in adherence, SMD, 0.369) or a physician (SMD, 0.356). There were no statistical differences between the two. The authors do not provide details about the trials or participants providing information. [l,m]				⨁⨁◯◯ LOW [f]	–
Adherence (medication adherence) (assessed with: Reeves, 2020*(113)*)												
20	randomized trials	very serious [n]	serious [o]	not serious	not serious [e]	none	The authors describe that 9/20 trials showed a statistically significant improvement in medication adherence in patients receiving additional pharmaceutical care, and that 4 suggested non-statistically significant improvement.				⨁◯◯◯ VERY LOW [f]	–
Mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												

–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; RR: Risk ratio

Explanations

a. Only one of the studies was judged at low risk of bias.

b. A systematic review (Morrisey, 2017*(114)*) explored whether there were differences in BP when interventions for improving adherence were delivered by pharmacists, nurses, or physicians. They report that neither of them, nor the three combined made a difference.

c. A systematic review of studies from low- and middle-income countries (Anand, 2019) found that task sharing with pharmacists results in a higher reduction in SBP (MD, -8.12 mmHg' 95% CI, -10.23 to -6.01) and DBP (-3.74 mmHg; 95% CI, -5.15 to -3.32) when compared to not doing it. This effect was not importantly different than the effect of sharing with dieticians, nurses, or community health workers.

d. The authors report that one RCT had high RoB and the other five had medium RoB.

e. The authors do not provide enough information for this assessment.

f. The reporting quality of the systematic review is suboptimal (lack of description of trials that reported the outcomes, lack of description of relative and absolute numbers, no forest plots, etc), and did not allow making confident assessments of the certainty of the evidence.

g. The authors report that one study had low RoB, five had medium RoB, and one had high RoB.

h. The authors do not provide details but based on the other outcomes, it is likely that there are serious concerns.

i. The authors qualify the results across studies as "mixed".

j. The authors mention that five studies compared the intervention to usual care, but do not provide details for the other two studies.

k. The comparison was done between, not within studies.

l. Another review (Ruppar, 2017*(115)*) explored the same question in black people (as described by the review authors). They found the effect to be SMD, 0.52 (95% CI, 0.15 to 0.90) when the intervention was delivered by a pharmacist vs not, and SMD, 0.22 (95% CI, -0.05 to 0.48) when it was delivered by a physician vs not. There are no statistical differences between these.

m. Another review (Xu, 2018*(116)*) explored the same question in Chinese population. They found the effect to be SMD, 195 (95% CI 0.94 to 2.95) when the intervention was delivered by a pharmacist vs not, and SMD, 2.80 (95% CI 1.71 to 3.88) when it was delivered by a physician vs not. There are no statistical differences between these.

n. None of the trials was judged at low risk of bias.

o. According to the narrative description provided by the authors, it seems like there is serious inconsistency.

Table 98 Evidence profile 11b: Pharmacological management by a nurse compared to usual care in patients with hypertension

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Systolic BP (assessed with: Morrisey, 2017*(114)*)									
3	randomized trials	very serious [a]	not serious	very serious [b]	not serious [c]	none	In a systematic review about the effect of interventions to enhance medication adherence, a subgroup analysis showed that involvement of nurses was not statistically significantly associated with SBP. The authors do not provide details about specific effect, only a p-value for the comparison between involvement of nurses, pharmacists, and physicians	⨁◯◯◯ VERY LOW [d]	–
Adherence (no definition provided) (assessed with: Georgiopoulos, 2018*(117)*)									
10	randomized trials	not serious [c]	not serious	very serious [e]	not serious [c]	none	The authors describe that from the 10 studies included, 7 reported improvement in medication adherence after the implementation of a nursing intervention. They do not provide any details about the number of participants.	⨁⨁◯◯ LOW [d]	–
Adherence (no definition provided) (assessed with: Ruppar, 2017*(115)* and Xu, 2018*(116)*)									
	randomized trials	not serious [c]	not serious	very serious [b]	not serious [c]	none	Two systematic reviews examined differences in the effect of interventions to improve adherence to medication. Analyses showed that, among black people (as labelled by the review authors), the SMD was 0.45 (95% CI, 0.24 to 0.65) when the intervention was delivered by a nurse versus not, and 0.22 (95% -0.05 to 0.48) when the intervention was delivered by a physician versus not (Morrisey, 2017). Another review showed similar results in studies conducted in Chinese population (SMD for nurse vs not, 1.80 [95% CI, 0.92 to 2.65], SMD for physician vs not 2.80 [95% CI 1.71 to 3.88]) (Xu, 2018)	⨁⨁◯◯ LOW [d]	–
All-cause mortality – not reported									
–	–	–	–	–	–	–		–	–
Cardiovascular mortality – not reported									
–	–	–	–	–	–	–		–	–
Stroke – not reported									
–	–	–	–	–	–	–		–	–
Myocardial infarction – not reported									
–	–	–	–	–	–	–		–	–
End-stage kidney disease – not reported									
–	–	–	–	–	–	–		–	–
Heart failure – not reported									
–	–	–	–	–	–	–		–	–
Serious adverse events – not reported									
–	–	–	–	–	–	–		–	–
Patient satisfaction – not reported									
–	–	–	–	–	–	–		–	–

