OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE
Evidence-Based Practice Summary
Controlling Hypertension in the Clinical Setting

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BACKGROUND AND RATIONALE

Hypertension is a very significant health issue in the United States. Fifty million or more Americans have high blood pressure that warrants treatment, according to the National Health and Nutrition Examination Survey (NHANES) survey. The United States Preventive Services Task Force (USPSTF) recommends that clinicians screen adults aged 18 and older for high blood pressure. (PQRS 236, 2015).

The most frequent and serious complications of uncontrolled hypertension include coronary heart disease, congestive heart failure, stroke, ruptured aortic aneurysm, renal disease, and retinopathy. The increased risks of hypertension are present in individuals ranging from 40 to 89 years of age. For every 20 mmHg systolic or 10 mmHg diastolic increase in blood pressure, there is a doubling of mortality from both ischemic heart disease and stroke. Better control of blood pressure has been shown to significantly reduce the probability that these undesirable and costly outcomes will occur. The relationship between the measure (control of hypertension) and the long-term clinical outcomes listed is well established. In clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence (35-40 percent), myocardial infarction incidence (20-25 percent) and heart failure incidence (>50 percent) (PQRS 236, 2015). The National Quality forum based their measure for screening high blood pressure and follow-up on the JNC 7 (2003) recommendations. In 2014 the 2003 JNC 7 was updated with the JNC 8, but PQRS measure 236, to-date, has not been updated to reflect the most recent JNC recommendations. We have included both guidelines in this brief as well as a comparison table on pages 33-35 for further information.

There is strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90 mm Hg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mm Hg. However, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so a BP of less than 140/90 mm Hg for is recommended for those groups. The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years. There is evidence to support initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy (JNC 8, 2014).

Office of Clinical Integration and EBP GRADE Table

ASK THE QUESTION

In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?

SEARCH FOR EVIDENCE

Databases included Ovid MEDLINE, Cochrane Database of Systematic Reviews, and National Guideline Clearinghouse and looked at references and citing articles

Ovid MEDLINE search strategy included:

1   exp Hypertension/dh, dt, nu, rh, su, th [Diet Therapy, Drug Therapy, Nursing, Rehabilitation, Surgery, Therapy] (42454)
2   limit 1 to yr="2007 - 2017" (22582)
3   exp "Outcome Assessment (Health Care)"/ (830471)
4   2 and 3 (4920)
5   exp Mortality/ (255780)
6   mo.fs. (344978)
7   5 or 6 (478289)
8   2 and 7 (1072)
9   4 or 8 (5643)
10   limit 9 to (meta analysis or systematic reviews) (496)
11   limit 10 to english language (459)
12   limit 10 to abstracts (431)
13   11 or 12 (487)
14   limit 9 to randomized controlled trial (1374)
15   limit 14 to english language (1278)
16   limit 14 to abstracts (1341)
17   15 or 16 (1354)
18   17 not 13 (1343)
19   limit 18 to yr="2012 -Current" (712)
20   limit 18 to yr="2007 - 2011" (631)
21   exp "Continuity of Patient Care"/ (136951)
22   9 and 21 (100)
23   (follow* adj2 up adj10 (patient* or care or therap* or treat* or regimen* or interven*)).mp. (294247)

24   9 and 23 (517)
25   22 or 24 (606)
26   exp Time/ (725345)
27   9 and 26 (841)
28   ((long* adj2 term*) or (follow* adj2 up) or (follow* adj5 patient*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1190316)
29   27 and 28 (397)
30   25 or 29 (868)
31   limit 30 to english language (808)
32   limit 30 to abstracts (853)
33   31 or 32 (863)
34   33 not (13 or 17) (539)
35   limit 13 to yr="2012 -Current" (273)
36   21 or 23 or 26 or 28 (1868554)
37   35 and 36 (88)
Filters/limits included systematic reviews published in English in the last 5 years

CRITICALLY ANALYZE THE EVIDENCE

The literature search resulted in numerous studies reporting on multiple interventions and outcomes. Due to the initial volume of studies, we narrowed our analysis to include systematic reviews from the 5 years. In order to simplify the review process, we grouped the evidence into treatments modalities with outcomes: (1) Blood Pressure Control with Diuretics; (2) Blood Pressure Control with renin-angiotensin (RAS) inhibitors; (3) Blood Pressure Control with Supplements; (4) Blood Pressure Control with Weight-Loss Drugs; (5) Blood Pressure Control with Non-Pharmacologic Modalities; (6) Mortality of Patients Controlling Hypertension with Diuretics (7); Mortality of Patients Controlling Hypertension with RAS inhibitors; (8) Mortality of Patients Controlling Hypertension with Beta-Blockers; (9) Mortality of Patients Controlling Hypertension with Weight-Loss Drugs; (10) Cardiovascular Morbidity of Patients Controlling Hypertension with Diuretics; (11) Cardiovascular Morbidity of Patients Controlling Hypertension with RAS inhibitors; (12) Cardiovascular Morbidity of Patients Controlling Blood Pressure with Beta-Blockers; (13) Cardiovascular Morbidity of Patients Controlling Blood Pressure with Weight-Loss Drugs; (14) Mortality of Patients Controlling Hypertension with Non-Pharmacologic Modalities; (15) Cardiovascular Morbidity of Patients Controlling Blood Pressure with Non-Pharmacologic Modalities

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Summary of Findings

The quality of the overall evidence ranged from very low to moderate mostly due to inconsistency among studies analyzed. Overall, thiazides and thiazide like diuretics lowered blood pressure (BP) more than RAS inhibitors, and there was no change in reduction of BP with higher doses of thiazides. RAS inhibitors lowered systolic blood pressure (SBP) more than alpha-blockers but not more than calcium channel-blockers and thiazides, and had the same effect on SBP as beta-blockers. Concerning diastolic blood pressure (DBP), RAS inhibitors have the same effect as thiazides.

Garlic, fish oil, and potassium supplements reduced BP, while vitamin D had no effect. Results varied for studies evaluating the effect of weight-loss drugs on reduction of BP.

Non-pharmacologic modalities varied in their effect on BP. Device-guided breathing devices, spinal manipulation therapy, and stress reduction techniques showed no significant decrease in blood pressure while tailored interventions had promising but not significant results. Weight reduction diets showed a significant change in BP.

Diuretics, beta-blockers and RAS inhibitors compared to placebos and to each other had no effect on mortality.

Diuretics, beta-blockers and RAS inhibitors lower the risk of composite cardiovascular events. The relative risk for cardiovascular events was the same for diuretics and RAS inhibitors, but RAS inhibitors decreased CV morbidity more than beta-blockers.

1. Blood Pressure Control with Diuretics: Five systematic reviews were found evaluating the treatment of hypertension with various diuretics. One review (Garjon 2017) sought to determine the differences in clinical outcomes between monotherapy and combination therapy with thiazides as an initial treatment for hypertension. This study was unable to draw any conclusions due to the low number of included participants. The second review (Peterzan 2012) examined the placebo-adjusted dose-response effect of hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure. The estimated dose of each drug predicted to reduce systolic BP by 10mmHg was 1.4 mg bendroflumethiazide, 8.6mg chlorthalidone, and 26.4 mg hydrochlorothiazide with a similar potency series for diastolic BP. There was no evidence of a difference in maximum reduction of systolic BP by high doses of different thiazides. The third review (Roush 2016) compared the antihypertensive effects of hydrochlorothiazide (HCTZ) and indapamide (INDAP). INDAP lowered systolic BP more than HCTZ (-5.1 mmHg vs -3.6 mmHg respectively). The fourth study (Xue 2015) evaluated the benefits and harms of RAS-inhibitors with thiazides. Thiazides lowered SBP to a greater degree than RAS inhibitors (WMD1.56. 95% CI 1.16-1.96), but had the same effect as RAS inhibitors on DBP. The fifth systematic review (Yano 2014) examined the effects of antihypertensive treatments (which included diuretics) on cardiovascular disease in Asian populations. Blood pressure decreased using pharmacologic antihypertensive treatments from 160.3 ± 17.8/87.3 ± II. I mmHg to 140.2 ± 16.6/ 78.4 ± 9.5 mmHg.
   Quality of Evidence: Moderate

2. Blood Pressure Control with renin-angiotensin (RAS) inhibitors: We reviewed two systematic reviews assessing the impact of RAS inhibitors on blood pressure. The first review (Xue 2015) compared RAS inhibitors with calcium channel blockers (CCBs), thiazides, beta-blockers, alpha-blockers, and central nervous system (CNS) active drugs. RAS inhibitors lowered SBP more than alpha-blockers (WMD -2.38, 95% CI -3.98 to -0.78), but not more than CCBS and thiazides. RAS inhibitors had the same effect on SBP as CNS active drugs and beta-blockers. RAS inhibitors had the same effect on DBP as thiazides, alpha-blockers, and CNS active drugs. Both CCBs and beta-blockers lowered DBP more than RAS inhibitors ([WMD 0.97, 95% CI 0.77 to 1.16 and WMD 0.52, 95% CI 0.17 to 0.87] respectively). The second review (Yano 2014) examined the effects of antihypertensive treatments (which included diuretics) on cardiovascular disease in Asian populations. Their analysis found no difference between RAS inhibitors and CCBs and diuretics for blood pressure control.
Quality of Evidence: Moderate

3. Blood Pressure Control with Supplements: Four systematic reviews studied the effects of various supplements on blood pressure control. One systematic review (Beveridge 2015) studied whether vitamin D or its analogues reduce blood pressure. At both the trial and individual level, no effect of vitamin D supplementation was seen on SBP and DBP. The second review (Campbell 2013) reviews whether supplementation with fish oil lowers blood pressure. The meta-analysis showed a statistically significant decrease in both SBP and DBP with fish oil supplementation (SBP MD 2.56 mmHg, 95% CI 0.58 to 4.53 and DBP MD 1.47 mmHg, 95% CI 0.41 to 2.53). The third review (Poorolajal 2017) assessed the effect of oral potassium supplementation on patients with primary hypertension. Compared to the placebo, the analysis resulted in a modest, but statistically significant reduction in SBP and DBP (MD -4.25 mmHg; 95% CI: -5.96 to -2.53; and MD -2.53 mmHg; 95% CI: -4.05 to -1.02; respectively). The fourth review (Wang 2015) is an update on the evidence associated between garlic intake and BP. Meta-analysis with sensitivity analysis of subgroups in the study indicated a significant reduction in SBP and DBP in hypertensive patients (-4.4mmHg; 95% CI -7.37 to -1.42 and -2.68mmHg; 95% CI, -4.93to -0.42 respectively).
Quality of Evidence: Moderate

4. Blood Pressure Control with Weight-Loss Drugs: One systematic review (Siebenhofer 2016) assessed the long-term effects of pharmacologically induced reduction in body weight in adults with hypertension. There were various effects on blood pressure from the three drugs. Orlistat reduced SBP by 2.5mmHg (95%CI, -4.0 to -0.9) and DBP by 1.9 (95% CI, -3.0 to -0.9), Sibutramine increased DBP by 3.2 mmHg (95% CI, 1.4 to 4.9), and the one trial that assessed phentermine suggested that it lowered overall BP.
Quality of Evidence: Low

5. Blood Pressure Control with Non-Pharmacologic Modalities: Five systematic reviewes analyzed the effects of non-pharmacologic modalities on blood pressure control. One review (Mahtani 2012) evaluated whether device-guided breathing (DGB) lowered BP in adults. A sensitivity analysis that

excluded the trials sponsored by the DGB manufacturer revealed no overall effect on BP. The second review (Mangum 2012) reviewed the efficacy of spinal manipulation therapy (SMT) for treating hypertension. Statistically significant decreases in blood pressure were not observed in clinical trials with low bias when SMT was compared with effleurage massage and a 5-minute wait (The maximum improvement observed in any SMT group, in low risk of bias studies was -9.7 [95% CI, -21.1 to 1.8] systolic improvement and -9.0 [95% CI, -16.8 to -1.2] diastolic). The third review (Nagele 2014) assessed the clinical effectiveness of stress-reduction techniques in adults with hypertension. The data indicated a blood pressure-lowering effect, but the studies had methodological shortcomings and heterogeneity between them was high. Mean group differences for DBP ranged from -10 to 1 mmHg and for SBP from -12 to 10 mmHg. The fourth review (Radhakrishnan 2014) evaluated the evidence on the effectiveness of tailored interventions on self-management behaviors in individuals with hypertenstion. In some studies, improvement in self-management behaviors in the tailored intervention group, though non-significant, was accompanied by an important improvement in other outcomes associated with improvement in diastolic BP. The greatest improvement in blood pressure was found in the group that combined tailored interventions with home BP monitoring in a study that compared four formats of interventions. The fifth review (Semlitsch 2016) assessed the long-term effects of weight-reducing diets in people with hypertension on change from baseline in systolic blood pressure, change from baseline in diastolic blood pressure, and body weight reduction. The mean difference for SBP was -4.5mmHg (95% CI, -7.2 to -1.8) and the mean difference for DBP was -3.2mmHg (95% CI, -4.8 to -1.5).
Quality of Evidence: Moderate

6. Mortality of Patients Controlling Hypertension with Diuretics: There were three reviews that measured mortality as an outcome of hypertension control with diuretics. The first review (Garjon 2017) sought to determine the differences in clinical outcomes between monotherapy and combination therapy with thiazides as an initial treatment for hypertension. The confidence interval for mortality was wide (RR 1.35; 95% CI, 0.08-21.72) and the authors were unable to draw any conclusions. The second review (Wiysonge 2017) assessed the effects of beta-blockers on mortality endpoints in adults with hypertension. There was no difference in all-cause mortality between beta-blockers and placebo (RR 0.99, 95% CI 0.88 to 1.11), diuretics or renin-angiotensin system inhibitors. The third review (Xue 2015) compared RAS inhibitors with calcium channel blockers (CCBs), thiazides, beta-blockers, alpha-blockers, and central nervous system (CNS) active drugs. Compared to diuretics, the relative risk of mortality for RAS inhibitors was not significantly different (RR 1.1; 95% CI, 1.00-1.11).
Quality of Evidence: Moderate