CI: Confidence interval

Explanations

a. Although there are not details about which trials provided this information, none of the trials included in this systematic review was judged at low risk of bias.
b. This is a between-study comparison.
c. The authors do not provide information to assess this domain.
d. Due to the poor reporting quality of the systematic review, we did not have the elements necessary to make an optimal assessment of the certainty of the evidence.
e. The authors do not specify the definition for adherence, nor provide details about the populations, interventions, and outcomes. We are very uncertain about the applicability of these results.

Table 99 Evidence profile 11c: Self-management (self-monitoring) compared to usual care in patients with hypertension

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management (self-monitoring)	Usual care	Relative (95% CI)	Absolute (95% CI)		
Systolic BP (follow up: 12 months; assessed with: Tucker, 2017*(118)*)*												
15	randomized trials	serious [a]	serious [b]	not serious	not serious	none	3493	2807	–	MD 3.24 mmHg lower (4.92 lower to 1.57 lower) [c,d]	⨁⨁◯◯ LOW [e]	–
Diastolic BP (follow up: 12 months; assessed with: Tucker, 2017*(118)*)*												
15	randomized trials	serious [a]	serious [b]	not serious	not serious	none	3493	2807	–	MD 1.5 mmHg lower (2.24 lower to 0.75 lower) [d,f]	⨁⨁◯◯ LOW [e]	–
Uncontrolled BP (BP above target) (follow up: 12 months; assessed with: Tucker, 2017*(118)*)*												
15	randomized trials	serious [a]	serious [b]	not serious	not serious	none	-/3493	-/2807	RR 0.70 (0.56 to 0.86) [g]	0 fewer per 1,000 (from 0 fewer to 0 fewer) [d,h]	⨁⨁◯◯ LOW [e]	–
Adherence (percentage) (follow up: median 6 months; assessed with: Fletcher, 2015*(119)*; Scale from: 0 to 1)												
13	randomized trials	very serious [i]	not serious	not serious	not serious	none	915	894	–	MD 21 % higher (8 higher to 34 higher)	⨁⨁◯◯ LOW	–
Mortality (assessed with: Reboussin, 2018*(120)*)												
4	randomized trials	not serious [j]	not serious	not serious	very serious [k]	none	A systematic review reports that 4 studies addressed mortality, and that none of them "reported a significant difference". They do not provide any more details.				⨁⨁◯◯ LOW	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Patient satisfaction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. Although the authors describe that the trials were at low risk of bias, due to the nature of the intervention it was not possible to blind participants, which increases the risk of performance bias.