7. Mortality of Patients Controlling Hypertension with RAS inhibitors: Three systematic reviews measured mortality as an outcome of hypertension control with RAS inhibitors. The first review (Wiysonge 2017) assessed the effects of beta-blockers on mortality endpoints in adults with hypertension. There was no difference in all-cause mortality between beta-blockers and placebo (RR 0.99, 95% CI 0.88 to 1.11), diuretics or renin-angiotensin system inhibitors. The third review (Xue 2015) compared RAS inhibitors with calcium channel blockers (CCBs), thiazides, beta-blockers, alpha-blockers, and central nervous system (CNS) active drugs. Compared to diuretics, calcium channel blockers and beta-blockers, the relative risk of

mortality for RAS inhibitors was not significantly different (RR 1.03; 95% CI, 0.98-1.09, RR 1.0; 95% CI 1.00-1.11, and RR.89; 95% CI .78-1.01 respectively). The third review (Yano 2014) examined the effects of antihypertensive treatments (which included diuretics) on cardiovascular disease in Asian populations. Their analysis found RAS inhibitors has similar effects on all-cause mortality compared to CCBs (OR 0.98; 95%CI 0.78-1.22; P=.85).
Quality of Evidence: Moderate

8. Mortality of Patients Controlling Hypertension with beta-blockers: Two systematic reviews examined the mortality of patients controlling hypertension with beta-blockers. The first review (Wiysonge 2017) assessed the effects of beta-blockers on mortality endpoints in adults with hypertension. There was no difference in all-cause mortality between beta-blockers and placebo (RR 0.99, 95% CI 0.88 to 1.11), diuretics or renin-angiotensin system inhibitors, but it was higher for beta-blockers compared to calcium-channel blockers (RR 1.07, 95% CI 1.00 to 1.14). The second review (Xue 2015) compared RAS inhibitors with calcium channel blockers (CCBs), thiazides, beta-blockers, alpha-blockers, and central nervous system (CNS) active drugs. There was no difference in mortality between beta-blockers and RAS inhibitors (RR .89, 95%CI, .78-1.01).
Quality of Evidence: Moderate

9. Mortality of Patients Controlling Hypertension with Weight-Loss Drugs: The one review (Siebenhofer 2016) that assessed the long-term effects of pharmacologically induced reduction in body weight in adults with hypertension found no studies that included mortality as a predefined outcome.
Quality of Evidence: Very Low

10. Cardiovascular Morbidity of Patients Controlling Hypertension with Diuretics: Three studies examined cardiovascular morbidity of patients controlling hypertension with diuretics. The first study (Garjon 2017) sought to determine the differences in clinical outcomes between monotherapy and combination therapy with thiazides as an initial treatment for hypertension. The confidence interval for cardiovascular morbidity was wide and the number of events too small (RR .98; 95% CI, 0.22-4.41) for the authors to draw any conclusions. The second study (Xue 2015) evaluated the benefits and harms of RAS-inhibitors with thiazides. Compared to thiazides, RAS inhibitors had a similar effect on cardiovascular morbidity (RR 1.05,95% CI 1.00-1.11). The third systematic review (Yano 2014) examined the effects of antihypertensive treatments (which included diuretics) on cardiovascular disease in Asian populations. The intervention group had a lower risk of composite CVD events (OR 0.73; 95%CI, 0.66-0.81). The meta-regression line among the 18 trials indicated that a 10 mm Hg reduction in systolic BP was associated with a reduced risk for composite CVD events (-39.5%).
Quality of Evidence: Moderate

11. Cardiovascular Morbidity of Patients Controlling Hypertension with RAS inhibitors: Two systematic reviewed evaluated the cardiovascular (CV) morbidity of patients controlling their hypertension with RAS inhibitors. The first review (Xue 2015) compared RAS inhibitors with calcium channel

blockers (CCBs), thiazides, beta-blockers, alpha-blockers, and central nervous system (CNS) active drugs. Compared to diuretics and calcium channel blockers, the relative risk of CV morbidity for RAS inhibitors was not significantly different (RR 1.05; 95% CI, 1.00-1.011 and RR 0.98; 95% CI 0.93-1.02, respectively). Compared the beta-blockers, RAS inhibitors decreased CV morbidity (RR.88; 95% CI 0.8-.98). The second review (Yano 2014) examined the effects of antihypertensive treatments (which included diuretics) on cardiovascular disease in Asian populations. Their analysis found that the intervention group had a lower risk of composite CV morbidity (OR 0.73; 95%CI, 0.66-0.81)
Quality of Evidence: Moderate

12. Cardiovascular Morbidity of Patients Controlling Blood Pressure with Weight-Loss Drugs: The one review (Siebenhofer 2016) that assessed the long-term effects of pharmacologically induced reduction in body weight in adults with hypertension found no studies that included CV morbidity as a predefined outcome.
Quality of Evidence: Very Low

13. Cardiovascular Morbidity of Patients Controlling Blood Pressure with Beta-Blockers: Two systematic reviews examined the CV morbidity of patients controlling hypertension with beta-blockers. The first review (Wiysonge 2017) assessed the effects of beta-blockers on mortality endpoints in adults with hypertension. Total CV morbidity was lower for beta-blockers compared to placebo (RR 0.88, 95% CI 0.79 to 0.97). The second review (Xue 2015) compared RAS inhibitors with calcium channel blockers (CCBs), thiazides, beta-blockers, alpha-blockers, and central nervous system (CNS) active drugs. Total CV morbidity was lower for patients using RAS inhibitors than beta-blockers (RR .88, 95% CI 0.8-.98).
Quality of Evidence: Moderate

14. Mortality of Patients Controlling Hypertension with Non-Pharmacologic Modalities: For the two systematic reviews that originally had mortality as an outcome, neither found studies that reported data for mortality (Nagele 2014 and Semlitsch 2016).
Quality of Evidence: Very Low

15. CV morbidity of Patients Controlling Hypertension with Non-Pharmacologic Modalities: Two systematic reviews assessed CV morbidity as an outcome of controlling hypertension with non-pharmacologic modalities. One review (Nagele 2014) was not able to find a study that reported data for CV morbidity. The other review (Semlitsch 2016) included one study that found that the HR for CV morbidity from dietary weight loss was 0.70 (95%CI, .57-.87).
Quality of Evidence: Low

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied*)
Outcome: Blood Pressure Control **Modality: Diuretics**						☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome*)
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 5 # of Systematic Reviews: 5						
Garjon, J. (2017) *Cochrane Database of Systematic Reviews*	To determine if there are differences in clinical outcomes between monotherapy and combination therapy with thiazides as initial treatment for primary hypertension	Systematic Review	3 studies (monotherapy: 335 participants; combination therapy: 233 participants)	The numbers of included participants and, hence the number of events, were too small to draw any conclusion about the relative efficacy of monotherapy versus combination therapy as initial treatment for primary hypertension	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain*)
Peterzan, M. A. (2012) *Hypertension*	To examine the placebo-adjusted dose-response effect of thiazide and thiazide-like diuretic monotherapy on BP.	Systematic Review with meta-analysis	26 trials examined hydrochlorothiazide, 3 examined chlorthalidone, and 1 examined bendroflumethiazide. Studies included a total of 4683 subjects	Meta-regression of the effect of thiazides on systolic BP showed a log-linear relationship with a potency series: bendroflumethiazide>chlorthalidone>hydrochlorothiazide. The estimated dose of each drug predicted to reduce systolic BP by 10 mm Hg was 1.4, 8.6, and 26.4 mg, respectively, and there was no evidence of a difference in maximum reduction of systolic BP by high doses of different thiazides.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found*) Increase Quality Rating if: ☐ Large Effect

				Potency series for diastolic BP, serum potassium, and urate were similar to those seen for systolic BP		☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect
Roush, G. C. (2016) *Hypertension*	To compare hydrochlorothiazide (HCTZ) with indapamide (INDAP) and chlorthalidone on antihypertensive potency or metabolic effects	Systematic review	14 randomized trials with 883 patients	In random effects meta-analysis, INDAP lowered systolic blood pressure more than HCTZ: -5.1 mmHg (95% confidence interval, -8.7 to -1.6); P=0.004 and -3.6 mmHg (95% confidence interval, -7.3 to 0.0); P=0.052, respectively. There were no detectable differences between HCTZ and INDAP in metabolic adverse effects, including effects on serum potassium.	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low
Xue, H. (2015) *Cochrane Database of Systematic Reviews*	To evaluate the benefits and harms of first-line RAS inhibitors compared to other first-line antihypertensive drugs in patients with hypertension.	Systematic Review	RAS vs thiazides: 9 studies 25817 participants	Thiazides lowered SBP to a greater degree than RAS inhibitors (WMD 1.56, 95% CI 1.16 to 1.96), but had much the same effect as RAS inhibitors on DBP (WMD -0.15, 95% CI -0.40 to 0.10;)	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	
Yano, Y. (2014) *Journal of the American Society of Hypertension*	To examine the effects of antihypertensive treatment on cardiovascular disease (CVD) in Asian populations.	Systematic Review where the trials were divided and analyzed in two sub groups. The first subgroup compared active antihypertensive treatments (which include diuretics) with reference group and the second subgroup compared different classes of antihypertensive agents (RAS-inhibitors and calcium channel blockers) with similar BP control.	18 trials with 23,215 and 21,986 hypertensive patients in the intervention (ie, strict blood pressure [BP] lowering or add-on treatment) and reference groups, respectively (mean age, 65 years; follow-up duration, 3.2 years)	In the first subgroup analysis, BP was decreased in the intervention group from 160.3 ± 17.8/87.3 ± II. I mm Hg to 140.2 ± 16.6/ 78.4 ± 9.5 mm Hg (reference group from 160.0 ± 16.9/ 87.2 ± 10.9 m Hg to 146.5 ± 16.4/80.8 ± 9.8 mm Hg) (P < .00 I in BP difference between groups). In the second subgroup analysis, BP was lower in the intervention group than reference group; mean difference was -0.7 mm Hg in SBP (95% CI, -1 .. I to -0.3; P < .00 I) and was -0.5 mm Hg in DBP (95% CI, -0.7 to -0.2; P = .002), with significant heterogeneity between studies (P < .001)	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

Office of Clinical Integration and EBP GRADE Table

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied*)
Outcome: Blood Pressure Control **Modality: RAS-inhibitors**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome*)
Total # of Studies: 2 # of Systematic Reviews: 2						
Xue, H. (2015) *Cochrane Database of Systematic Reviews*	To evaluate the benefits and harms of first-line RAS inhibitors compared to other first-line antihypertensive drugs in patients with hypertension.	Systematic Review	RAS inhibitors vs calcium channel-blockers: 19 studies, 36210 participants RAS vs thiazides: 9 studies 25817 participants RAS inhibitors vs beta-blockers: 15 studies 1-805 participants RAS vs. alpha blockers: 3 studies, 38- participants RAS vs Central Nervous System (CNS) active drug: 1 study 56 participants	CCBs lowered SBP and DBP to a greater degree than RAS inhibitors (SBP: WMD 1.20, 95% CI 0.86 to 1.53; DBP: WMD 0.97, 95% CI 0.77 co 1.16). Thiazides lowered SBP co a greater degree than RAS inhibitors (WMD 1.56, 95% CI 1.16 to 1.96), but had much the same effect as RAS inhibitors on DBP (WMD -0.15, 95% CI -0.40 to 0.10;) Beta-blockers lowered DBP more than RAS inhibitors (DBP: WMD 0.52, 95% CI 0.17 to 0.87). The effect on SBP did not differ between the two classes of drug (WMD -0.49, 95% CI -1.16 to 0.18). RAS inhibitors lowered SBP more than alpha-blockers did (WMD -2.38, 95% CI -3.98 to -0.78); but did not differ in their effect on DBP (DBP, WMD -0.12, 95% CI -1.09 to 0.85) When compared with CNS active drugs in one small trial, RAS inhibitors did not differ in their effect on SBP (WMD 1.30, 95% CI -6.01 to 8.61), DBP (WMD - 0.30, 95% CI -1.85 to 1.25)	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain*) ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

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Yano, Y. (2014) *Journal of the American Society of Hypertension*	To examine the effects of antihypertensive treatment on cardiovascular disease (CVD) in Asian populations.	Systematic Review where the trials were divided and analyzed in two sub groups. The first subgroup compared active antihypertensive treatments (which include diuretics) with reference group and the second subgroup compared different classes of antihypertensive agents (RAS-inhibitors and calcium channel blockers) with similar BP control.	18 trials with 23,215 and 21,986 hypertensive patients in the intervention (ie, strict blood pressure [BP] lowering or add-on treatment) and reference groups, respectively (mean age, 65 years; follow-up duration, 3.2 years)	In the first subgroup analysis, BP was decreased in the intervention group from 160.3 ± 17.8/87.3 ± II. I mm Hg to 140.2 ± 16.6/ 78.4 ± 9.5 mm Hg (reference group from 160.0 ± 16.9/ 87.2 ± 10.9 m Hg to 146.5 ± 16.4/80.8 ± 9.8 mm Hg) (P < .00 I in BP difference between groups). In the second subgroup analysis, no difference was found for any outcome between RAS inhibitors and CCBS or diuretics	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	<u>Increase Quality Rating if:</u> ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						<u>Lower Quality Rating if:</u> ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied*)
Outcome: Blood Pressure Control **Modality: Supplements**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome*)
Total # of Studies: 4 # of Systematic Reviews: 4						
Beveridge, L. A. (2015) *JAMA Internal Medicine*	To systematically review whether supplementation with vitamin D or its	Systematic review with meta-analysis	52 studies included in systematic review, 46 trials included in meta-analysis (4541 patients) with 27 individual patient data sets (3092 participants)	At the trial level, no effect of vitamin D supplementation was seen on SBP (effect size, 0.0 [95% CI, -0.8 to 0.8] mm Hg; P=.97; I2=21%) or DBP (effect size, -0.1 [95% CI, -0.6 to 0.5] mm Hg; P=.84; I2=20%). Similar results were found analyzing individual patient data for SBP (effect size, -0.5 [95% CI, -1.3 to 0.4] mm	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was	