b. There is statistically significant heterogeneity between subgroups.
c. The authors conducted a subgroup analysis to explore different co-interventions. The MD obtained with self-monitoring with no feedback was -1.02 mmHg (95% CI, -3.27 to 1.23); whereas for all other subgroups the CI did not cross the null effect threshold (web/phone feedback: MD, -1.98; 95% CI, -3.74 to -0.21; web/phone feedback + education: MD, -4.42 mmHg; 95% CI, -7.11 to -1.73; counselling/ tele counselling: MD, -6.10; 95% CI, -9.02 to -3.18).
d. The differences in the presence and magnitude of the effect suggest that self-management probably has an effect (or not) when complemented with other interventions.
e. The certainty of the evidence is moderate within each subgroup, as there are no serious inconsistency concerns.
f. The authors conducted a subgroup analysis to explore different co-interventions. The MD obtained with self-monitoring with no feedback was -1.10 mmHg (95% CI, -2.39 to 0.19), and for web/phone feedback it was -0.46 (95% CI, -1.47 to 0.56); whereas for the other subgroups the CI did not cross the null effect threshold (web/phone feedback + education: MD, -1.91 mmHg; 95% CI, -2.87 to -0.94; counselling/ tele counselling: MD, -2.32; 95% CI, -4.04 to -0.59).
g. The authors conducted a subgroup analysis to explore different co-interventions. The RR obtained with self-monitoring with no feedback was 0.99 (95% CI, 0.72 to 1.37), and for web/phone feedback it was 0.90 (95% CI, 0.69 to 1.15); whereas for all other subgroups the CI did not cross the null effect threshold (web/phone feedback + education: RR, 0.57; 95% CI, 0.44 to 0.73; counselling/ tele counselling: RR, 0.70; 95% CI, 0.56 to 0.86).
h. Number of patients experiencing the event is not reported, and thus this cannot be calculated.
i. Most of the studies were judged to have more than 1 domain at high risk of bias.
j. The authors do not provide sufficient information to make this assessment.
k. The authors describe that the number of events was small, and the "overall risk ratio was not different from 1.0".
A newer version of this systematic review was published recently Sheppard 2019(121)* and its results are consistent with what was reported in this table.

Table 100 Evidence profile 11d: Pharmacological management by a pharmacist compared to usual care in patients with hypertension in low- and middle-income countries

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological management by pharmacist	Usual care	Relative (95% CI)	Absolute (95% CI)		
Systolic BP (change) (assessed with: Anand, 2019*(122)*)												
6	randomized trials	very serious [a]	not serious	not serious	not serious	none	522	491	–	MD 8.12 mmHg lower (10.23 lower to 6.01 lower)	⨁⨁◯◯ LOW	–
Diastolic BP (change) (assessed with: Anand, 2019*(122)*)												
6	randomized trials	very serious [a]	not serious [b]	not serious	not serious	none	522	491	–	MD 3.74 mmHg lower (5.15 lower to 2.32 lower)	⨁⨁◯◯ LOW	–
Mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adherence – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Patient satisfaction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; MD: Mean difference

Explanations

a. All included studies were judged at high risk of bias.

b. Although the statistical heterogeneity is high, all studies showed the same direction of effect, and only one study suggested a higher magnitude.

Table 101 Evidence profile 11e: Pharmacological management by a nurse compared to usual care in patients with hypertension in low- and middle-income countries

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological management by nurse	Usual care	Relative (95% CI)	Absolute (95% CI)		
Systolic BP (change) (assessed with: Anand, 2019*(122)*)												
11	randomized trials	very serious [a]	not serious [b]	not serious	not serious	none	975	979	-	MD 5.34 mmHg lower (9 lower to 1.67 lower)	⨁⨁◯◯ LOW	–
Diastolic BP (change) (assessed with: Anand, 2019*(122)*)												
9	randomized trials	very serious [a]	serious [c]	not serious	not serious	none	790	788	-	MD 3.18 mmHg lower (6.36 lower to 0.01 lower)	⨁◯◯◯ VERY LOW	–
Mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adherence – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	—
Patient satisfaction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	

CI: Confidence interval; MD: Mean difference

Explanations

a. All included trials were judged at high risk of bias.

b. Although there is high statistical heterogeneity, all studies are consistent in the direction of the effect.

c. There is high statistical heterogeneity, some studies suggest a different magnitude and direction of effect, and not all confidence intervals overlap.