	analogues reduce BP.			Hg; P=.27; I2=0%) and DBP (effect size, 0.2 [95% CI, -0.3 to 0.7] mm Hg; P=.38; I2=0%). Subgroup analysis did not reveal any baseline factor predictive of a better response to therapy.	not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain*)
Campbell, F. (2013) *European Journal of Preventative Medicine*	To systematically review whether supplementation with fish oil will lower BP.	Systematic review with meta-analysis	17 studies with 1524 normotensive and hypertensive participants with BP 140/85 mmHg at least.	**Hypertensive participants:** The meta-analysis showed a statistically significant reduction in SBP in hypertensive patients given fish-oil supplements for a minimum of 8 weeks (2.56 mmHg, 95% CI 0.58 to 4.53). A statistically significant reduction in DBP was also found (1.47 mmHg, 95% CI 0.41 to 2.53). **Normotensive participants**: The meta-analysis showed a non-significant reductions in SBP and DBP (0.50 mmHg, 95% CI 0.45 to 1.44; 0.53 mmHg, 95% CI 0.19 to 1.24, respectively) in participants taking fish-oil capsules for a minimum of 8 weeks	Study Limitations = ☒ None *Systematic Review* ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect
Poorolajal, J. (2017) *PLoS ONE*	To assess the effect of oral potassium supplementation on blood pressure in patients with primary hypertension.	Systematic Review with meta-analysis	23 trials with 1213 participants	Compared to placebo, potassium supplementation resulted in modest but significant reductions in both SBP (MD -4.25 mmHg; 95% CI: -5.96 to -2.53; I2 = 41%) and DBP (MD -2.53 mmHg; 95% CI: -4.05 to -1.02; I2 = 65%). The mean changes in SBP (MD -8.89 mmHg; 95% CI: -13.67 to -4.11) and DBP (MD -6.42 mmHg; 95% CI: -10.99 to -1.84) was significantly higher in the intervention group than the control group.	Study Limitations = ☐ None *Systematic Review* ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low
Wang, H. P. (2015) *Journal of*	To update the evidence on the association	Systematic Review	17 studies (799 for DBP and 735 for SBP)	Pooled analysis showed that garlic intake caused a 3.75-mm Hg reduction (95% confidence interval [CI], -5.04 to -2.45, I(2)	Study Limitations = ☐ None *Systematic Review*	

Clinical Hypertension	between garlic intake and BP and to examine the association according to dosage and duration			=30.7%; P<.001) in systolic BP and a 3.39-mm Hg reduction (95% CI, -4.14 to -2.65, I(2) =67%; P<.001) in diastolic BP compared with controls. Meta-analysis of subgroups showed a significant reduction in systolic BP in hypertensive (-4.4 mm Hg; 95% CI, -7.37 to -1.42, I(2) =0.0%; P=.004) but not normotensive patients. No significant reduction in diastolic BP was seen. After sensitivity analysis, heterogeneity disappeared and significant diastolic BP reduction (-2.68 mm Hg, 95% CI, -4.93 to -0.42, I(2) =0.0%; P=.020) was shown in hypertensive patients.	☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied*)
Outcome: Blood Pressure Control **Modality: Weight loss drugs**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 1 # of Systematic Reviews: 1						☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome*) ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide*
Siebenhofer, A. (2016) *Cochrane Database of Systematic Reviews*	To assess the long-term effects of pharmacologically induced reduction in body weight in adults with essential hypertension on all-cause mortality, cardiovascular	Systematic Review	9 studies compared orlistat, sibutramine, and phentermine/topiramate	Orlistat reduced systolic blood pressure as compared to placebo by -2.5 mm Hg (mean difference (MD); 95% confidence interval (CI): -4.0 to -0.9 mm Hg) and diastolic blood pressure by -1.9 mm Hg (MD; 95% CI: -3.0 to -0.9 mm Hg). Sibutramine increased diastolic blood pressure compared to placebo by +3.2 mm Hg (MD; 95% CI: +1.4 to +4.9 mm Hg). The one trial that investigated phentermine/topiramate suggested it lowered blood pressure.	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	

| | morbidity, and adverse events | | | | | *confidence intervals and the results are uncertain)*

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low |

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☒ Studies inconsistent *(wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*
Outcome: Blood Pressure Control Modality: Non-pharmacologic						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 5 # of Systematic Reviews: 5						

						□ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome*)
Mahtani, K. R. (2012). *Journal of Hypertension*	To evaluate whether device-guided breathing (DGB) lowers blood pressure (BP) in adults.	Systematic review with meta-analysis	8 trials of the Resperate device (InterCure Ltd, Lod, Israel), consisting of 494 adult patients	Use of this device resulted in significantly reduced SBP by 3.67 mmHg [95% confidence interval (CI) = -5.99 to -1.39; P = 0.002] and decreased DBP by 2.51 mmHg (95% CI = -4.15 to -0.87; P = 0.003). However, sensitivity analysis was carried out excluding the five trials sponsored by or involving the manufacturers of the device, which revealed no overall effect on BP using the device.	Study Limitations = □ None ***Systematic Review*** □ Review did not address focused clinical question □ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain*) □ Publication Bias
Mangum, K. (2012) *Journal of Manipulative &Physiological Therapeutics*	To perform a qualitative literature review on the efficacy of Spinal Manipulation Therapy (SMT) for treating HTN	Systematic review	10 studies	The maximum improvement observed in any SMT group, in low risk of bias studies was -9.7 (95% confidence interval [CI], -21.1 to 1.8) systolic improvement and -9.0 (95% CI, -16.8 to -1.2) diastolic; and in unclear risk of bias studies, it was -17.2 (95% CI, -20.7 to -13.7) systolic and -13.0 (95% CI, -15.4 to -10.6) diastolic. **Statistically significant decreases in blood pressure were not observed in clinical trials with low bias when SMT was compared with effleurage massage and a 5-minute wait.** The studies with more risk of bias showed a greater treatment effect.	Study Limitations = □ None ***Systematic Review*** □ Review did not address focused clinical question □ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	(*e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found*) Increase Quality Rating if: □ Large Effect □ Dose-response gradient □ Plausible confounders or other biases increase certainty of effect
Nagele, E. (2014) *Journal of Hypertension*	To assess the clinical effectiveness of stress-	Systematic Review	17 RCTs	The data indicated a blood pressure-lowering effect, but the studies had methodological shortcomings and heterogeneity between them was high.	Study Limitations = □ None ***Systematic Review*** □ Review did not address focused clinical question	Quality (certainty) of evidence for studies as a whole: □ High

	reduction techniques in adults with essential hypertension.			Mean group differences for DBP ranged from -10 to 1 mmHg and for SBP from -12 to 10 mmHg.	☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☒ Moderate ☐ Low ☐ Very Low
Radhakrishnan, K. (2012) *Journal of Advanced Nursing*	To evaluate the evidence on the effectiveness of tailored interventions on self-management behaviors in individuals with heart disease, hypertension or type 2 diabetes.	Systematic Review	10 studies	In some studies, improvement in self-management behaviours in the tailored intervention group, though non-significant as compared to the control group, was accompanied by an important improvement in other outcomes associated with long-term condition management such as improvement in diastolic BP.

The greatest improvement in blood pressure was found in the group that combined tailored interventions with home BP monitoring in a study that compared four formats of interventions. | Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies | |
| Semlitsch, T. (2016) *Cochrane Database of Systematic Reviews* | to assess the long-term effects of weight-reducing diets in people with hypertension on all-cause mortality, cardiovascular morbidity, and adverse events and to assess the long-term effects of weight-reducing diets in people with hypertension on change from baseline in systolic blood | Systematic review | 3 studies, 731 participants | systolic blood pressure: mean difference (MD) -4.5 mm Hg (95% CI -7.2 to -1.8 mm Hg), and diastolic blood pressure: MD -3.2 mm Hg (95% CI -4.8 to -1.5 mm Hg) | Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies | |

	pressure, change from baseline in diastolic blood pressure, and body weight reduction				

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied*)
Outcome: Mortality **Modality: Diuretics**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 3 # of Systematic Reviews: 3						☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome*) ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain*) ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness*
Garjon, J. (2017) Cochrane Database of Systematic Reviews	To determine if there are differences in clinical outcomes between monotherapy and combination therapy with thiazides as initial treatment for primary hypertension	Systematic Review	3 studies, 568 participants	Mortality outcome: RR 1.35 (95% CI .08-21.72) The numbers of included participants and, hence the number of events, were too small to draw any conclusion about the relative efficacy of monotherapy versus combination therapy as initial treatment for primary hypertension.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	
Wiysonge, C. S. (2017) *Cochrane Database of Systematic Reviews*	To assess the effects of beta-blockers on morbidity and mortality endpoints in	Systematic Reviews	13 Studies 40,245 participants	There was no difference in all-cause mortality between beta-blockers and placebo (RR 0.99, 95% CI 0.88 to 1.11), diuretics or renin-angiotensin system inhibitors, but it was higher for beta-	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive	

					Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	*of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect
	adults with hypertension			blockers compared to calcium-channel blockers (RR 1.07, 95% CI 1.00 to 1.14).		
Xue, H. (2015) *Cochrane Database of Systematic Reviews*	To evaluate the benefits and harms of first-line RAS inhibitors compared to other first-line antihypertensive drugs in patients with hypertension	Systematic Review	RAS vs thiazides: 1 study 24,309 participants	RAS vs thiazides: RR 1.0 (95% CI 1.00-1.11)	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low ☐ Very Low

The GRADE criteria used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?	Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across*
Outcome: Mortality	

Modality: RAS-inhibitors						*studies, populations, interventions, or outcomes varied)*
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	☐ Studies are indirect
Total # of Studies: 3 # of Systematic Reviews: 3						*(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*
Wiysonge, C. S. (2017) *Cochrane Database of Systematic Reviews*	To assess the effects of beta-blockers on morbidity and mortality endpoints in adults with hypertension	Systematic Reviews	13 Studies 40,245 participants	There was no difference in all-cause mortality between beta-blockers and placebo (RR 0.99, 95% CI 0.88 to 1.11), diuretics or renin-angiotensin system inhibitors, but it was higher for beta-blockers compared to calcium-channel blockers (RR 1.07, 95% CI 1.00 to 1.14).	Study Limitations = ☒ None **Systematic Review** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*
Xue, H. (2015) *Cochrane Database of Systematic Reviews*	To evaluate the benefits and harms of first-line RAS inhibitors compared to other first-line antihypertensive drugs in patients with hypertension	Systematic Review	RAS vs CCS: 5 Studies 35,226 participants RAS vs thiazides: 1 study 24,309 participants RAS vs beta blockers: 1 study 9193 participants	RAS vs CCBs: RR 1.03 (95%CI .98-1.09) RAS vs thiazides: RR 1.0 (95% CI 1.00-1.11) RAS vs beta blockers: RR .89 (95% CI .78-1.01)	Study Limitations = ☐ None **Systematic Review** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if:
Yano, Y. (2014) *Journal of the American Society of Hypertension*	To examine the effects of antihypertensive treatment on cardiovascular disease (CVD) in Asian populations.	Systematic Review where the trials were divided and analyzed in two sub groups. The first subgroup compared active antihypertensive treatments (which include diuretics) with reference group and the second subgroup compared different classes of antihypertensive agents (RAS-inhibitors and calcium channel blockers) with similar BP control.	18 trials with 23,215 and 21,986 hypertensive patients in the intervention (ie, strict blood pressure [BP] lowering or add-on treatment) and reference groups, respectively (mean age, 65 years; follow-up duration, 3.2 years)	Subgroup 1: intervention group showed a significant reduction of all-cause mortality (OR 0.82; 95% CI, 0.72-.93; P=.003) Subgroup2: no difference was found RAS inhibitors has similar effects on all-cause mortality compared to CCBs (OR 0.98; 95%CI 0.78-1.22; P=.85)	Study Limitations = ☐ None **Systematic Review** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High

						☒ Moderate ☐ Low ☐ Very Low

The GRADE criteria used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*
Outcome: Mortality **Modality: Beta-Blockers**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*
Total # of Studies: 2 # of Systematic Reviews: 2						
Wiysonge, C. S. (2017) *Cochrane Database of Systematic Reviews*	To assess the effects of beta-blockers on morbidity and mortality endpoints in adults with hypertension	Systematic Reviews	13 Studies 40,245 participants	There was no difference in all-cause mortality between beta-blockers and placebo (RR 0.99, 95% CI 0.88 to 1.11), diuretics or renin-angiotensin system inhibitors, but it was higher for beta-blockers compared to calcium-channel blockers (RR 1.07, 95% CI 1.00 to 1.14).	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	☐ Studies are imprecise *(When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*
Xue, H. (2015) *Cochrane Database of Systematic Reviews*	To evaluate the benefits and harms of first-line RAS inhibitors compared to other first-line	Systematic Review	RAS vs CCS: 5 Studies 35,226 participants RAS vs thiazides: 1 study 24,309 participants	RAS vs CCBs: RR 1.03 (95%CI .98-1.09) RAS vs thiazides: RR 1.0 (95% CI 1.00-1.11) RAS vs beta blockers: RR .89 (95% CI .78-1.01)	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question	☐ Publication Bias *(e.g. pharmaceutical company sponsors study*

| | antihypertensive drugs in patients with hypertension | | RAS vs beta blockers: 1 study 9193 participants | | ☐ Search was not detailed or exhaustive
☒ Quality of the studies was not appraised or studies were of low quality
☐ Methods and/or results were inconsistent across studies | *on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☒ Moderate
☐ Low
☐ Very Low |

The GRADE criteria used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*
Outcome: Mortality **Modality: Weight-loss drugs**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 1 # of Systematic Reviews: 1						☐ Studies are indirect
Siebenhofer, A. (2016) Cochrane Database of Systematic Reviews	To assess the long-term effects of pharmacologically induced reduction in body weight in adults	Systematic Review	9 studies	No study included mortality and cardiovascular morbidity as predefined outcomes.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not	*(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*

| | with essential hypertension on all-cause mortality, cardiovascular morbidity, and adverse events | | | | appraised or studies were of low quality
☒ Methods and/or results were inconsistent across studies | ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain*)

☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☐ Low
☒ Very Low |

The GRADE criteria used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?	Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations,*
Outcome: Cardiovascular morbidity **Modality: Diuretic**	

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Author/Date	Purpose of Study	Study Design & Methods	Sample	Outcomes	Design Limitations	interventions, or outcomes varied)
	**Total # of Studies: 3 # of Systematic Reviews: 3**	☐ Studies are indirect
Garjon, J. (2017) Cochrane Database of Systematic Reviews	To determine if there are differences in clinical outcomes between monotherapy and combination therapy with thiazides as initial treatment for primary hypertension	Systematic Review	3 studies, 568 participants	RR .98 (95% CI .22-4.41) The numbers of included participants and, hence the number of events, were too small to draw any conclusions.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	*(PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain)*
Xue, H. (2015) *Cochrane Database of Systematic Reviews*	To evaluate the benefits and harms of first-line RAS inhibitors compared to other first-line antihypertensive drugs in patients with hypertension	Systematic Review	RAS vs thiazides: 2 studies 24,379 participants	RAS vs thiazides: RR 1.05 (95% CI 1.00-1.11)	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient
Yano, Y. (2014) *Journal of the American Society of Hypertension*	To examine the effects of antihypertensive treatment on cardiovascular disease (CVD) in Asian populations.	Systematic Review where the trials were divided and analyzed in two sub groups. The first subgroup compared active antihypertensive treatments (which include diuretics) with reference group and the second subgroup compared different classes of antihypertensive agents (RAS-inhibitors and calcium channel blockers) with similar BP control.	18 trials with 23,215 and 21,986 hypertensive patients in the intervention (ie, strict blood pressure [BP] lowering or add-on treatment) and reference groups, respectively (mean age, 65 years; follow-up duration, 3.2 years)	Subgroup 1: intervention group had a lower risk of composite CVD events (odd ratio [OR], 0.73; 95% confidence interval [CI], 0.66-0.81) Subgroup2: no difference was found The meta-regression line among the 18 trials indicated that a 10 mm Hg reduction in systolic BP was associated with a reduced risk for composite CVD events (-39.5%)	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality	☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low