Table 102 Evidence profile 11f: Pharmacological management by a dietitian compared to usual care in patients with hypertension in low- and middle-income countries

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological management by dietitian	Usual care	Relative (95% CI)	Absolute (95% CI)		
Systolic BP (assessed with: Anand, 2019*(122)*)												
4	randomized trials	very serious [a]	not serious	not serious	not serious	none	689	671	-	MD 4.67 mmHg lower (7.09 lower to 2.24 lower)	⨁⨁◯◯ LOW	–
Diastolic BP (assessed with: Anand, 2019*(122)*)												
4	randomized trials	very serious [a]	not serious	not serious	not serious	none	689	671	-	MD 3.3 mmHg lower (4.69 lower to 1.92 lower)	⨁⨁◯◯ LOW	–
Mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adherence – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Patient satisfaction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; MD: Mean difference

Explanations

a. All included studies were judged at high risk of bias.

Table 103 Evidence profile 11g: Pharmacological management by a community health worker compared to usual care in patients with hypertension in low- and middle-income countries

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmacological management by a community health worker	Usual care	Relative (95% CI)	Absolute (95% CI)		
Systolic BP (change) (assessed with: Anand, 2019*(122)*)												
11	randomized trials	very serious [a]	not serious	not serious	not serious	none	4712	4450	-	MD 3.67 mmHg lower (4.58 lower to 2.77 lower)	⨁⨁◯◯ LOW	–
Diastolic BP (change) (assessed with: Anand, 2019*(122)*)												
10	randomized trials	very serious [a]	not serious [b]	not serious	not serious	none	3617	3459	-	MD 2.29 mmHg lower (3.31 lower to 1.27 lower)	⨁⨁◯◯ LOW	–
Mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Cardiovascular mortality – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Stroke – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Myocardial infarction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
End-stage kidney disease – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Heart failure – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Adherence – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Serious adverse events – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–
Patient satisfaction – not reported												
–	–	–	–	–	–	–	–	–	–	–	–	–

CI: Confidence interval; MD: Mean difference

Explanations

a. All included studies were judged at high risk of bias.

b. Although there is high statistical heterogeneity, most of the studies agree with the direction of the effect and their confidence intervals overlap.

Evidence to decision for PICO question 11

Values and preferences

No research evidence

Resources required

Fu, 2020*(123)*: Different elements are required to perform high-quality home BP monitoring (HBPM). They include access to accurate BP monitors, skills, and knowledge to perform HBPM, motivation to perform HBPM regularly, and accurate reflection of HBPM readings to their health care providers. Patients may not have the hardware, skill, and knowledge to implement successful HBPM. They need health care providers' instruction and feedback to practise HBPM independently. Their skills and BP records should be reviewed regularly in order to ensure their compliance with HBPM protocol, such as measurement preparation, procedure, and how to record BP readings. In a busy primary care practice, time constraints may preclude physicians from taking time to educate HBPM and review patients' home BP records.

Walker, 2020*(108)*: Participants in programmes in which remote monitoring was initially provided at no cost to the patient voiced concern about the introduction of ongoing expenses and servicing costs after an initial period. Two studies in Taiwan and one in Australia found patients concerned that they would not be able afford the on-going costs of remote monitoring.

Beyhaghi, 2019*(124)*: To date, ambulatory BP monitoring (ABPM) has not been widely used in clinical practice in the United States, partly because the costs of this diagnostic strategy were often not reimbursable by healthcare payers.

Jamshidnezhad, 2019*(125)*: Mobile phones have become an appropriate opportunity for self-care purposes due to their adaptability to different communities and their interactive nature. The use of smartphones is increasing due to the global trend of lower prices for these devices. Reports suggest that smartphones and tablets have become the most popular and widely used type of mobile phones. At the present time, out of 6 billion phone subscriptions in the world, only 17% are non-smartphones

Markez, 2006*(126)*: It would be easy to apply in practice because the introduction of monitors among hypertensive patients has already started, being taken up spontaneously, without having to be encouraged by health professionals. The principal problem is its high cost.

Cost effectiveness

Based on a systematic review of the literature that included 31 studies, Jacob and colleagues*(127)* report the results of cost effectiveness of team-based interventions to improve BP outcomes. When necessary, they converted intervention costs per unit reduction in SBP to lifetime intervention cost per QALY using published algorithms (QALY/mmHg of 0.093 and 0.009 in two references). They conclude that team-based care to improve BP control were cost effective with 10 studies showing a $/QALY of less than $50,000. They did not conduct a quality assessment of included studies.

Kulchatanaroaj and colleagues*(128)* constructed a Markov model with a six-month cycle length and a lifetime time horizon comparing pharmacist led collaborative intervention and usual care and found the intervention to be cost effective ($26,807.83/QALY). The intervention provided the greatest benefit in the high-risk patients.

Equity

Fu, 2020*(123)*: Under-privileged patients, such as those from lower socioeconomic class, those with lower educational levels, or those with limited health literacy or numeracy, were found to have a poorer outcome in overall noncommunicable diseases. Patients with inadequate health literacy were more likely to have poorer disease knowledge, poorer self- efficacy, and misconception in cardiovascular disease.

Jaana, 2007*(109)*: Despite existing evidence on the effectiveness of telemonitoring for patients experiencing hypertension, there is no empirical evidence of its potential success over longer periods of time as well as its generalizability to patients with various backgrounds and educational levels who might react differently to this approach. However, several studies identified potential savings and a reduction in the number of visits to healthcare providers.

Acceptability

Walker, 2019*(108)*: Patients with chronic conditions reported that remote monitoring enabled increased understanding of their condition. They gained awareness of what their "normal" clinical values and symptoms were, as well as clinically significant changes in signs and symptoms. Collecting clinical data at home enabled some to obtain accurate and frequent measurements of their own health status. Patients felt more frequent data collection at home validated their symptoms and prompted clinicians to take earlier action in response to these data. Patients were more certain of when it was necessary to seek medical attention. Remote monitoring promoted confidence to self-manage, including independently making changes to medication regimens. Patients also felt being able to discuss their monitoring data made them feel empowered and a more equal partner in their care, allowing them to be "better equipped to engage with health care services". Remote monitoring provided patients with peace of mind and reduced their anxiety and stress.

Walker, 2019*(108)*: Providing management by non-physicians can make patients concerned that their care could become more focused on clinical data rather than personal interaction and this might lead to fewer face-to-face

consultations with clinicians. This personal contact was important to patients as it helped to establish trust and allowed for better communication.

Walker, 2019*(108)*: Patients were reluctant to commence remote monitoring because they believed that learning how to use the technology would create an additional burden for them. Older patients, in particular, were concerned that they would be confused by the data and this may consequently rigger additional anxiety. Others feared they would not understand the written instructions and could not safely operate the technology

Zhao, 2019*(129)*: In self-management, patients, along with their family, community, and health care professionals, take greater responsibility for health decisions and actively engage in behaviour that might benefit their disease conditions.

Jamshidnezhad, 2019*(125)*: In similar studies that assessed users' satisfaction, participants were generally satisfied with the use of applications for self-care.

Gwadry, 2013*(93)*: A significant improvement in medication adherence was found with increasing age and provider visits, and reductions in multiple-dosing regimens and medication classes.

Parati, 2011*(130)*: Study showed very high patients compliance with BP telemonitoring schedules, and a high degree of acceptability of these techniques by both patients and their doctors.

Jaana, 2007*(109)*: Home telemonitoring of hypertension appears to be well accepted by patients and produces positive effects on their attitudes and behaviour, irrespective of their cultural background. In fact, two studies that involved African American patients showed that telemonitoring was associated with a good compliance rate with the transmission of BP data and a significant improvement in disease knowledge. Specifically, Bondmass et al. reported an 88% compliance rate with data transmission at least once a day and a 69% compliance rate with data transmission at least twice a day.

Jaana, 2007*(109)*: In a larger randomized study involving 121 patients, Rogers et al. reported high satisfaction among patients in the telemonitoring group and an increased feeling that physicians had all necessary information for their diagnosis and treatment when using this approach.

Feasibility

Choi, 2020*(131)*: The studies that examined patients' experiences with the mobile health technologies to support self-management of concurrent diabetes and hypertension reported that the usability and acceptability of the systems were generally high. Findings regarding areas for improvement included connectivity issues between medical devices and mobile terminals, lack of compatibility and interoperability of the system with different mobile operating systems and terminals, lack of integration with health electronic health records, and low visibility of the content due to the small screens of mobile devices.

Jamshidnezhad, 2019*(125)*: Due to old age of people with hypertension and the importance of ease of working with mobile devices and applications, usability issues can play an important role in the effectiveness of an application.

McKoy, 2015*(132)*: Although the following scenarios are not exhaustive, legal risks can arise in telehealth in relation to privacy and security requirements, jurisdictional boundaries, and informed consent. It has been recognized that legal or ethical guidance for health practitioners to safely navigate these circumstances is lacking. Regulatory oversight will focus on those mobile medical apps that are likely to present a risk to patients if they do not work as intended. Although the FDA has taken steps to clarify the regulatory framework applying to mobile health applications (i.e. by stipulating which medical applications they will focus their attention on), a gap may still exist in relation to the multitude of applications that do not fall within those criteria.

Indirect evidence, Gu, 2015*(8)*: While China rapidly expanded health insurance coverage nationally within the past decade, many Chinese adults still have limited access to hypertension screening and follow-up for hypertension treatment and monitoring. For example, in the New Rural Cooperative Medical Scheme, which now covers over 95% of the rural population, most coverage is for inpatient hospitalizations, and the costs of basic medical services, including hypertension education, screening, treatment, and monitoring, are not usually covered.

Indirect evidence, Jamshidnezhad, 2019*(125)*: Self-care in hypertension is directly associated with health literacy and patient education

Cheema, 2014*(133)*: In the National Health Service in the UK, a new contractual framework for community pharmacies was introduced in 2005, with the intention of moving pharmacists towards a more clinical service-oriented role. For example, UK community pharmacies can provide health checks for people aged 40–74 years. Within these health checks, pharmacists can carry out a full vascular risk assessment and provide advice and support to help to reduce the risk of heart disease, strokes, diabetes and obesity.

Outcome utilities

Please refer to Table 104 below.

Table 104 Utilities per outcome for PICO question 11

Outcomes	Utility	Systematic review	Primary studies reported in the SR
Hypertension	0.96	Ren 2020*(14)*	Li 2015*(15)*
	0.98 (range: 1 – 0.95)	Kawalec 2015*(16)*	Burstrom 2001*(17)*, Sullivan 2008*(18)*, Wang 2008*(19)*
Type 2 diabetes mellitus	0.985	Gad 2020*(20)*	Salomon 2012*(21)*
MACE	Time NR: All CVD excluding stroke: 0.73 (95%CI: 0.69–0.76)	Kawalec 2015*(16)*	Lunde, 2013*(22)*
Stroke	First month after onset: 0.55	Ren 2020*(14)*	Li 2015*(15)*
	Days 1-3: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4-28: 0.88	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.65	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.70 (95%CI: 0.67-0.73)	Kawalec 2015*(16)*	Golicki 2010*(24)*
MI	First month after onset: 0.60	Ren 2020*(14)*	Li 2015*(15)*
	Days 1-3: 0.58	Gu 2015*(8)*	Salomon 2012*(21)*
	Days 4-28: 0.94	Gu 2015*(8)*	Salomon 2012*(21)*
	Chronic state: 0.70	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: Disability weight 0.124	Gad 2020*(20)*	Salomon 2012*(21)*
ESRD	ESRD pre-dialysis: 0.73 (95% CI: 0.62–1)	Cooper 2020*(25)*	Jesky 2016*(26)*
	Hemodialysis: 0.75 (SD: 0.25)	Cooper 2020*(25)*	Briggs 2016*(27)*
Cognitive impairment/dementia	Patient rating: 0.85 (SD: 0.19)	NA	Rowen 2015*(28)*
	Patient rating: mild dementia 0.79 (SD: 0.22) moderate dementia: 0.72 (0.23)	NA	Orgeta 2015*(29)*
	Carer rating: mild dementia 0.63 (SD: 0.27) moderate dementia: 0.52 (0.27)	NA	Orgeta 2015*(29)*
HF events	First month after onset: 0.63	Ren 2020*(14)*	Li 2015*(15)*
	Chronic state: 0.73	Ren 2020*(14)*	Huang 2017*(23)*
	Time NR: 0.79	Gad 2020*(20)*	Salomon 2012*(21)*
Adverse events	Common: 0.88	Gu 2015*(8)*	Clinical Judgement
	Infrequent: 0.70	Gu 2015*(8)*	Salomon 2012*(21)*

AMSTAR table

First author last name																
	1. Components of PICO			4. Comprehensive literature search strategy			8. Included studies characteristics			12 & 13. Potential RoB impact assessment						
		2. Development of methods a priori			5. Study selection in duplicate			9 a, b. Satisfactory RoB assessment			14. Explanation for and discussion of any heterogeneity					
			3. Clear selection criteria			6. Data extraction in duplicate			10. Source of funding in included studies			15. Adequate investigation of publication bias				
							7. List of excluded studies			11. Appropriate statistical combination					16. Report of conflict of interest	
																Quality
Hong (2018) *(1)*	Yes	Partial yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	H
Sundstrom (2015) *(2)*	Yes	Partial yes	Yes	Yes	No	No	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	M
Brunstrom (2019) *(3)*	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Brunstrom (2016) *(4)*	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	M
Zonneveld (2018) *(5)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Thomopoulos (2016) *(38)*	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes	No	Yes	CL
Taverny (2016) *(45)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Parsons (2016) *(46)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	H
Van Middelaar (2018) *(47)*	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Wright (2018) *(49)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Xiao (2018) *(50)*	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes	Yes	No	No	Yes	No	Yes	Yes	Yes	L
Musini (2015) *(51)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Tully (2016) *(52)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Ang (2018) *(53)*	Yes	No	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	M
Kunutsor (2017) *(54)*	Yes	No	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	M
Dimou (2019) *(55)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Hussain (2018) *(56)*	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Musini (2019) *(57)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	H
Wong (2015) *(58)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Zhang (2020) *(59)*	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	M
Chen (2018) *(60)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Xu (2015) *(61)*	Yes	No	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	M
Wiysonge (2017) *(62)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	M

Wang (2018) *(63)*	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	M
Bangalore (2016) *(64)*	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	M
Palla (2017) *(65)*	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	M
Tran (2017) *(66)*	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	M
Ohtsubu (2019) *(67)*	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	M
Lin (2017) *(134)*	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	M
Jeffers (2017) *(70)*	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Partial yes	No	No	No	Yes	CL
Garjon (2020) *(71)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Huang (2016) *(73)*	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	M
He (2017) *(74)*	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	M
Lu (2017) *(76)*	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Cheng (2016) *(77)*	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	M
Mallat (2016) *(97)*	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	H
Kawalec (2018) *(98)*	Yes	Partial yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	H
Du (2018) *(99)*	Yes	No	No	Yes	Yes	Yes	Partial yes	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	M
Arguedas (2020) *(101)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Murad (2019) *(102)*	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	M
Garrison (2017) *(103)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Saiz (2017) *(104)*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Greer (2016) *(111)*	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	H
Conn (2015) *(112)*	Yes	No	Yes	Yes	Yes	Yes	Partial yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	M
Reeves (2021) *(113)*	Yes	Partial yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	NA*	NA*	No	NA*	Yes	M
Morrissey (2017) *(114)*	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	H
Ruppar (2017) *(115)*	Yes	No	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	H
Xu (2018) *(116)*	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	M
Georgiopoulos (2018) *(117)*	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No	NA*	NA*	No	No	Yes	CL
Tucker (2017) *(118)*	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Fletcher (2015) *(119)*	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	H
Reboussin (2018) *(120)*	Yes	Partial yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	H
Sheppard (2020) *(121)*	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	L
Anand (2019) *(122)*	Yes	Yes	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	H

NA*: No meta-analysis conducted
H: high quality, M: moderate quality, L: low quality, CL: critically low

The following are primary studies, statistical reports, meta-analyses based on individual patient data or non-systematic reviews: Anderson (1994), Berglund (1976), Birtwistle (2004), Chahoud (2015), Cheung (2017), Ding (2020), Karmali (2018), NGC (2019), Omura (2004), Park (2017), Pedrosa (2011), Rahman (2006), Rakugi (2013), Rimoldi (2013), Tobe (2011), Virani (2020), Wood (2020), and Xu (2015). AMSTAR is n/a for these types of reports.

Full text of questions addressed

1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study design for the inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?

9a. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (RCT)

9b. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (NRSI)

10. Did the review authors report on the sources of funding for the studies included in the review?

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? (RCT)

11b If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? (RCT)

12 If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

13 Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

14 Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

15 If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

16 Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

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