					Methods and/or results were inconsistent across studies	☐ Very Low

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied*)
Outcome: Cardiovascular morbidity **Modality: RAS-inhibitors**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome*)
Total # of Studies: 2 # of Systematic Reviews: 2						
Xue, H. (2015) *Cochrane Database of Systematic Reviews*	To evaluate the benefits and harms of first-line RAS inhibitors compared to other first-line antihypertensive drugs in patients with hypertension	Systematic Review	RAS vs CCS: 6 Studies 35,223 participants RAS vs thiazides: 2 study 24,379 participants RAS vs beta blockers: 2 study 9239 participants	RAS vs CCBs: RR 0.98 (95%CI .93-1.02) RAS vs thiazides: RR 1.05 (95% CI 1.00-1.11) RAS vs beta blockers: RR .88 (95% CI 0.8-.98)	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	☐ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain*)
Yano, Y. (2014) *Journal of the American Society of Hypertension*	To examine the effects of antihypertensive treatment on cardiovascular disease (CVD) in Asian populations.	Systematic Review where the trials were divided and analyzed in two sub groups. The first subgroup compared active antihypertensive treatments (which include diuretics) with reference group and the second subgroup compared different classes of antihypertensive agents (RAS-inhibitors and calcium channel blockers) with similar BP control.	18 trials with 23,215 and 21,986 hypertensive patients in the intervention (ie, strict blood pressure [BP] lowering or add-on treatment) and reference groups, respectively (mean age, 65 years; follow-up duration, 3.2 years)	Subgroup 1: intervention group had a lower risk of composite CVD events (odd ratio [OR], 0.73; 95% confidence interval [CI], 0.66-0.81) Subgroup2: no difference was found The meta-regression line among the 18 trials indicated that a 10 mm Hg reduction in systolic BP was associated with a reduced risk for composite CVD events (-39.5%)	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality	☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found*)

| | | | | | | ☐ Methods and/or results were inconsistent across studies | Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☒ Moderate
☐ Low
☐ Very Low |

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied*)
Outcome: Cardiovascular morbidity **Modality: Beta-blocker**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome*)
Total # of Studies: 5 # of Systematic Reviews: 5						
Wiysonge, C. S. (2017) *Cochrane Database of Systematic Reviews*	To assess the effects of beta-blockers on morbidity and mortality endpoints in adults with hypertension	Systematic Reviews	13 Studies 40,245 participants	Total CVD was lower for beta-blockers compared to placebo (RR 0.88, 95% CI 0.79 to 0.97)	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or	☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence*

					studies were of low quality ☐ Methods and/or results were inconsistent across studies	*intervals and the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company*
Xue, H. (2015) *Cochrane Database of Systematic Reviews*	To evaluate the benefits and harms of first-line RAS inhibitors compared to other first-line antihypertensive drugs in patients with hypertension	Systematic Review	RAS vs beta blockers: 2 study 9239 participants	RAS vs beta blockers: RR .88 (95% CI 0.8-.98)	Study Limitations = ☒ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☐ Quality of the studies was not appraised or studies were of low quality ☐ Methods and/or results were inconsistent across studies	*sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☒ Moderate ☐ Low

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☒ Studies inconsistent *(wide variation of treatment effect across studies, populations, interventions, or outcomes varied)*
Outcome: Cardiovascular morbidity **Modality: Weight-loss drugs**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 1 # of Systematic Reviews: 1						☐ Studies are indirect *(PICO question is quite different from the available evidence in regard to population, intervention,*
Siebenhofer, A. (2016) *Cochrane Database of*	To assess the long-term effects of pharmacologica lly induced	Systematic Review	9 studies	No study included mortality and cardiovascular morbidity as predefined outcomes.	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question	

					Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	*comparison, or outcome)* ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain*) ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)*
Systematic Reviews	reduction in body weight in adults with essential hypertension on all-cause mortality, cardiovascular morbidity, and adverse events					

Increase Quality Rating if:
☐ Large Effect
☐ Dose-response gradient
☐ Plausible confounders or other biases increase certainty of effect

Quality (certainty) of evidence for studies as a whole:
☐ High
☐ Moderate
☒ Low
☐ Very Low

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

OHSU

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☐ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied*)
Outcome: Mortality **Modality: Non-pharmacologic**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	
Total # of Studies: 2 # of Systematic Reviews: 2						☒ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome*)
Nagele, E. (2014) *Journal of Hypertension*	To assess the clinical effectiveness of stress-reduction techniques in adults with essential hypertension.	Systematic Review	17 RCTs	Data was not reported for mortality	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and the results are uncertain*)
Semlitsch, T. (2016) *Cochrane Database of Systematic Reviews*	to assess the long-term effects of weight-reducing diets in people with hypertension on all-cause mortality, cardiovascular morbidity, and adverse events and to assess the long-term effects of weight-reducing diets in people with hypertension	Systematic review	3 studies, 731 participants	None of the included studies was designed to evaluate the effects of weight loss diet versus no diet on mortality	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found*) Increase Quality Rating if: ☐ Large Effect

on change from baseline in systolic blood pressure, change from baseline in diastolic blood pressure, and body weight reduction						☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

PICO Question: In patients 18-85 years of age who had a diagnosis of hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg), what are the most effective clinical implementation tools and strategies for controlling blood pressure (systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)?						Lower Quality Rating if: ☒ Studies inconsistent (*wide variation of treatment effect across studies, populations, interventions, or outcomes varied*)
Outcome: Cardiovascular morbidity **Modality: Non-pharmacologic**						
Author/Date	*Purpose of Study*	*Study Design & Methods*	*Sample*	*Outcomes*	*Design Limitations*	☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome*) ☒ Studies are imprecise (*When studies include few patients and few events and thus have wide confidence intervals and*
Total # of Studies: 2 # of Systematic Reviews: 2						
Nagele, E. (2014) *Journal of Hypertension*	To assess the clinical effectiveness of stress-reduction techniques in adults with essential hypertension.	Systematic Review	17 RCTs	Data was not reported for cardiovascular morbidity	Study Limitations = ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	
Semlitsch, T. (2016) *Cochrane Database of*	to assess the long-term effects of	Systematic review	1 study, 294 participants	CVD morbidity: HR .70 (95% CI .57-.87)	Study Limitations = ☐ None ***Systematic Review***	

Systematic Reviews	weight-reducing diets in people with hypertension on all-cause mortality, cardiovascular morbidity, and adverse events and to assess the long-term effects of weight-reducing diets in people with hypertension on change from baseline in systolic blood pressure, change from baseline in diastolic blood pressure, and body weight reduction				☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised or studies were of low quality ☒ Methods and/or results were inconsistent across studies	*the results are uncertain)* ☐ Publication Bias *(e.g. pharmaceutical company sponsors study on effectiveness of drug, only small, positive studies found)* Increase Quality Rating if: ☐ Large Effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect Quality (certainty) of evidence for studies as a whole: ☐ High ☐ Moderate ☒ Low ☐ Very Low

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. For more detailed information, see Appendix A.

Guideline Recommendations:

In 2003, the **Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)** released an updated report on the prevention and management of hypertension. The key messages of this report are:

- In those older than age 50, systolic blood pressure (SBP) of >140mmHg is a more important cardiovascular disease (CVD) risk factor than diastolic BP (DBP);
- Beginning at 115/75 mmHg, CVD risk doubles for each increment of 20/11 mmHg;
- Those who are normotensive at 55 years of age will have a 90 percent lifetime risk of developing hypertension;

- Pre-hypertensive individuals (SBP 120-139 mmHg or DBP 80-89 mmHg) require health-promoting lifestyle modifications to prevent the progressive rise in blood pressure and CVD;
- For uncomplicated hypertension, thiazide diuretic should be used in drug treatment for most, either alone or combined with drugs from other classes;
- This report delineates specific high-risk conditions, which are compelling indications for the use of other antihypertensive drug classes (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta blockers, calcium channel blockers);
- Two or more antihypertensive medications will be required to achieve BP (<140/90 mmHg, or <130/80 mmHg for patients with diabetes and chronic kidney disease);
- For patients whose BP is >20 mmHg above the SBP goal or 10 mmHg above the DBP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered;
- Regardless of therapy or care, hypertension will only be controlled if patients are motivated to stay on their treatment plan. Positive experiences, trust in the clinician, and empathy improve patient motivation and satisfaction. This report serves as a guide, and the committee continues to recognize that the responsible physician's judgement remains paramount.

In 2014, the **Joint National Committee (JNC 8)** released an updated set of recommendations on the prevention, detection, evaluation, and treatment of high blood pressure including the following recommendations:

- Recommendation 1: In the general population aged 60 years or older, initiate pharmacologic treatment to lower BP at systolic blood pressure of 150 mm Hg or higher or diastolic blood pressure (DBP) of 90 mm Hg or higher and treat to a goal lower than 150 mm Hg and goal DBP lower than 90 mm Hg.
  Strong Recommendation – Grade A
- Recommendation 2: In the general population younger than 60 years, initiate pharmacologic treatment to lower BP at DBP of 90 mm Hg or higher and treat to a goal DBP of lower than 90 mm Hg.
  Strong Recommendation – Grade E
- Recommendation 3: In the general population younger than 60 years, initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher and treat to a goal SBP of lower than 140 mm Hg.
  Expert Opinion – Grade E
- Recommendation 4: In the population aged 18 years or older with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher or DBP of 90 mm Hg or higher and treat to goal SBP of lower than 140 mm Hg and goal DBP lower than 90 mm Hg.
  Expert Opinion – Grade E
- Recommendation 5: In the population aged 18 years with diabetes, initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher or DBP of 90 mm Hg or higher and treat to a goal SBP of lower than 140 mm Hg and goal DBP lower than 90 mm Hg.

Expert Opinion – Grade E

- <u>Recommendation 6:</u> In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB).
  Moderate Recommendation – Grade B

- <u>Recommendation 7:</u> In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.
  For general black population: Moderate Recommendation – Grade B
  For black patients with diabetes: Weak Recommendation – Grade C

- <u>Recommendation 8:</u> In the population aged 18 years or older with CKD and hypertension, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status.
  Moderate Recommendation – Grade B

- <u>Recommendation 9:</u> The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using the drugs in recommendation 6 because of contraindication or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed.
  Expert Opinion – Grade E

Comparison of Current Recommendations with JNC 7 Guidelines

Differences between JNC7 and JNC 8 are outlined below. It is important to note that the National Quality Forum is based on JNC 7 and has not been updated to reflect JNC 8 recommendations to date.

<u>Topic</u>	<u>JNC 7</u>	<u>JNC 8</u>
Methodology	- Nonsystematic literature review by expert committee including a range of study designs - Recommendations based on consensus	- Critical questions and review criteria defined by expert panel with input from methodology team. - Initial systematic review by methodologists restricted to RCT evidence.

		• Subsequent review of RCT evidence and recommendations by the panel according to a standardized protocol.
Definitions	• Defined hypertension and prehypertension	• Definitions of hypertension and prehypertension not addressed, but thresholds for pharmacologic treatment were defined.
Treatment Goals	• Separate treatment goals defined for "uncomplicated" hypertension and for subsets with various comorbid conditions (diabetes and CKD)	• Similar treatment goals defined for all hypertensive populations except when evidence review supports different goals for a particular subpopulation.
Lifestyle Recommendations	• Recommended lifestyle modifications based on literature review and expert opinion	• Lifestyle modifications recommended by endorsing the evidence-based Recommendations of the Lifestyle Work Group.
Drug Therapy	• Recommended 5 classes to be considered as initial therapy but recommended thiazide-type diuretics as initial therapy for most patients without compelling indication for another class. • Specified particular antihypertensive mediation classes for patients with compelling indications, ie, diabetes, CKD, heart failure, myocardial infarction, stroke, and high CVD risk. • Included a comprehensive table of oral antihypertensive drugs including names and usual dose ranges.	• Recommended selection among 4 specific medication classes (ACEI or ARB, CCB or diuretics) and doses based on RCT evidence. • Recommended specific medication classes based on evidence review for racial, CKD, and diabetic subgroups. • Panel created a table of drugs and doses used in the outcomes trials.
Scope of Topics	• Addressed multiple issues (blood pressure measurement methods, patient evaluation components, secondary hypertension, adherence to regimens, resistant hypertension, and hypertension in special	• Evidence review of RCTs addressed a limited number of questions, those judged by the panel to be of highest priority.

	populations) based on literature review and expert opinion.	
Review process prior to publication	• Reviewed by the National High Blood Pressure Education Program-Coordinating Committee, a coalition of 39 major professional, public, and voluntary organizations and 7 federal agencies	• Reviewed by experts including those affiliated with professional and public organizations and federal agencies; no official sponsorship by any organization should be inferred.

Abbreviations: ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; JNC, Joint National Committee; RCT, randomized controlled trial

USPTF Recommends:

1) The USPSTF recommends screening for high blood pressure in adults aged 18 years or older. The USPSTF recommends obtaining measurements outside of the clinical setting for diagnostic confirmation before starting treatment

Guideline Ratings

Guideline Issuer and Date	JNC 7 2003	JNC 8 2014	USPTF 2015
1. Transparency	B	A	A
2. Conflict of interest	A	A	A
3. Development group	B	A	A
4. Systematic Review	B	A	A
5. Supporting evidence	B	A	A
6. Recommendations	B	A	A
7. External Review	A	A	A
8. Currency and updates	C	A	A

See appendix B for full description of the Trustworthy Guideline grading system.

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Appendix A. GRADE criteria for rating a body of evidence on an intervention
Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high Observational study–low Any other evidence–very low

Criteria for increasing or decreasing level

Reductions Study quality has serious (–1) or very serious (–2) problems Important inconsistency in evidence (–1) Directness is somewhat (–1) or seriously (–2) uncertain Sparse or imprecise data (–1) Reporting bias highly probable (–1) **Increases** Evidence of association† strong (+1) or very strong (+2) †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:

Who wrote the initial draft
How the committee voted on or otherwise approved recommendations

Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.

C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.
NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:

Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.

Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like "should" or "should not" for strong recommendations, and passive language like "consider" for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.

B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers' stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst's discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated