VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE DIAGNOSIS AND MANAGEMENT OF HYPERTENSION IN THE PRIMARY CARE SETTING

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendations.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

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The Diagnosis and Management of Hypertension Working Group

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Background

This guideline developed under the auspices of the Veterans Health Administration (VHA) and the Department of Defense (DoD) pursuant to directives from the Department of Veterans Affairs (VA) is an update to the 2004 VA/DoD Clinical Practice Guideline for Diagnosis and Management of Hypertension in the Primary Care Setting.

Hypertension (HTN) is clinically defined as a systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood pressure (DBP) of ≥90 mmHg. Prehypertension is classified as SBP 120-139 or DBP 80-89. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) went on to further classify hypertension into stages [1] (Stage 1: SBP 140-159 mmHg or DBP 90-99; Stage 2: SBP ≥160 mmHg or DBP ≥100 mmHg), though the use of these stages has begun to be phased out. Hypertension is usually asymptomatic; therefore, routine screening is important in order to diagnose the condition. Also, because patients will mostly likely not feel symptoms, the asymptomatic nature of hypertension can lead to challenges with adherence to treatment.

Patients with hypertension either have primary or secondary hypertension. Primary, or essential, hypertension accounts for about 95% of cases and is a heterogeneous disorder in which different causal factors, including genetic predisposition, central adiposity, sedentary lifestyle, and dietary choices, can lead to high blood pressure. [2] Secondary hypertension is high blood pressure that results from an underlying and identifiable cause. [3] Main causes of secondary hypertension include adverse effects of medications, tobacco products or illegal drugs, renal disease, obstructive sleep apnea, pheochromocytoma, aldosteronism, and aortic coarctation.

Complications of hypertension include damage to the large arteries (macrovascular complications) that can lead to stroke, myocardial infarction (MI), or peripheral arterial diseases, as well as damage to the smaller arteries (microvascular complications) that can lead to chronic kidney disease (CKD) or retinopathy. In addition to these arterial complications, hypertension by itself can lead to left ventricular hypertrophy (LVH) and chronic heart failure (CHF), another frequent cause of death in the United States (US).

In the US, about 77.9 million adults (one out of every three) have hypertension. Of those only 81.5% are aware of their condition, 74.9% are undergoing treatment, and just over half (52.5%) have their hypertension controlled. [4] Uncontrolled hypertension has been shown to be higher in older Americans, non-Hispanic blacks and individuals with certain co-morbid conditions, including diabetes and CKD. [5]

In a 2008 study, it was found that 13% of active duty Service Members had hypertension, the majority of whom were <40 years of age. [6] It was reported that, as in the civilian population, increased age, increased body mass index (BMI), male sex, black race/ethnicity, and senior rank were all independently associated with hypertension. Another study surveyed active duty Service Members at baseline (2001-2003) and then again after three years (2004-2006) and found that while military personnel who were deployed had a lower incidence of hypertension in general than those who were not deployed,

deployment with multiple stressful combat exposures was an independent risk factor for newly reported hypertension. [7] Over 37% of Veterans have hypertension, making it the most common chronic medical condition among Veterans. [8] The control of hypertension, however, has significantly improved among Veterans. While only 45.7% of Veterans had their blood pressure controlled in 2000, by 2010, the rate had improved to 76.3%. [9]

This clinical practice guideline (CPG) on the management of HTN in the primary care setting is intended to promote evidence-based management of hypertension and thereby improve patient's clinical outcomes. It can assist primary care providers or specialists in the screening and diagnosis of HTN, determination of appropriate treatment, and delivery of individualized interventions. Although it was developed for a broad range of clinical settings, it should be applied with enough flexibility to accommodate local practice and individual situations.

About this Clinical Practice Guideline (CPG)

The VA/DoD CPG for the Diagnosis and Management of Hypertension in the Primary Care Setting is intended to assist healthcare providers in all aspects of outpatient care for patients with hypertension. The system-wide goal of evidence-based guidelines is to improve the patient's health and wellbeing. The overall expected outcome of successful implementation of this guideline is to:

- Formulate an efficient and effective assessment of the patient's condition
- Optimize the use of therapy to reduce symptoms and enhance functionality
- Minimize preventable complications and morbidity
- Emphasize the use of personalized, proactive, patient-driven care

This guideline represents a significant step toward achieving these goals for patients in the VA and DoD. However, as with other CPGs, remaining challenges involve developing effective strategies for guideline implementation and evaluating the effect of guideline adherence on clinical outcomes.

The guideline is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns evolve. The guideline is based on information available at the date of publication, and is intended to provide a general guide to best practice. However, it should be emphasized that evidence-based clinical practice involves using the best available research evidence, but also exercising the practitioner's clinical judgment to take into account individual patient indicators and preferences. The guideline can assist healthcare providers, but the use of a CPG must always be considered as a recommendation, within the context of a provider's clinical judgment, in the care of an individual patient.

Scope of this CPG

This CPG is designed to assist primary care providers in identifying and managing patients with hypertension. The target audience of the CPG is VA/DoD and other primary care physicians who

treat active duty, reserve, National Guard and retired military personnel and their adult family members. The CPG addresses the following elements:

Population

The patient population of interest for this CPG is adults (men and women) who are eligible for care in the VA and DoD healthcare delivery systems. It includes Veterans as well as deployed and non-deployed active duty Service Members. This CPG does not provide recommendations for the management of hypertension in pregnant women, peri-operative/inpatient adults, children or adolescents.

Intervention

This CPG addresses various management strategies for patients with hypertension. This includes assessing the benefits and harms associated with antihypertensive pharmacologic therapies as well as the blood pressure thresholds to initiate therapy and appropriate blood pressure targets. In addition to primary care provider pharmacological management strategies, the CPG discusses the impact of non-pharmacologic therapies (e.g., weight reduction, sodium reduction, physical activity) on improving hypertension management. The CPG also reviews what measurement techniques are the best indicators to initiate hypertension therapy.

Key Differences in This Guideline Update

This document is an update of the 2004 clinical practice guideline on the Diagnosis and Management of Hypertension in the Primary Care Setting. As such, there are aspects of this guideline that have been modified from the previous version based on new evidence and the current Guideline Work Group's interpretation of the clinically appropriate scope of the guideline. Clinicians may find that this updated VA/DoD guideline has recommendations that differ from recommendations generated by other groups that have published guidelines on the management of hypertension. For example, this updated VA/DoD guideline recommends using particular blood pressure thresholds for initiating pharmacologic therapy and blood pressure goals that differ from other published guidelines. These differences may derive in part from differences in the basis for guideline development. For this guideline, the Guideline Work Group first developed key research questions to examine available evidence pertaining to the optimal blood pressure thresholds for initiating pharmacotherapy and the available evidence pertaining to optimal goals for treating blood pressure. The systematic evidence review also addressed systolic and diastolic thresholds and goals independently. Based on the evidence for treatment initiation thresholds and the evidence for treatment goals, the Guideline Work Group recommends SBP thresholds and goals that are somewhat higher than those to which many clinicians have been accustomed.

Another way in which this guideline tends to differ from some other recently published guidelines is that it is less inclusive of drug classes recommended for first-line therapy. This guideline recommends using thiazide-type diuretics as first-line therapy and then proceeds to recommend certain other drug classes for supplemental therapy as clinically indicated. The recommendation pertaining to first-line therapy is based on the totality of evidence, including numerous placebo controlled trials, and in part on the Guideline Work Group's determination from the available evidence that findings of many clinical trials that have supported drug classes other than thiazide-type diuretics as first-line therapy did not use

optimal doses of thiazides for reducing adverse cardiovascular and cerebrovascular outcomes in their control groups.

The guideline update also uses a different system to evaluate evidence than the 2004 version. This guideline uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method for appraising the quality of a body of evidence and creating evidence-based recommendations. The GRADE system began to be developed in 2000 and many US and international organizations have provided input into the development of the approach and endorsed it. Among those that are using it (or near modifications of it) are: the Agency for Healthcare Research and Quality Evidence-based Practice Centers, Centers for Disease Control and Prevention advisory panels, Cochrane Collaboration, Kaiser Permanente, National Institute for Health and Care Excellence (United Kingdom[UK]), National Kidney Foundation Kidney Disease Outcomes Quality Initiative, World Health Organization, and medical professional societies (e.g., American College of Chest Physicians, American College of Physicians, American Gastroenterological Association, Canadian Cardiovascular Society, The Endocrine Society, and Society of Critical Care Medicine). Further information on evaluating evidence and developing recommendations using the GRADE method can be found in the Grading Recommendations section.

Compared to the 2004 version of the VA/DoD guideline, clinicians will notice that the Guideline Work Group has added recommendations, based on literature published in the last several years, pertaining to the use of home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension though HBPM and ABPM are not currently in widespread use for that purpose. Also, many recommendations pertaining to managing hypertension with certain highly prevalent comorbid conditions were not carried forward to this version of the guideline. The Guideline Work Group determined that those topics were out of scope for this guideline, as they are largely covered in the VA/DoD clinical practice guidelines for diabetes mellitus,[1] chronic kidney disease,[2] and chronic heart failure.[3]

Methods

The methodology used in developing the 2014 CPG follows the *Guideline for Guidelines*, [10] an internal document of the VA and DoD Evidence-Based Practice Working Group (EBPWG). This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and DoD, known as the Work Group, and ultimately, the submission of an updated HTN CPG.

[1] See the VA/DoD Clinical Practice Guideline for the Management of Diabetes Mellitus in Primary Care. Available at: http://www.healthquality.va.gov/guidelines/CD/diabetes/index.asp
[2] See the VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease. Available at: http://www.healthquality.va.gov/guidelines/cd/ckd/index.asp
[3] See the VA/DoD Clinical Practice Guideline for the Management of Chronic Heart Failure. Available at: http://www.healthquality.va.gov/guidelines/cd/chf/index.asp

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and publishing a guideline document to be used by providers within the VA/DoD healthcare system. Specifically, the Champions for this guideline were responsible for identifying the key questions of greatest clinical relevance, importance and interest for the diagnosis and management of patients with HTN. In addition, the Champions assisted in:

1. Conducting the evidence review, including providing direction on inclusion and exclusion criteria;
2. Assessing the level and quality of the evidence;
3. Identifying appropriate disciplines to be included as part of the Work Group;
4. Directing and coordinating the Work Group; and
5. Participating throughout the guideline development and review processes.

The VA Office of Quality, Safety and Value, in collaboration with the Clinical Performance Assurance Directorate, Office of Evidence-Based Practice, US Army Medical Command, the lead agency for the DoD, identified two clinical leaders, Dr. William Cushman from VA and Dr. Travis Harrell from DoD, as Champions for the 2014 HTN CPG.

The Lewin Team (Team), including DutyFirst Consulting, was contracted by VA and DoD to support the development of this CPG and conduct the evidence review. The Team held the first conference call in September 2013, with participation from the contracting officer's representatives (COR), leaders from the VA and DoD evidence-based guideline development program, and the Champions. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing specific research questions on which to base a systematic review about the diagnosis and management of HTN. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the diagnosis and management of HTN, from which the Work Group members were recruited. The specialties and clinical areas of interest included: Primary Care, Internal Medicine, Nursing, Pharmacy, Dietetic and Nutritional Services, Geriatrics, and Physical Therapy.

The guideline development process for the 2014 CPG consisted of the following steps:

1. Formulating evidence questions (Key Questions);
2. Conducting the systematic review;
3. Convening a three and a half day face-to-face meeting with the CPG Champions and Work Group members; and
4. Drafting and submitting a final CPG on the management of HTN to the VA/DoD EBPWG.

Appendix A provides a detailed description of each of these tasks.

Reconciling 2004 Guideline Recommendations

Evidence-based CPGs should be current, which typically requires revisions based on new evidence, or as scheduled, subject to time-based expirations. For example, the U.S. Preventive Services Task Force (USPSTF) has a process for refining or otherwise updating its recommendations pertaining to preventive

services. [11] Further, the inclusion criteria for the National Guideline Clearinghouse specify that a guideline must have been developed, reviewed or revised within the past five years.

The HTN Guideline Work Group focused largely on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the key questions. In addition to those new and updated recommendations, the Guideline Work Group considered the current applicability of other recommendations that were included in the previous CPG on management of HTN, published in 2004, subject to evolving practice in today's environment. Subject to Guideline Work Group consensus, recommendations that were no longer relevant to the current practice environment, or were otherwise out of scope for this CPG, were not carried forward to this CPG. Recommendations that were considered to be relevant to the current practice environment and still in scope for this CPG, and that required no substantive (i.e., entailing clinically meaningful) rewording, were carried forward in this CPG. The wording was, however, modified slightly to be best utilized in today's clinical environment and to uphold the GRADE recommendation format. (For more information on GRADE methodology, please refer to Grading Recommendations in Appendix A.) For some modified recommendations, the Guideline Work Group referred to the available evidence as summarized in the body of the 2004 CPG, though not all of these were the object of a systematic evidence review for the 2004 CPG. Some modified recommendations carried forward from the 2004 HTN CPG, however, were based on an updated systematic review conducted since the 2004 HTN CPG due to the topic being a priority area addressed by the key questions. These "modified" recommendations, and whether or not an updated systematic review was conducted, are noted in the list on page 16.

The Guideline Work Group recognized the need to accommodate the transition in evidence rating systems from the 2004 CPG to the current CPG. In order to report the strength of all recommendations using a consistent format (i.e., the GRADE system), the Guideline Work Group converted the USPSTF strengths of the recommendation accompanying the carryover recommendations from the 2004 guideline to the GRADE system. As such, the Guideline Work Group considered the strength of the evidence cited for each recommendation in the 2004 CPG as well as harms and benefits, values and preferences, and other implications, where possible. In some instances, peer-reviewed literature published since the 2004 CPG was considered along with the evidence base used for that CPG. Where such newer literature was considered when converting the strength of the recommendation from the USPSTF to GRADE system, it is noted in the discussion that follows the corresponding recommendation.

The Guideline Work Group recognizes that, while there are practical reasons for incorporating findings from a previous systematic review or previous recommendations [12] or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive systematic review and therefore may introduce bias.

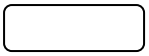
Algorithm Format

This CPG includes an algorithm, which is designed to maximally facilitate clinical decision-making for the diagnosis and management of HTN. The use of the algorithm format was chosen based on the understanding that such a format can allow for diagnostic and therapeutic decision-making, and has the

potential to change patterns of resource use. The algorithm format allows the provider to follow a linear approach to critical information needed at the major decision points in the clinical process. It includes:

- An ordered sequence of steps of care
- Recommended observations
- Decisions to be considered
- Actions to be taken

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed. [13]

	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No.
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the guideline.

Patient-Centered Care

Guideline recommendations are patient-centered. Regardless of setting or the availability of professional expertise, any patient in the healthcare system should be provided with the interventions that are recommended in this guideline and found to be appropriate to the patient's specific condition.

Treatment and care should take into account a patient's needs and preferences. Good communication between healthcare professionals and the patient is essential. It should be supported by evidence-based information tailored to the patient's needs. The information that patients are given about treatment and care should be culturally appropriate and available to people who do not speak or read English or who have limited literacy skills. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities.

Care of Veterans and Service Members in transition between facilities, services, or from the DoD health-care system to the VHA should have a transition plan and be managed according to best practice guidance. Healthcare teams should work collaboratively to provide assessment and services to patients within this transitioning population. Management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

Implementation

This CPG and algorithm are designed to be adapted by individual facilities in consideration of local needs and resources. The algorithm serves as a guide that providers can use to determine best interventions and timing of care for their patients in order to optimize quality of care and clinical outcomes.

Although this CPG represents the prevailing practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on current published information. New technology and more research will improve patient care in the future. The CPG can assist in identifying priority areas for research and optimal allocation of resources. Future studies examining the results of CPGs may lead to the development of new practice-based evidence.

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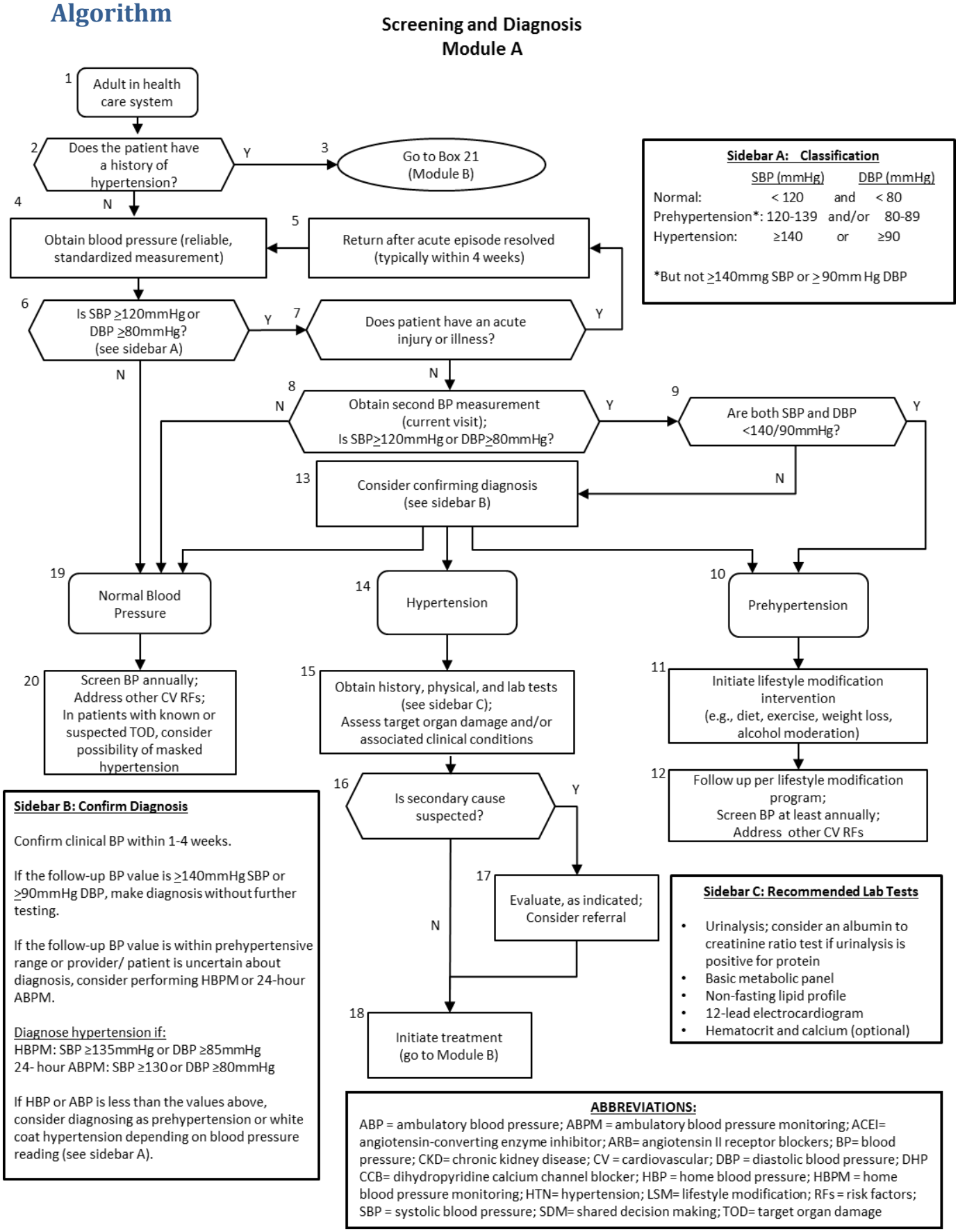
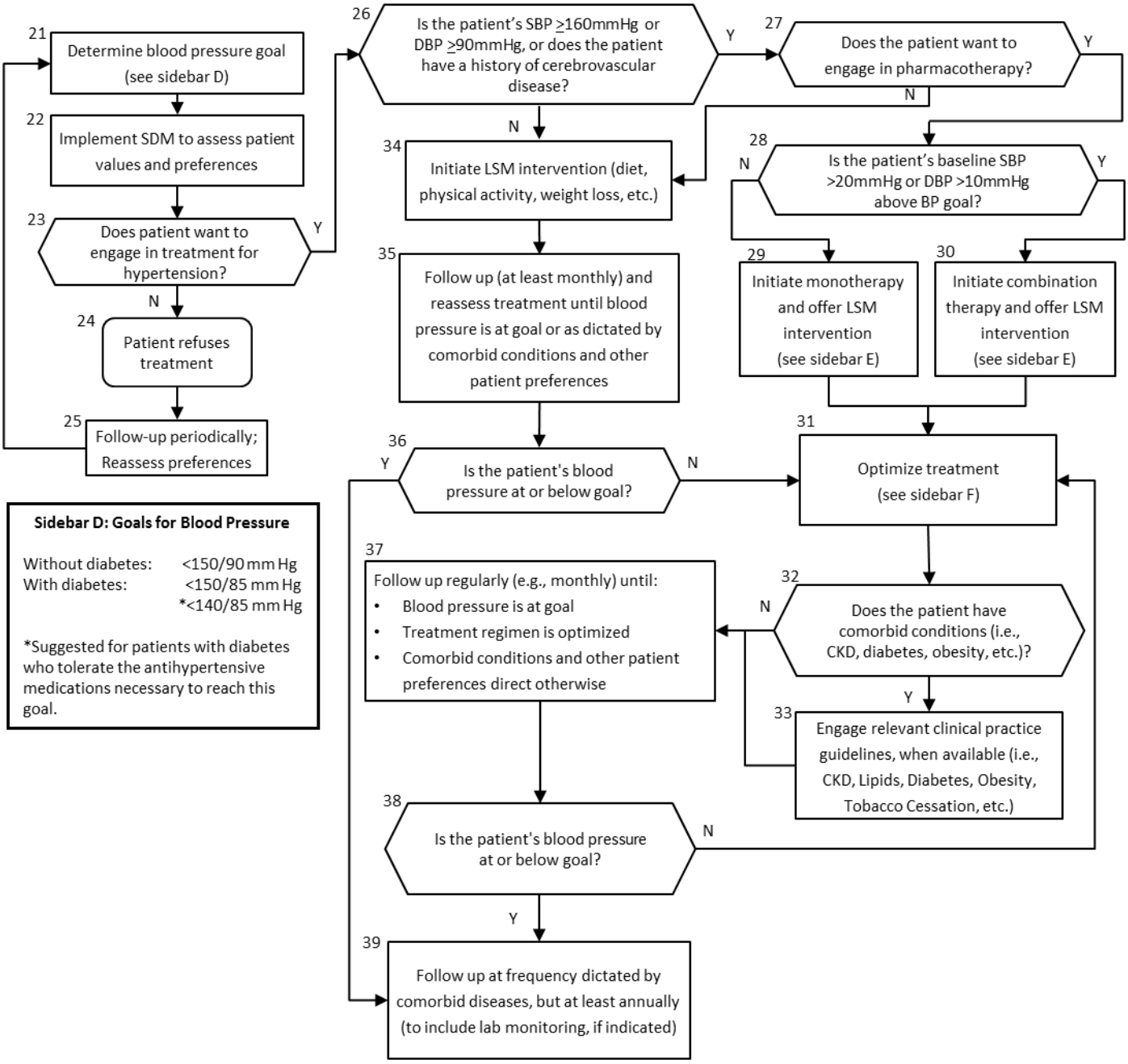
Algorithm


Screening and Diagnosis
Module A
1 Adult in health care system
2 Does the patient have a history of hypertension?
Y
3 Go to Box 21 (Module B)
4 N
Obtain blood pressure (reliable, standardized measurement)
5 Return after acute episode resolved (typically within 4 weeks)
6 Is SBP ≥120mmHg or DBP ≥80mmHg? (see sidebar A)
Y
7 Does patient have an acute injury or illness?
Y
N
N
8 Obtain second BP measurement (current visit); Is SBP≥120mmHg or DBP≥80mmHg?
N
Y
9 Are both SBP and DBP <140/90mmHg?
Y
N
13 Consider confirming diagnosis (see sidebar B)
19 Normal Blood Pressure
14 Hypertension
10 Prehypertension
20 Screen BP annually; Address other CV RFs; In patients with known or suspected TOD, consider possibility of masked hypertension
15 Obtain history, physical, and lab tests (see sidebar C); Assess target organ damage and/or associated clinical conditions
11 Initiate lifestyle modification intervention (e.g., diet, exercise, weight loss, alcohol moderation)
12 Follow up per lifestyle modification program; Screen BP at least annually; Address other CV RFs
16 Is secondary cause suspected?
Y
17 Evaluate, as indicated; Consider referral
N
18 Initiate treatment (go to Module B)
Sidebar A: Classification
SBP (mmHg) DBP (mmHg)
Normal: < 120 and < 80
Prehypertension*: 120-139 and/or 80-89
Hypertension: ≥140 or ≥90
*But not ≥140mmg SBP or ≥ 90mm Hg DBP
Sidebar B: Confirm Diagnosis
Confirm clinical BP within 1-4 weeks.
If the follow-up BP value is ≥140mmHg SBP or ≥90mmHg DBP, make diagnosis without further testing.
If the follow-up BP value is within prehypertensive range or provider/ patient is uncertain about diagnosis, consider performing HBPM or 24-hour ABPM.
Diagnose hypertension if:
HBPM: SBP ≥135mmHg or DBP ≥85mmHg
24- hour ABPM: SBP ≥130 or DBP ≥80mmHg
If HBP or ABP is less than the values above, consider diagnosing as prehypertension or white coat hypertension depending on blood pressure reading (see sidebar A).
Sidebar C: Recommended Lab Tests
• Urinalysis; consider an albumin to creatinine ratio test if urinalysis is positive for protein
• Basic metabolic panel
• Non-fasting lipid profile
• 12-lead electrocardiogram
• Hematocrit and calcium (optional)
ABBREVIATIONS:
ABP = ambulatory blood pressure; ABPM = ambulatory blood pressure monitoring; ACEI= angiotensin-converting enzyme inhibitor; ARB= angiotensin II receptor blockers; BP= blood pressure; CKD= chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; DHP CCB= dihydropyridine calcium channel blocker; HBP = home blood pressure; HBPM = home blood pressure monitoring; HTN= hypertension; LSM= lifestyle modification; RFs = risk factors; SBP = systolic blood pressure; SDM= shared decision making; TOD= target organ damage

Management
Module B



Sidebar D: Goals for Blood Pressure

Without diabetes:	<150/90 mm Hg
With diabetes:	<150/85 mm Hg
	*<140/85 mm Hg

*Suggested for patients with diabetes who tolerate the antihypertensive medications necessary to reach this goal.

Sidebar E: Initiate Drug Therapy

General Population (including patients with coronary disease, prior MI, or diabetes):

1st Line:	Thiazide-type diuretics
2nd Line:	ACEIs, ARBs, or long-acting DHP CCBs

Additional drug classes may be added as needed to reach BP goal.
(Refer to Appendix E, Table E-1)

Specific Populations:

•For patients with **CKD**, recommend ACEIs or ARBs as 1st line therapy.

•For **African American** patients, recommend **not** using ACEIs or ARBs as monotherapy.

•For **African American patients with CKD**, suggest combining a thiazide-type diuretic with an ACEI or ARB.

Sidebar F: Optimize Treatment

- Optimize treatment (Refer to Appendix E, Table E-1)
  - Titrate initial drug
  - Add another agent from a different class
- Assess adherence
- Reevaluate diagnosis (resistant HTN)
- Consider evaluation for interfering substances or contributing secondary causes of hypertension
- Consider specialty consultation for patients with resistant hypertension

Recommendations

Recommendation	Strength of Recommendation
Screening, Diagnosis and Measurement of Hypertension	
Screening	
1. We recommend screening adults for elevated blood pressure occur periodically, preferably annually. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.*)*	Strong for
2. We suggest that screening occur at the time of routine preventive care or routine health assessment. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	Weak for
Diagnosis	
3. We recommend the diagnosis of hypertension be determined based on at least two blood pressure readings on two separate patient visits. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	Strong for
Measurement Techniques	
4. We recommend that blood pressure be measured with a technique recommended for the measurement of blood pressure in adults using a properly calibrated and validated sphygmomanometer. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	Strong for
5. For patients whose diagnosis of hypertension remains uncertain, we recommend offering home blood pressure monitoring to confirm diagnosis prior to beginning pharmacologic treatment. (Two to three times a day for seven consecutive days, disregard the first day and take the average of measurements.)	Strong for
6. For patients whose diagnosis of hypertension remains uncertain, we suggest offering 24 hour ambulatory blood pressure monitoring as an alternative to home blood pressure monitoring to confirm diagnosis prior to beginning pharmacologic treatment.	Weak for
Adherence to Therapy	
7. We suggest offering a multi-modal approach to adherence interventions, which could include telemonitoring, multi-disciplinary group medical appointments, (e.g., shared medical appointments), case management (by pharmacists, nurses, social workers), patient and provider education, behavioral therapy, etc.	Weak for
Lifestyle Modification	
8. We recommend offering lifestyle modification interventions for patients with prehypertension or hypertension based on patient indications and preferences as well as assessment of available local resources. *(Modified from 2004 VA/DoD HTN CPG)*	Strong for
Weight Reduction	
9. We recommend discussing healthy weight range and advising overweight or obese hypertensive patients to reduce their body mass index to below 25. *(Modified from 2004 VA/DoD HTN CPG)*	Strong for

Recommendation	Strength of Recommendation
10. If a normal body mass index (<25) cannot be achieved, we suggest advising patients that a weight reduction of at least 10 pounds can achieve a decrease in blood pressure.	Weak for
Exercise/Physical Activity	
11. We recommend a target for aerobic exercise of 30 to 45 minutes per session, at least four times per week. *(Modified from 2004 VA/DoD HTN CPG)*	Strong for
12. We suggest the use of a self-monitoring device (e.g., pedometer, mobile apps, etc.) to increase adherence to physical activity.	Weak for
Mind-body Therapies	
13. For patients interested in complementary and alternative medicine, we suggest considering mind-body therapies such as transcendental meditation or yoga.	Weak for
14. We suggest not offering Tai Chi for the treatment of hypertension as there is a moderate body of evidence that shows this intervention does not reduce blood pressure.	Weak against
Dietary Modification	
15. We recommend a dietitian-led Dietary Approaches to Stop Hypertension (DASH) Diet for the treatment and/or prevention of hypertension for patients with hypertension and/or interested patients with prehypertension and other cardiovascular risk factors. *(Modified from 2004 VA/DoD HTN CPG)*	Strong for
16. In patients with additional cardiovascular risk factors, such as dyslipidemia, we suggest considering a dietitian-led Mediterranean Diet as an alternative to the DASH Diet.	Weak for
17. We recommend against the use of soy protein supplements for the treatment of hypertension.	Strong against
Sodium Reduction	
18. In patients with hypertension or prehypertension, we recommend that sodium intake be limited to no more than 2300mg/day (100mmol/day), with referral to a dietitian or other support as appropriate. *(Modified from 2004 VA/DoD HTN CPG)*	Strong for
Alcohol Reduction	
19. We recommend advising hypertensive and prehypertensive patients to limit alcohol intake to no more than 1 oz per day for men or 0.5 oz of alcohol per day for women. (This is approximately 2 drinks/day in men and 1 drink/day in women, where a drink is 1.5 oz 80-proof liquor, 12 oz beer, or 5 oz wine [all 14g]). *(Modified from 2004 VA/DoD HTN CPG)*	Strong for
Pharmacological Therapy	
Initiation of Pharmacotherapy	
20. We recommend offering pharmacologic treatment for hypertensive patients 60 years and older with a systolic blood pressure ≥ 160 mmHg.	Strong for
21. We suggest considering pharmacologic treatment using a shared decision-	Weak for

Recommendation	Strength of Recommendation
making model for hypertensive patients 60 years and older with systolic blood pressure <160 mmHg.	
22. We suggest offering pharmacologic treatment to patients with a history of cerebrovascular disease (stroke, transient ischemic attack, or asymptomatic carotid artery disease) and a systolic blood pressure ≥140 mmHg.	Weak for
23. We suggest pharmacologic treatment for hypertensive patients younger than 60 with a systolic blood pressure ≥160 mmHg, regardless of diastolic blood pressure.	Weak for
24. We recommend offering pharmacologic treatment for patients 30 years and older with a diastolic blood pressure ≥90 mmHg.	Strong for
25. We suggest offering pharmacologic treatment for patients age 18 to 29 with a diastolic blood pressure ≥90 mmHg.	Weak for
Blood Pressure Goals	
26. For patients 60 years and over, we recommend treating to a systolic blood pressure goal of <150 mmHg.	Strong for
27. For patients below 60 years of age, we suggest treating to a systolic blood pressure goal of <150 mmHg.	Weak for
28. We recommend treating to a diastolic blood pressure goal <90 mmHg in patients 30 years and older.	Strong for
29. We suggest treating to a diastolic blood pressure goal <90 mmHg in patients age 18 to 29.	Weak for
30. For patients with diabetes (all age groups), we recommend treating to a systolic blood pressure goal of <150 mmHg.	Strong for
31. For patients with diabetes (all age groups) who tolerate antihypertensive drugs, we suggest treating to a systolic blood pressure goal of <140 mmHg.	Weak for
32. For patients with diabetes, we recommend treating to a diastolic blood pressure goal <85 mmHg.	Strong for
Hypertension Control and Follow-up	
33. We suggest that patients be seen within one month of initiation of lifestyle or pharmacological therapy to determine adequacy of hypertension control, degree of patient adherence, and presence of adverse effects. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	Weak for
34. Once the patient's blood pressure is controlled, we suggest follow-up at least annually, or more frequently as indicated, depending on patient preference. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	Weak for
Monotherapy or Combination Therapy	
35. We suggest taking into consideration the patient's baseline blood pressure and presence of comorbidities, when deciding on either monotherapy or combination therapy (two drugs) when initiating drug therapy. *(Modified from*	Weak for

Recommendation	Strength of Recommendation
2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)	
36. We suggest initiating combination therapy for patients with a baseline systolic blood pressure of >20 mmHg or diastolic blood pressure of >10 mmHg above the patient's goal. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	Weak for
First-Line Therapy	
37. We recommend the use of thiazide-type diuretics for the treatment of hypertension.	Strong for
38. We suggest the use of thiazide-type diuretics at recommended treatment doses as first-line therapy for drug treatment of hypertension either as monotherapy or in combination with other agents. *(Modified from 2004 VA/DoD HTN CPG)*	Weak for
39. To initiate treatment of hypertension with a thiazide-type diuretic, we suggest the use of chlorthalidone or indapamide over hydrochlorothiazide.	Weak for
40. We do not suggest switching from hydrochlorothiazide to chlorthalidone or indapamide if the patient is adequately controlled on and tolerating hydrochlorothiazide.	Weak against
41. We suggest considering a switch from hydrochlorothiazide to chlorthalidone for patients whose hypertension is inadequately controlled on 50mg/day of hydrochlorothiazide.	Weak for
42. We recommend a dosage of 12.5-25mg/day of chlorthalidone, 25-50mg/day of hydrochlorothiazide, or a dosage of 2.5mg/day immediate-release or 1.5-2.5mg/day sustained-release (not currently available in the US) of indapamide.	Strong for
Alternative or Supplementary Therapies	
43. We recommend using the following as alternative therapies for patients who cannot tolerate thiazide-type diuretics, as supplementary therapies for patients who do not reach their hypertensive goals, or for those starting on combination therapy: a. Angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers (but not together) b. Long-acting dihydropyridine calcium channel blockers *(Modified from 2004 VA/DoD HTN CPG)*	Strong for
44. We recommend against the use of more than one of the following three drug classes together in the same patient: angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors.	Strong against
45. We recommend additional therapy in refractory hypertension (for those who do not tolerate or are not adequately controlled with triple therapy [i.e., thiazide-type diuretics, ACEI or ARB, and CCBs] described in Recommendation 43) or as supplementary therapy in some clinical indications. Drug classes for consideration can include (not in priority order): a. Aldosterone/mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone)	Strong for

Recommendation	Strength of Recommendation
b. Other potassium-sparing diuretic (i.e., amiloride) c. Alpha adrenergic blockers d. Beta adrenergic blockers e. Non-dihydropyridine calcium channel blockers f. Combined alpha-beta adrenergic blockers g. Peripherally acting antiadrenergic agents (reserpine, pending availability) h. Direct acting vasodilators (e.g., hydralazine, minoxidil) i. Centrally acting antiadrenergic drugs (e.g., clonidine, methyldopa)	
46. We recommend against the use of alpha-adrenergic blockers as monotherapy, but this class of agents may be used as supplemental therapy or if warranted by comorbid conditions (e.g., symptomatic prostatic hypertrophy). *(Modified from 2004 VA/DoD HTN CPG)*	Strong against
Specific Populations	
47. In patients with hypertension and chronic kidney disease (reduced kidney function with albuminuria), we recommend treatment with an angiotensin-converting-enzyme inhibitor, or angiotensin II receptor blocker for improving kidney outcomes. *(Modified from 2004 VA/DoD HTN CPG)*	Strong for
48. In African American patients with hypertension, we recommend against using an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker as monotherapy.	Strong against
49. In African American patients with hypertension and stage 1-3 chronic kidney disease, we suggest a combination of a thiazide-type diuretic (for cardiovascular protection) with either an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker (for renal protection).	Weak for

* For additional information please refer to Reconciling 2004 CPG Recommendations.

Screening, Diagnosis and Measurement of Hypertension

Screening

Recommendations

1. We recommend screening adults for elevated blood pressure occur periodically, preferably annually. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*
2. We suggest that screening occur at the time of routine preventive care or routine health assessment. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*

Discussion

A 2007 updated review of the evidence for the USPSTF describes the rationale for blood pressure screening. [14] Based on their review, the USPSTF concludes that the benefits of blood pressure screening far outweigh any risks. The risk for cardiovascular events and the potential benefit from screening and subsequent treatment of hypertension depend on both the degree and duration of blood pressure elevation and the presence of other cardiovascular risk factors, such as age, gender, lipid disorders, smoking, and diabetes. Because the degree and duration of blood pressure elevation are unknown before screening, selective screening to identify individuals who would benefit most from detection and treatment of hypertension would need to target individuals with other cardiovascular risk factors. No studies were found that examined the relative effectiveness, cost-effectiveness, or harms of targeting screening for hypertension only to those patients with other cardiovascular risk factors instead of to all patients who present at a physician's office. Additionally, no studies were found that examined the optimal frequency of screening based on a patient's prior blood pressure levels or other cardiovascular risk factors.

For patients who are screened, estimates of the potential benefit of treatment can be improved both by carefully measuring the degree of blood pressure elevation and by assessing the contribution of other risk factors to global cardiovascular risk. [15-17]

Since increasing age is related to greater incidence of hypertension, and because lifetime risk is so high (approximating 90% for octogenarians), it is sensible to screen periodically. The risk of proceeding to hypertension is summarized in **Table 1**, which was adapted from Vasan et al. (2001). [18]

Table 1. Incidence Rates of Hypertension at 1, 2 and 3 Years

Baseline Blood Pressure (BP) Category†	Age 35-64 Years	Age 65-94 Years
*% hypertension at 1 year (95 CI)**		
Optimum BP	1.3 (1.1-1.6)	4.3 (3.1-5.7)
Normal BP	4.7 (4.0-5.5)	7.1 (5.5-9.0)
High Normal BP	11.0 (9.6-12.6)	15.7 (13.0-18.8)
*% hypertension at 2 year (95 CI)**		
Optimum BP	2.7 (2.2-3.2)	8.3 (6.2-11.1)
Normal BP	9.2 (7.9-10.7)	13.7 (10.8-17.2)
High Normal BP	20.8 (18.3-23.5)	28.9 (24.2-34.0)

Baseline Blood Pressure (BP) Category†	Age 35-64 Years	Age 65-94 Years
*% hypertension at 3 year (95 CI)**		
Optimum BP	4.0 (3.3-4.8)	12.2 (9.2-16.1)
Normal BP	13.5 (11.6-15.7)	19.8 (15.7-24.6)
High Normal BP	29.6 (26.2-33.1)	40.1 (34.0-46.4)
*Rates are per 100, and are adjusted for sex, age, body mass index, baseline examinations, and baseline systolic and diastolic BP. † Optimal BP: <120/80 mmHg; Normal BP: SBP 120-129 mmHg and DBP= 80-84 mmHg; High Normal: SBP= 130-139 mmHg and DBP= 85-89 mmHg		

The optimal screening intervals have not been determined in clinical studies; however, as most patients over 50 years old routinely seek care at least annually for medical conditions and/or other preventive care (e.g., immunizations and screening for colorectal cancer, breast cancer, skin cancer, osteoporosis, and/or diabetes), it is clinically appropriate to also screen for hypertension at that time. In addition, consideration should be given to annual screening for those patients of any age who have other cardiovascular risk factors. Younger patients without risk factors have a lower incidence of hypertension in the short term, but, if possible, annual screening–which is relatively easy to perform when patients attend clinics for preventive care or routine health assessments–should be considered.

Diagnosis

Recommendation

3. We recommend the diagnosis of hypertension be determined based on at least two blood pressure readings on two separate patient visits. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*

Discussion

The definition of hypertension is somewhat arbitrary because the relationship between systemic arterial pressure and morbidity appears to be linear from 115/75 mmHg, [19] but the evidence supporting benefit from treatment of elevated blood pressure starts at a higher threshold. **Table 2** below reflects thresholds for establishing the diagnosis of hypertension, which remains independent of treatment thresholds and intervention decisions. Further complicating this diagnosis, the defined limits for optimal blood pressure vary based on time of day and method of measurement. **Table 2** is useful to facilitate the diagnosis of hypertension in adults aged 18 years or older based on office blood pressure readings. Treatment decisions based on the diagnostic criteria listed in the table are discussed extensively below, and are determined by age and comorbid conditions.

Table 2. Follow-Up Based on Initial Classification of Blood Pressure for Adults

	SBP (mmHg)	DBP (mmHg)	Follow-up
Optimal	< 120	< 80	Recheck in two years
Prehypertension	120-139	80-89	Recheck in one year

	SBP (mmHg)	DBP (mmHg)	Follow-up
Hypertension	≥ 140	≥ 90	Confirm within 1-4 weeks

Due to significant variability in office readings, we suggest that the diagnosis of hypertension should be made after at least two elevated measurements per visit on multiple visits one to four weeks apart. Typically, the blood pressure will decrease with subsequent readings. This suggestion is supported by the evidence review for the Eighth Joint National Committee (JNC8) as well as the evidence review for the USPSTF recommendations. [20] Special attention must be paid to proper measurement of blood pressure, as improper equipment or technique may lead to misdiagnosis (see **Recommendation 4**). Measurements are only accurate for diagnosis of hypertension when the patient is not acutely ill or injured.

Prehypertension is not a disease category, but a classification to signify an increased risk for progression to hypertension. Patients in the upper range of prehypertension, with a systolic blood pressure of 130–139 mmHg or a diastolic blood pressure of 85–89 mmHg are at twice the risk to develop hypertension compared to the normotensive population. In addition, observational data suggests the risk of cardiovascular events and mortality doubles with each 20 mmHg increase in SBP and 10 mmHg increase in DBP beginning with a BP of 115/75 mmHg. The designation of prehypertension can alert both the patient and provider to increased cardiovascular risk and mortality, and open a discussion on risk reduction options.

Medical history and physical examination

The patient's medical history pertinent to hypertension should include:

1. Duration, levels, and nature of BP elevation
2. History or symptoms of coronary heart disease (CHD), heart failure (HF), cerebrovascular disease, peripheral vascular disease, renal disease, obstructive sleep apnea, diabetes mellitus (DM), dyslipidemia, and gout
3. Screening for baseline symptoms of sexual dysfunction, depression, cough, and angioedema
4. Family history of hypertension, premature CHD, cerebrovascular accident (CVA), DM, dyslipidemia, or renal disease
5. Other symptoms suggesting other causes of elevated BP
6. Results and adverse effects of any previous antihypertensive therapy
7. History of recent change in weight, physical activity, tobacco use
8. Dietary habits, including intake of sodium and total caloric intake
9. History of all prescribed and over-the-counter medications, herbal remedies, and dietary supplements, some of which may raise blood pressure or interfere with the effectiveness of antihypertensive medications
10. History of alcohol and illicit drug use (especially cocaine and other stimulants)
11. Psychosocial and environmental factors (e.g., family situation, employment status and working conditions, level of comprehension) that may influence hypertension control

A physical exam should include an evaluation for signs of secondary hypertension or hypertensive organ damage. At a minimum, vital signs should include height, weight, and two or more blood pressure readings to include one in each arm, with the patient seated. All hypertensive patients should have a thorough history and physical examination, but need only a limited number of routine investigations. It is beyond the scope of these guidelines to discuss every detail of the clinical evaluation, but it may be useful to summarize the aims, which are to elicit and document:

- Causes of secondary hypertension (e.g., renal disease, endocrine causes)
- Contributory factors for primary hypertension (e.g., obesity, excess sodium intake, excess alcohol intake)
- Complications of hypertension (e.g., previous stroke, LVH, ischemic heart disease [IHD], CKD, HF)
- Cardiovascular risk factors (e.g., smoking, family history)
- Relative or absolute contraindications to specific drugs (e.g., asthma [beta-blockers], angioedema [ACEIs])

Presence of any target organ damage, associated clinical condition, or history or evidence of a previous cardiovascular event substantially increases the risk of subsequent events in hypertensive patients (see **Table 3**).

Table 3. Initial Evaluation of the Hypertensive Patient

Most common causes of secondary hypertension [21]

• **Renal**
  o Renal artery stenosis
  o Polycystic kidney disease
  o Chronic reflux nephropathy
  o Chronic glomerulonephritis
  o Polyarteritis nodosa
  o Systemic sclerosis
• **Endocrine**
  o Cushing's syndrome
  o Conn's syndrome
  o Pheochromocytoma
  o Acromegaly
  o Hyperparathyroidism
  o Polycystic ovarian syndrome
• **Other**
  o Obstructive sleep apnea
  o Aortic coarctation
  o Pre-eclampsia
  o Drugs (combined oral contraceptive pill, cyclosporin, steroids)
  o Central nervous system disturbances (raised intracranial pressure, familial dysautonomia)

Contributory factors to primary hypertension
• Overweight or obesity • Excess alcohol intake (>2 drinks/day for men, >1 drink/day for women) • Excess sodium intake • Low potassium intake • Lack of physical activity

Complications of hypertension/target organ damage
• Stroke, transient ischemic attack (TIA), dementia • Left ventricular hypertrophy (LVH), heart failure • Myocardial infarct, angina, coronary artery bypass graft (CABG) or angioplasty • Peripheral vascular disease • Fundal hemorrhages or exudates • Proteinuria • Renal impairment
Associated clinical conditions [22]
• **Diabetes** • **Cerebrovascular disease** o Ischemic stroke o Cerebral hemorrhage o Transient ischemic attack • **Heart disease** o Myocardial infarction o Angina o Coronary revascularization o Chronic heart failure • **Chronic kidney disease** o Diabetic nephropathy o Glomerulonephritis o Hypertensive renovascular disease • **Aortic disease** o Dissecting aneurysm o Fusiform aortic aneurysm • **Peripheral arterial disease**

Routine laboratory tests

Routine tests for all patients at the time of diagnosis of hypertension may include such tests as:

- Urinalysis (UA); if the UA is positive for protein consider a quantitative measure of an albumin to creatinine ratio
- Blood chemistry (potassium, sodium, blood urea nitrogen [BUN], creatinine, glucose, non-fasting lipid profiles)
- Twelve-lead electrocardiography (ECG)

Urinalysis is useful in the detection of overt proteinuria. Blood chemistry may be helpful in identifying underlying kidney disease, diabetes, and baseline electrolyte abnormalities. Non-fasting lipid profiles may assist in global risk factor modification. Twelve-lead ECGs are recommended to assist in the identification of LVH or ischemic heart disease. Other tests may be indicated depending upon presence of other risk factors and current comorbid conditions (e.g., uric acid for known gout).

Measurement Techniques

Recommendations

4. We recommend that blood pressure be measured with a technique recommended for the measurement of blood pressure in adults using a properly calibrated and validated sphygmomanometer. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*
5. For patients whose diagnosis of hypertension remains uncertain, we recommend offering home blood pressure monitoring to confirm diagnosis prior to beginning pharmacologic treatment. (Two to three times a day for seven consecutive days, disregard the first day and take the average of measurement.)
6. For patients whose diagnosis of hypertension remains uncertain, we suggest offering 24 hour ambulatory blood pressure monitoring as an alternative to home blood pressure monitoring to confirm diagnosis prior to beginning pharmacologic treatment.

Discussion

The diagnosis of hypertension has been traditionally based on measurement of blood pressure in a medical clinic or office. A minimum of two measurements made at least one minute apart are averaged, according to American Heart Association (AHA) guidelines. These same criteria were used in outcomes trials demonstrating the benefit of antihypertensive therapy. [23] A confounding variable in these measurements is the phenomenon of the alerting reaction or "white coat effect" which is exhibited by most patients. The initial one to two blood pressures are typically higher than subsequent BP readings and the extent of this "white coat effect" varies widely among patients. Studies evaluating this phenomenon have documented higher readings when blood pressure is taken by physicians than when taken by a nurse or medical assistant. To obtain the values most representative of the patient's office blood pressure, it is recommended that at least two readings be taken on each of two occasions, at least one day apart. The AHA recommendations for blood pressure measurement include the following key points: [24]

- Patient should be seated quietly for five minutes with back supported, feet on the floor, and arm bared, unrestricted by clothing, and supported at heart level. Measurement of BP in the standing position may be indicated for patients at risk for postural hypotension or at the discretion of the clinician. Standing BP should be measured with the bared arm supported at heart level.
- Smoking, exercise, or caffeine ingestion should not have occurred within 30 minutes prior to the BP measurement.
- The urinary bladder should be emptied before the BP measurement.
- The appropriate blood pressure cuff size should be chosen for the patient (see **Table 4**). The cuff should be wrapped snugly around the arm with the bladder centered over the brachial artery. The bladder should encircle at least 80% of the arm and should not overlap.

Table 4. Appropriate Cuff Size Based on Patient's Arm Circumference [23,24]

Arm circumference (cm)	Cuff size
22-26	Small adult
27-34	Adult
35-44	Large adult
45-52	Very large adult

- If the patient is talking, laughing, sneezing or coughing during the BP measurement (activities that affect blood pressure), the reading should be discarded and the measurement repeated.
- On the initial clinic visit, blood pressure should be measured in both arms. If there is a consistently large (>10-15 mmHg) difference between arms, the arm with the higher blood pressure readings should be used routinely as the patient's blood pressure.

For Auscultatory Measurements Only:

- Palpated radial pulse obliteration pressure should be used to estimate the SBP. The cuff should then be inflated 20-30 mmHg above this level for the auscultatory determinations.
- Position the stethoscope over the brachial artery and rapidly inflate the cuff. Deflate the cuff at a rate of 2 to 3 mmHg per second, listening for Phase 1 and Phase 5 Korotkoff sounds. The first appearance of sound (Phase 1) is used to record the SBP. Phase 5, at the disappearance of sound, is the diastolic blood pressure (DBP). Listen for 10 to 20 mmHg below Phase 5 for any further sound then deflate the cuff completely.
- The BP should be recorded in even numbers to the nearest 2 mmHg with the patient's position, arm used, and cuff size documented.
- BP readings should be repeated in the same arm and averaged, if different. One-two minutes should elapse before repeating the BP measurement. If the readings differ by more than 5mmHg, additional measurements should be obtained.

The recommendations for blood pressure measurements follow the methods used in the many randomized trials that have established the benefits of antihypertensive therapy (e.g., Systolic Hypertension in the Elderly Program [SHEP], Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT]). Using these methods allows the provider to accurately risk stratify patients, since epidemiological studies (e.g., Framingham) also used the same measurement techniques.

Blood pressure in the office is most commonly measured with a sphygmomanometer of either the ascultatory or oscillometric type. Due to variability in individual blood pressure measurements (occurring as a result of instrument, observer, and patient factors), it is recommended that hypertension be diagnosed only after two or more elevated readings are obtained on at least two visits over a period of one to four weeks, unless there is evidence of hypertension target organ damage.

Office blood pressure measurement is the standard screening test for hypertension. When performed correctly, sphygmomanometers provide a measure of blood pressure that is correlated with intra-arterial measurement and predictive of cardiovascular risk. [25] However, office blood pressure

measurements can in some cases exhibit significant variability and may not represent the patient's usual blood pressure outside the office setting.

Over the past two decades a proliferation of manual and automated home blood pressure monitoring (HBPM) devices and more widespread use of ambulatory blood pressure monitoring (ABPM) has allowed comparisons of clinic/office blood pressures with those measured outside the clinic/office, either at home (HBPM) or periodically throughout the entire 24 hour day (ABPM). For patients who exhibit persistently elevated office blood pressures, confirmatory out of office blood pressure measurements should be considered. Home blood pressure devices are usually more readily available than ambulatory blood pressure devices, but ABPM results can be utilized when office BP is high and home BP is not elevated.

Home blood pressure

Monitoring of blood pressure at home may selectively assist in diagnosing and managing hypertension. Recent studies indicate that self-monitoring may help in differentiating white-coat hypertension (i.e. persistently elevated office BP with normotensive BP by home or ambulatory BP readings) from chronically high blood pressure readings and/or may provide additional readings in patients who are already being treated for hypertension but who also have a white-coat component. [26-28] There is some evidence to suggest that home blood pressure monitoring has good prognostic efficacy for predicting cardiovascular events. [27,29,30] Home blood pressure monitoring may also identify patients who have a normal blood pressure in the office but not at home (so-called "masked" hypertension). [27]

Several studies have examined the number of measurements, the times of the day and the number of days over which the measurements should be made to define the optimal home blood pressure (HBP). Collectively, the results of several of these studies suggest that the optimal number of home measurements is 12 to 14. [31] A commonly utilized protocol involves measuring blood pressure twice daily, morning and evening, for seven days. Measurements are usually made with an automated oscillatory device with the subject seated utilizing AHA guidelines for blood pressure measurement. Often the blood pressures measured on the first day are discarded since they tend to exhibit the greatest variability. In order to improve accuracy and interpretation of home blood pressure measurements, the use of a device with a memory function is recommended rather than relying on the patient's recall or diary, though these types of devices may not always be available. From a practical standpoint, it may be helpful for patients to bring in their self-monitoring device to the clinic in order to calibrate it against an office manometer.

Based on the results of several observational studies, [29,30,32] other guidelines recommend HBP criteria for the diagnosis of hypertension to be $\geq$135/85 mmHg, as opposed to $\geq$140/90 mmHg for clinic BP criteria. [33] Collectively, the results of these observational studies underscore the value of HBP for predicting fatal and nonfatal cardiovascular events, and changes in surrogate cardiac and renal markers of cardiovascular injury. However, outcome trials reviewed did not use out of office BPs as either entry criteria or as treatment goals, nor have there been randomized trials comparing outcomes when using office versus out of office BPs as treatment goals. Therefore, it is not clear if using out of office BPs to manage hypertension would improve patient outcomes.

Ambulatory blood pressure

If there is a significant discrepancy between HBPM and clinic blood pressure (CBP), ABPM can be considered as an alternate for confirming the diagnosis of hypertension in a patient with persistently elevated office blood pressure. The ABPM device includes a cuff affixed to the patient's arm, connector tubing and a combination inflator, programmable recorder, and battery pack with a strap which can be secured to the waist or worn over the shoulder. The device is most commonly programmed to obtain readings every 15-20 minutes during the day and every 30 minutes at night. After 24 hours of data collection, the memory is downloaded to a computer for analysis. ABPM is currently the primary way to capture information about blood pressure when the patient is sleeping.

Like HBP, ambulatory blood pressure has been reported to be a stronger predictor of cardiovascular events and of target organ damage than CBP in observational studies. [34,35] However, it should be reiterated that there are no outcome trials that have used out of office BPs as either entry criteria or as treatment goals, nor have there been randomized trials comparing outcomes when using office versus out of office BPs as treatment goals. Therefore, it is not clear if using out of office BPs to manage hypertension would improve patient outcomes.

While we did not identify head-to-head comparison studies between home and ambulatory blood pressure, both approaches seem to improve the predictive value of office blood pressure to a similar extent and seem to be of similar value to help make a decision for medication initiation. As home blood pressure is more readily available to patients and require fewer resources, we recommend offering home blood pressure for most patients whose diagnosis of hypertension remains uncertain.

Adherence to Therapy

Recommendation

7. We suggest offering a multi-modal approach to adherence interventions, which could include telemonitoring, multi-disciplinary group medical appointments, (e.g., shared medical appointments), case management (by pharmacists, nurses, social workers), patient and provider education, behavioral therapy, etc.

Discussion

Inadequate blood pressure control may be attributed to patients not adequately adhering to the medication regimen [36] and successful treatment for hypertension has been related to adherence. [37-40] It has been reported inadequate adherence to prescribed medications is found in the majority of cases of uncontrolled hypertension. [41,42]

Numerous causes of poor medication adherence have been suggested, including long-term therapy, cognitive impairment, number of medications prescribed, frequency of administration, complexity of the drug regimen, cost of medications, side effects, and factors related to the patient's health decisions (e.g., acceptance of the disease, perceived severity, satisfaction with healthcare interaction, etc.). [42] Other factors may include patient and/or caregiver education on the disease and its management,

healthcare practitioner patient communication skills, the extent to which the patient is involved in self-management of HTN, and monitoring by the healthcare professional. [43]

Several approaches to improving adherence to hypertension treatment regimens have been studied. In general, multi-modal approaches to improving adherence have been the most effective. Approaches which focused only on provider or patient education [44-48] or a self-monitoring device [49] outside of a structured supervision program were not successful in decreasing blood pressure or increasing the percentage of patients with controlled hypertension.

The Hypertension Intervention Nurse Telemedicine Study (HINTS) was a Department of Veterans Affairs based study which found that combining nurse administered behavioral management and medication management interventions demonstrated sustained improvements in blood pressure. [50-52]

Group medical clinics (GMCs) at two Veterans Affairs Medical Centers (VAMCs), which consisted of a primary care general internist, a pharmacist, and a nurse or other certified diabetes educator, were also shown to improve blood pressure control compared to usual care. [53]

Multiple studies have focused on improvements in adherence to antihypertensive medications and its effect on the control of hypertension through the use of nurse- or pharmacist-directed case management. These have used a variety of techniques, including telemonitoring, [54] electronic-web based monitoring and communication, [55] and structured in-person or telephone-based follow-up for medication management. [56-59] Each of these strategies improved the adherence to medications, decreased blood pressure, and improved the percent of patients with adequate control of hypertension. In addition, the study by Dennison et al. demonstrated a reduction in the percent of patients who developed left ventricular hypertrophy after five years. [56] These interventions were performed in different populations and different clinical settings. The common feature for them was a focus on structured follow-up and monitoring for the patients.

Two studies utilized an electronic health record-based clinical decision support system which suggested specific changes in medications for patients not meeting individualized blood pressure goals. However, they did not demonstrate a significant difference in change in systolic blood pressure and diastolic blood pressure compared to usual care. [60,61]

Many of the multi-modal or nurse/pharmacist-directed case management models are successful but can be resource intensive. However, it is important to understand the baseline rates of hypertension control, medical adherence, cultural barriers, and local resources prior to implementing a specific intervention. Additionally, the effects of these programs tend to decrease over time or when the frequency of monitoring is decreased. Therefore, patients should be monitored for a decrease in control or enrolled into a chronic disease management program to help maintain control. For patients with a decrease in control of hypertension, providers should consider enrolling them back into a more intensive program.

Further research should focus on how to identify the aspects of a system or population which will predict the adherence intervention modality which is most likely to improve adherence to

pharmacologic and lifestyle modification therapy and control of hypertension. Currently, it appears that patients who have high baseline blood pressure values or poor baseline control rates derive the greatest benefit from these intervention programs.

Lifestyle Modification Therapies

Recommendation

8. We recommend offering lifestyle modification interventions for patients with prehypertension or hypertension based on patient indications and preferences as well as assessment of available local resources. *(Modified from 2004 VA/DoD HTN CPG)*

Discussion

Lifestyle modification should be prescribed by clinicians for patients whose blood pressure is in the prehypertension or hypertension range. Lifestyle modification strategies which have been demonstrated to lower blood pressure include: weight reduction for patients who are overweight or obese, increased physical activity, mind-body therapies, change in dietary pattern, sodium reduction, and moderation of alcohol intake. These interventions can be combined with each other and with pharmacologic treatments to lower blood pressure as well. Some of these lifestyle modifications have health benefits beyond their blood pressure lowering effects, such as reduced risk for diabetes, improved lipid profile, and decreased risk for cardiovascular and liver disease.

Weight Reduction

Recommendation

9. We recommend discussing healthy weight range and advising overweight or obese hypertensive patients to reduce their body mass index to below 25. *(Modified from 2004 VA/DoD HTN CPG)*
10. If a normal body mass index (<25) cannot be achieved, we suggest advising patients that a weight reduction of at least 10 pounds can achieve a decrease in blood pressure.

Discussion

Overweight and obesity represent a significant burden to the DoD and VA healthcare systems, with national surveys estimating that 60.5% [62] of active duty military personnel and 71.5% [63] of Veterans are overweight or obese. Excess body weight has been linked directly to multiple disease processes, including hypertension. Weight loss as part of a comprehensive lifestyle management program has been shown to reduce blood pressure in individuals with or without hypertension.

Multiple studies have examined the impact of weight loss on cardiovascular risk factors. The Look AHEAD (Action for Health in Diabetes) trial evaluated the long-term impact of intensive lifestyle interventions (ILI) on cardiovascular morbidity and mortality in overweight or obese individuals with type 2 diabetes. [64] The study examined the impact of an ILI, which included dietary modification and physical activity, compared with usual care and examined the changes in weight, fitness, glycemic control and cardiovascular disease risk factors. At the end of four years, individuals in the ILI group

averaged a 6.15% weight loss compared to a 0.88% loss in the control group. Both groups experienced reductions in SBP and DBP; however, reductions were only statistically significant for the ILI group. While 80% of the subjects had a history of hypertension, the mean blood pressure at baseline was only 128-129/70 mmHg.

From February 1999 to February 2002, Esposito et al. examined the impact of weight loss and lifestyle on inflammatory markers in healthy, obese women. [65] One hundred twenty premenopausal obese women were assigned to either the lifestyle intervention group, which received detailed counseling on a 10% weight reduction, or the control group, which was only given written information on healthy food choices and exercise. After two years, both groups showed significant weight loss; however, women in the intervention group lost significantly more body weight than those in the control group. Both groups also showed significant decreases in blood pressure with a larger effect in the intervention group. [65]

Gardner et al. compared the effects of four weight-loss diets representing a spectrum of high to low carbohydrate recommendations on weight loss and related metabolic variables over 12 months in 311 normotensive premenopausal women with a BMI of 27 to 40. [66] Participants were randomly assigned to follow the Atkins, Zone, Lifestyle Exercise Attitudes Relationships Nutrition [LEARN], or Ornish diets and received weekly instruction for two months and then were followed-up for an additional ten months without further instruction. At study end, the percentage of weight lost in women assigned to the Atkins diet was greater compared to all other groups (Atkins -2.9%, Zone -1.3 %, LEARN -1.0%, Ornish -1.5%). All groups showed reductions in SBP and DBP from baseline; however, the Atkins group showed significantly greater average reduction in SBP compared to all other groups. Although only significantly different than the Ornish group, the Atkins group also demonstrated greater reductions in DBP. [66]

A systematic review of several randomized controlled trials (RCTs) by Aucott et al. [67] examined the long-term effect of weight loss on hypertension outcome measures after two years. The findings of this review suggested that a 5 kg weight loss may be correlated with an average reduction in SBP of 5.6 mmHg. Similarly, a meta-analysis of 25 shorter term studies [68] suggested decreases of 1.05 mmHg and 0.92 mmHg for SBP and DBP, respectively, when expressed per kilogram of weight loss.

Exercise/Physical Activity

Recommendation

11. We recommend a target for aerobic exercise of 30 to 45 minutes per session, at least four times per week. *(Modified from 2004 VA/DoD HTN CPG)*
12. We suggest the use of a self-monitoring device (e.g., pedometer, mobile apps, etc.) to increase adherence to physical activity.

Discussion

The target for aerobic exercise should be 30 to 45 minutes per session, [69-71] at least four per week to reduce blood pressure, which is consistent with the 2008 Physical Activity Guidelines for Americans, which address the prevention of a larger range of health conditions. [72] Although evidence for resistance training is limited, there is no basis to exclude resistance training from a program of exercise,

and it may confer benefits in patients. The use of self-monitoring adherence devices is recommended for maximum benefits from physical activity. Self-monitoring devices, such as pedometers, have been shown to improve adherence to exercise regimens, causing greater reductions in blood pressure when compared to patient education or prescriptions for exercise alone. [73,74] Structured and supervised exercise programs provide greater blood pressure reduction when compared to usual care or counseling. [75,76]

Mind-body Therapies

Recommendations

13. For patients interested in complementary and alternative medicine, we suggest considering mind-body therapies such as transcendental meditation or yoga.
14. We suggest not offering Tai Chi for the treatment of hypertension as there is a moderate body of evidence that shows this intervention does not reduce blood pressure.

Discussion

Limited studies on transcendental meditation suggest that this technique may decrease the progression of hypertension when practiced regularly. [77,78] Yoga, when performed regularly for 35-40 minutes per day, five days per week, may provide a reduction in blood pressure. [79] Tai Chi, another form of mind-body therapy, has not been proven to be an effective form of alternative therapy in the reduction of blood pressure. [80]

Dietary Modification

Recommendations

15. We recommend a dietitian-led Dietary Approaches to Stop Hypertension (DASH) Diet for the treatment and/or prevention of hypertension for patients with hypertension and/or interested patients with prehypertension and other cardiovascular risk factors. *(Modified from 2004 VA/DoD HTN CPG)*
16. In patients with additional cardiovascular risk factors, such as dyslipidemia, we suggest considering a dietitian-led Mediterranean Diet as an alternative to the DASH Diet.
17. We recommend against the use of soy protein supplements for the treatment of hypertension.

Discussion

Clinical trials on supplements frequently produce different or even opposite results than those expected based on epidemiologic data showing associations between food constituents and health outcomes. As we consume whole foods rather than isolated nutrients, it is more useful to confirm that a pattern of whole foods confers benefit, rather than that a micro/macronutrient is beneficial dependent on context.

Fiber and various micronutrients such as potassium, magnesium and calcium are thought to improve blood pressure based on epidemiologic data. The DASH diet represents the first major clinical trial to test a dietary pattern for the prevention and/or management of hypertension, and emphasized inclusion of these nutrients via commonly consumed foods, rather than supplements. [81] This approach allows for the detection of potential additive and/or synergistic effects of these nutrients which might

individually be too small to detect. The DASH diet has been shown to reduce SBP and DBP in both hypertensive and normotensive adults, whether at dietary sodium intakes similar to the average daily consumption [82] or in combination with varying degrees of sodium reduction. [83] Combining the DASH diet with sodium reduction consistently produces larger decreases in blood pressure than either intervention alone across diverse subgroups. [84] No new evidence met criteria for review during this CPG update; the current guideline continues to recommend the DASH diet based on the existing body of evidence to support its use in lowering blood pressure.

Epidemiologic data has also long suggested a cardio-protective effect of a Mediterranean style diet. Despite known variation in the cuisine of Mediterranean countries, certain characteristic features are commonly used to describe a traditional Mediterranean diet: high intake of vegetables, fruits, nuts, unrefined grains and olive oil; moderate intake of fish and poultry; low or moderate intake of wine; and low intake of red meat, processed meat, dairy and sweets. Toledo et al. [85] evaluated the effects of a Mediterranean diet on blood pressure in the PREDIMED (PREvención con DIeta MEDiterránea) trial in Spain, a large cohort of men and women at high cardiovascular risk. The two intervention groups received individual and group education on an energy-unrestricted Mediterranean diet from registered dietitians, as well as regular supplies of either extra-virgin olive oil or mixed nuts. The control group received a similar format of education on a low-fat diet. Statistically significant improvements in DBP, but not SBP, were found for both intervention groups when compared to controls at four years. [85] Furthermore, the two groups randomized to the Mediterranean diet experienced a significant 28-30% reduction in major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes). [86]

Additional research is needed to test the Mediterranean diet in RCTs of more diverse populations, and against controls with more dissimilar baseline and intervention dietary patterns. In the meantime, a Mediterranean-style dietary pattern may be beneficial to patients with hypertension, and presents a viable alternative to the DASH diet for patients who find lower fat diets unpalatable or otherwise prefer the Mediterranean dietary pattern. For either dietary pattern, patients should be offered referral to a registered dietitian to help achieve the desired changes.

Additional dietary information on both the DASH and Mediterranean diets can be found in **Appendix C**.

Howard et al. reported cardiovascular outcomes from the Women's Health Initiative Dietary Modification Trial. [87] This RCT tested an intensive behavioral modification intervention in a large, free-living cohort of postmenopausal women, and found that a low-fat diet did not reduce blood pressure, stroke or myocardial infarction at a mean follow-up of 8.1 years. While a low-fat diet may be desirable for other medical conditions, targeting fat content alone is not recommended as a sole dietary strategy for the treatment of hypertension specifically.

Epidemiologic data on soy and isoflavone intake in Asian countries suggests that phytoestrogen consumption may mitigate the increased cardiovascular disease incidence seen in postmenopausal women. However, an RCT from the Netherlands compared the effects of supplemental soy protein (containing 99mg isoflavones) to milk protein on vascular function in postmenopausal women. [88] After

12 months, SBP increased significantly more in the soy protein group when compared with the control group; a non-statistically significant increase in DBP was also noted for the intervention group. Subgroup analyses suggested improvements in SBP and DBP only for intervention subjects who produced the isoflavone metabolite equol, but the differences between equol and non-equol producers were not statistically significant. [88] To determine whether soy isoflavones reduce cardiovascular risk, research on soy isoflavone-rich foods in the context of an overall dietary pattern, rather than as a supplement to a Westernized diet, would be beneficial. Studies with larger samples are also warranted to explore the possibility of differential effects on the subset of equol-producers.

Sodium Reduction

Recommendation

18. In patients with hypertension or prehypertension, we recommend that sodium intake be limited to no more than 2300mg/day (100mmol/day), with referral to a dietitian or other support as appropriate. *(Modified from 2004 VA/DoD HTN CPG)*

Discussion

Many national and international organizations recommend reducing sodium intake for the prevention and management of hypertension, with the ultimate goal of reducing associated morbidity and mortality.

There is a strong body of evidence from animal studies and human observational and experimental studies noting a dose-dependent relationship between dietary sodium intake and blood pressure in both normotensive and hypertensive individuals, though there is known variation in "salt sensitivity" both within and among populations.

It should be noted that recommendations for dietary sodium reduction to reduce cardiovascular risk generally rely on surrogate markers (i.e., blood pressure) rather than clinical outcomes. The current guideline recommends a reduction to 2300mg/day. There is strong clinical evidence from the DASH-Sodium trial that a reduction from 3400mg (average daily intake of US adults) to 2300mg (the tolerable upper limit [UL] set by the Institute of Medicine [IOM] in 2005 [89]) improves blood pressure in the short term, [83] and limited observational research suggests cardiovascular disease event rates also decrease with reductions in sodium intake down to 2300mg. [90]

Only two relevant RCTs addressing blood pressure and/or mortality outcomes for reducing sodium intake met inclusion criteria for consideration in this CPG update. The Trials of Hypertension Prevention Phase II (TOHP II) study compared counseling on sodium reduction to usual care in overweight adults. [91] The intervention group achieved greater mean net decreases in SBP and DBP at both 18 and 36 months; the effect was statistically significant when compared with controls for SBP at both times and for DBP at 18 months only. Shea et al. [92] presented mortality outcome data from a post-hoc analysis of the Trial of Nonpharmacologic Interventions in the Elderly (TONE). While the TONE study [93] itself is outside the a priori date parameters established for this CPG update, the efficacy of the intervention in reducing blood pressure should be noted when evaluating the subsequent mortality outcomes presented for the cohort. Despite clinically and statistically significant improvements in blood pressure,

[93] no change in all-cause mortality was found for the intervention group when compared to usual care. [92]

Both TOHP II and TONE were lifestyle interventions in free-living cohorts rather than controlled feeding trials. Thus, the low percentage of intervention group participants who met the studies' goal of <80mmol/day (1840mg) average sodium intake (21% in TOHP II, roughly 40% in TONE) represents the inherent difficulty of lifestyle modification compounded by the ubiquity of sodium in the present US food supply. The studies support reducing sodium intake as a means to lower blood pressure, but do not justify a lower goal than 2300mg or confirm that clinical outcomes are improved. It is possible that an effect on mortality would have been detected had TONE intervention participants been more successful in lowering sodium intake.

Several organizations have specified lower targets for daily sodium intake. The 2010 Dietary Guidelines for Americans advise less than 1500mg sodium/day for individuals 51 years of age or older, and for select populations regardless of age (African Americans, hypertension, diabetes, or chronic kidney disease). [94] The American Heart Association's Strategic Impact Goals for 2020 went further, identifying 1500mg as a population-wide target, as the aforementioned salt-sensitive groups now comprise a majority of the US population. [95] Aside from the difficulty in limiting sodium to that extent without significant changes to the current food supply, this lower target is also controversial due to the lack of clinical outcomes data for reducing sodium to levels below 2300mg, and the suggestion of harm at low levels.

No studies demonstrating harmful effects of reducing sodium intake on either blood pressure or clinical outcomes met criteria for review during this CPG update. A 2013 IOM report evaluated the evidence on sodium intakes between 1500 and 2300mg, focusing on direct clinical outcomes. [96] The evidence reviewed was largely observational, though there were three Italian RCTs on heart failure patients which showed increased all-cause mortality [97] and/or adverse events [97-99] with lower sodium intakes (80 vs 120mmol/day [1840 vs 2760mg]). The generalizability of these results is limited by significant discrepancies in participants' medical treatment when compared with standard practice in the US (aggressive diuretic use and stringent fluid restriction); the reliability of two [97,98] of the three studies has since been questioned due to allegations of duplicate data. The IOM report concluded that sodium reduction at the population level is desirable to improve direct health outcomes, but that both the quantity and quality of evidence was insufficient to justify lowering sodium recommendations to 1500mg/day for either the general public or for subgroups of the population.

The average daily sodium intake in the US is over 3400mg/day excluding table salt, well above the more conservative recommendation of 2300mg/day. [100] Disagreement regarding the exact cut-point at which risks outweigh benefits should not distract from a unified public health message that a reduction in sodium intake from current levels is desirable. As dietary sodium recommendations rely heavily on research on surrogate markers, additional research is warranted to confirm that reducing blood pressure via reducing sodium intake has the predicted effect on morbidity and mortality. Future research is also needed to determine the efficacy and safety of lower sodium targets.

Alcohol Reduction

Recommendation

19. We recommend advising hypertensive and prehypertensive patients to limit alcohol intake to no more than 1 oz per day for men or 0.5 oz of alcohol per day for women. (This is approximately 2 drinks/day in men and 1 drink/day in women, where a drink is 1.5 oz 80-proof liquor, 12 oz beer, or 5 oz wine [all 14g]). *(Modified from 2004 VA/DoD HTN CPG)*

Discussion

Alcohol use has a direct relationship with blood pressure, especially at levels of three or more standard drinks per day (≥34 grams of ethanol per day). [101] In patients with chronic alcoholism, cessation of alcohol use has been shown to reduce blood pressure and prevalence of hypertension. [102] Patients with hypertension and alcohol dependence who receive regular counseling to reduce their alcohol intake have a small, but significant, reduction in their blood pressure. [103] For patients with hypertension and excessive alcohol intake, it is reasonable to recommend reduction of alcohol intake to a maximum of two drinks per day for men and one drink per day for women. A structured counseling program can increase adherence to reduction or abstinence of alcohol intake.

Pharmacological Therapy

Treatment of hypertension with drugs in clinical trials has reduced stroke incidence by 35 to 40%; myocardial infarction by 20 to 25%; and HF by more than 50%. [104] While most hypertensive patients benefit from pharmacotherapy, this benefit is larger among patients who already have complications of hypertension, such as target organ damage. For example, in the presence of CVD or target organ damage, only nine patients would require such BP reduction to prevent one death. [16] Similarly, in SHEP, HF was reduced by 49% with drug treatment in all patients, while it was reduced by 81% in those with a prior myocardial infarction. [105]

Initiation of Pharmacotherapy

A reference table for blood pressure thresholds to initiate pharmacotherapy can be found in **Appendix D**. Detailed recommendations and discussion can be found below.

Systolic Blood Pressure Thresholds

Recommendations

20. We recommend offering pharmacologic treatment for hypertensive patients 60 years and older with a systolic blood pressure ≥ 160 mmHg.
21. We suggest considering pharmacologic treatment using a shared decision-making model for hypertensive patients 60 years and older with systolic blood pressure <160 mmHg.
22. We suggest offering pharmacologic treatment to patients with a history of cerebrovascular disease (stroke, transient ischemic attack, or asymptomatic carotid artery disease) and a systolic blood pressure ≥140 mmHg.

23. We suggest pharmacologic treatment for hypertensive patients younger than 60 with a systolic blood pressure ≥160 mmHg, regardless of diastolic blood pressure.

Discussion

The recommendation for initiation of pharmacologic therapy to reduce blood pressure at systolic blood pressure greater than or equal to 160 mmHg for patients with hypertension is based on the evidence for reduction in clinical events from randomized control trials. Nearly all of the evidence is from clinical trials which enrolled a majority of patients starting at age 60 years of age or older. Multiple studies, such as SHEP, Medical Research Council (MRC) Working Party, and Hypertension in the Very Elderly Trial (HYVET), have demonstrated a reduction in the risk of stroke with treatment of systolic hypertension in elderly populations. [106-109] The HYVET study, which enrolled individuals age 80 or older with a systolic blood pressure of at least 160 mmHg and randomized subjects to either active pharmacologic treatment or placebo, demonstrated a significant 21% relative reduction in all-cause mortality and a 23% relative reduction in cardiovascular mortality after only a median of 1.8 years of treatment. [110] During a one year extension of the main trial, this reduction was found to be durable. [106] Several studies enrolled patients starting at age 60 (European Working Party, SHEP, Systolic Hypertension in Europe [Syst-Eur]) or age 65 (MRC Working Party) with SBP of at least 160 mmHg. Both the European Working Party [111] and SHEP trials [112] demonstrated significant reductions in cardiovascular mortality.

Only one study, the Hypertension-Stroke Cooperative Study, initiated treatment at an SBP of 140 mmHg or higher, and enrolled stroke survivors; but it did not demonstrate a reduction in stroke with active treatment, only a small reduction in heart failure. [113] This study is limited by its small sample size; therefore, any clinically significant effect on stroke could have been missed. This was also the only study included in our evidence base that included African Americans treated at a threshold below 160 mmHg. The benefit of treatment on stroke reduction or cardiovascular events in the Hypertension-Stroke Cooperative Study was not larger for African Americans than for whites with systolic blood pressure between 140 and 220 mmHg. Furthermore, data were stratified by baseline blood pressure. Among subjects with an SBP between 140 and 160 mmHg, no benefit of medication was observed (20.5% in the active medication group vs. 20.9% in the placebo group for stroke or cardiovascular events). While this analysis was not further stratified by race, about 80% of these study subjects were African American, suggesting that treating at a lower threshold of 140 mmHg may not be beneficial, even among African Americans. As African Americans have a higher prevalence of hypertension and have a higher incidence of stroke, it is important to assess whether the threshold for treatment should be lower in this population. This may be an area for future research.

Only one study in the evidence base enrolled patients younger than age 60 without a history of stroke. This was the Oslo study, [114] which enrolled relatively healthy subjects age 40-49 years with an SBP of 150-179 mmHg and randomized them to either usual care (control group) or active treatment with hydrochlorothiazide with or without methyldopa or propranolol. The difference in change in mean SBP was 17 mmHg between the active treatment and control groups. No difference in major cardiovascular events or mortality was seen between the two groups, thus limiting the base of evidence to make recommendations for SBP thresholds for people less than 60 years based on outcomes other than

surrogate outcomes, such as blood pressure. This study did not, however, demonstrate significant harm associated with the treatment of these younger patients.

The recommendations for suggested treatment at age less than 60 years or for SBP between 140 mmHg and 159 mmHg for individuals over 60 years were made based on potential benefit for reduction in cardiovascular events and low patient burden associated with pharmacologic treatment. However, given the lack of evidence from RCTs with outcomes other than intermediate outcomes (achieved BP) to support this recommendation, pharmacologic therapy should only be instituted after a discussion with the patient about his or her own values and preferences with regard to treatment of hypertension and prevention of hypertension-related disease.

Despite the recommendation of a systolic blood pressure threshold of 160 mmHg for the initiation of pharmacologic therapy, lifestyle modifications can and should be instituted, if not contraindicated, for adults at any age with a SBP value above 120 mmHg, both for the prevention of hypertension and because lifestyle modification therapies can potentially be associated with other favorable health outcomes and are unlikely to result in harm.

Research priorities should focus on examining outcomes for patients 60 years and older when pharmacologic therapy for hypertension is initiated at a SBP of less than 160 mmHg. A systolic BP threshold trial in patients younger than age 55 years would be difficult to conduct given that patients in this age group often have either diastolic hypertension or combined systolic/diastolic hypertension. While the currently ongoing Systolic Blood Pressure Intervention Trial (SPRINT) trial includes some participants <60 years of age (55 years and older), and has a SBP entry threshold of 130 mmHg, it is testing SBP goals of 120 mmHg vs <140 mmHg. [115] and will not test different thresholds for initiation of therapy.

Diastolic Blood Pressure Thresholds

Recommendation

24. We recommend offering pharmacologic treatment for patients 30 years and older with a diastolic blood pressure ≥90 mmHg.
25. We suggest offering pharmacologic treatment for patients age 18 to 29 with a diastolic blood pressure ≥90 mmHg.

Discussion

For most populations, the initiation threshold and target diastolic blood pressure of 90 mmHg is well-established. Multiple studies have demonstrated cardiovascular benefit for patients with treatment of diastolic hypertension in patients older than 60. [107,111,116] The Department of Veterans Affairs Cooperative Studies demonstrated a significant reduction in cardiovascular morbidity when antihypertensive pharmacologic therapy was initiated in a middle-aged male Veteran population whose DBP was 90-129mmHg. [117],[118] Subsequently, the Australian National BP study [119] demonstrated a reduction in fatal and nonfatal cardiovascular events when pharmacologic therapy was instituted when the DBP was 95-109 mmHg in a young, healthy population. Similarly, the National Institutes of Health (NIH) randomized nearly 11,000 diverse patients in a five-year trial comparing sequential care

versus routine community care. This was not placebo-controlled, and most community-care patients did, in fact, receive treatment for their hypertension, particularly in the higher baseline diastolic strata (105-114 mmHg, and 115 mmHg –plus, respectively). [120] In the predefined stratum of 90-104 mmHg baseline DBP, significant reductions in all-cause mortality and stroke were noted, approaching non-hypertensive population levels in the subgroup analyses. [121] There is evidence that all patients, regardless of age, with CKD or cerebrovascular disease (CVA, transient ischemic attack, carotid disease) derive mortality benefit with treatment for DBPs above 90 mmHg. [122,123]

There are no outcome studies published evaluating patients younger than age 30, so an appropriate threshold for initiating antihypertensive pharmacologic treatment is not clear. In this younger population, it may be appropriate to recommend a three to six month period of therapeutic lifestyle modification prior to offering medication management when their DBP is 90mmHg or higher.

Blood Pressure Goals

A reference table for blood pressure goals can be found in **Appendix D**. Detailed recommendations and discussion can be found below.

Systolic Blood Pressure Goals

Recommendations

26. For patients 60 years and over, we recommend treating to a systolic blood pressure goal of <150 mmHg.
27. For patients below 60 years of age, we suggest treating to a systolic blood pressure goal of <150 mmHg.

Discussion

The evidence supporting treating to a SBP goal less than 150 mmHg is strong and is based on several well-done randomized placebo-controlled trials in participants aged 60 and above with isolated systolic hypertension [109,124] and in hypertensive participants aged 80 and above. [110] These trials demonstrated significant benefits for major cardiovascular outcomes, and HYVET also demonstrated reduction in mortality. [110] Another placebo-controlled trial demonstrated benefits in major cardiovascular outcomes for a SBP goal less than 160 mmHg. [125] Other major outcome trials comparing a lower SBP goal (130-140 mmHg) to a higher SBP goal (140 to 160 mmHg or 140 to 149 mmHg) in older participants [126,127] and participants with a recent lacunar stroke [128] failed to demonstrate significant reduction in major cardiovascular events for the lower goal compared to the higher goal, although these trials did not conclusively disprove any benefit.

Although there is little evidence to support the previous recommendations to treat this population to a SBP goal of <140 mmHg, there is also little evidence for harm. For patients who are well-managed below 140 mmHg, not on a complex regimen and tolerating it well, it is not necessary to reduce therapy to try to aim for a target between 140 and 150 mmHg. However, for newly diagnosed patients, achieving a systolic goal of <150 mmHg is feasible and may require fewer resources than the previously recommended goal of 140 mmHg.

The committee has a high degree of confidence in the quality of the existing evidence. A high priority for research is determining if lower SBP goals are beneficial or harmful in this older population. One such trial already underway is the SPRINT, sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and expected to be completed by 2016-17. [115] It is testing whether an SBP goal of <120 mmHg reduces major cardiovascular and renal events, and dementia compared with an SBP goal of <140 mmHg in >9,000 high-risk non-diabetic patients, most of whom will be age ≥60 years with an SBP ≥130 mmHg.

Recommendation 27 is based on expert opinion interpretation of indirect evidence, since there are no major outcome trials in our review for non-diabetic, non-CKD hypertensive patients testing a specific SBP goal in persons younger than 60 years. In the absence of such evidence, and the stronger relationship between DBP and cardiovascular risk in younger persons, the committee suggests an SBP treatment goal of less than 150 mmHg in this population; an SBP goal of <150 mmHg has been demonstrated to reduce cardiovascular outcomes in patients above age 60 years and in patients with diabetes. The average achieved SBP will likely be much lower when recommended DBP goals are reached in this population. In DBP goal studies in this middle-aged and younger population, the achieved SBP levels averaged less than 140 mmHg. Therefore, as in the older population, for patients whose SBP is below 140 mmHg, and not on a complex regimen and tolerating the medications well, there is little evidence for harm and it is not necessary to reduce therapy to try to aim for a target between 140 and 150 mmHg if the DBP goal has been achieved.

Patients in this age group may prefer a lower SBP goal, since other guidelines recommend an SBP goal of <140 mmHg. Providers should discuss with these patients that there is little evidence for either additional harm or benefit for this lower goal, pending ongoing trials. Although an SBP goal of <140 mmHg may be desirable, there are no previous or current RCTs comparing a goal of <150 mmHg to <140 mmHg or other lower goals.

For patients with CKD and hypertension, refer to the VA/DoD CKD CPG[4] which recommends a SBP goal of <140 mmHg.

Diastolic Blood Pressure Goals

Recommendation

28. We recommend treating to a diastolic blood pressure goal <90 mmHg in patients 30 years and older.
29. We suggest treating to a diastolic blood pressure goal <90 mmHg in patients age 18 to 29.

Discussion

Strong clinical trial evidence exists demonstrating the benefits of treating hypertension to a DBP goal of less than 90 mmHg. Landmark studies such as the Veterans Administration Cooperative Study Group on Antihypertensive Agents, the Hypertension Detection and Follow-up Program (HDFP), and the MRC trial of treatment of mild hypertension all demonstrate substantial benefits in terms of reduced

[4] See the VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease. Available at: http://www.healthquality.va.gov/guidelines/cd/ckd/index.asp

cardiovascular events by treating to a target DBP of less than 90 mmHg. [117,118,120,122,129] Eligibility for these studies differed slightly, but generally included patients 30 years of age or older. In the Hypertension Optimal Treatment (HOT) trial, further reductions below 90 mmHg were not shown to be of benefit. In HOT, over 18,000 patients with diastolic blood pressures between 100 and 115 mmHg were randomized to target DBPs of ≤90, ≤85, or ≤80 mmHg. No significant differences among the groups were noted for a broad range of cardiovascular endpoints. [130] In the absence of specific evidence for DBP goals in patients age 18 to 29, it is reasonable to extrapolate the data from older populations to this younger group.

Specific Populations

Diabetic Population

Recommendations

30. For patients with diabetes (all age groups), we recommend treating to a systolic blood pressure goal of <150 mmHg.
31. For patients with diabetes (all age groups) who tolerate antihypertensive drugs, we suggest treating to a systolic blood pressure goal of <140 mmHg.
32. For patients with diabetes, we recommend treating to a diastolic blood pressure goal <85 mmHg.

Discussion

Recommendation 30 is based on moderate quality evidence from three SBP-goal RCTs [109,124,131] that treatment to an SBP goal of <150 mmHg improves major cardiovascular and cerebrovascular outcomes and lowers mortality in adults with diabetes and hypertension. No RCT addressed whether treatment to an SBP goal of <140 mmHg compared with a higher goal is beneficial in adults with diabetes and hypertension. Only the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial [132] compared an SBP goal lower than 140 mmHg (<120 mmHg) with a higher SBP goal (<140 mmHg) in patients with diabetes and hypertension. ACCORD BP did not show significant benefit for the primary cardiovascular disease outcome for the SBP <120 mmHg group, but did show a reduction in stroke and an increase in serious adverse events. This was not sufficient evidence to support a lower SBP goal in diabetes.

Recommendation 31, suggesting an SBP goal of <140 mmHg for patients with diabetes who tolerate antihypertensive medications, is supported by the <140 mmHg SBP goal control group in the ACCORD BP trial, [132] in which this control group (SBP goal of 140 mmHg) had similar cardiovascular outcomes but fewer serious adverse events than the lower SBP goal group, and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, [133] which showed that mortality was reduced with a combination of a thiazide-type diuretic and an angiotensin-converting enzyme inhibitor (ACEI) to lower blood pressure in persons with diabetes mellitus. (In the ADVANCE trial, although there was not an SBP goal, the mean achieved SBP of 135 mmHg is consistent with an SBP goal of <140 mmHg.)

Achieving these goals is feasible and should require fewer resources than the recommended goal of <130 mmHg in diabetes in many previous guidelines (but not the 2004 VA/DoD Hypertension CPG which recommended <140 mmHg). Patients may prefer a lower SBP goal than 150 or 140 mmHg, since previous guidelines in the past decade have recommended a lower SBP goal. Providers should discuss with these patients to determine the best balance between a decreased stroke risk, but higher adverse effect risk, with a lower goal (as shown in the ACCORD BP trial [132]). A trial testing a SBP goal lower than 150 mmHg (e.g., 120 or 130 mmHg) in patients with diabetes mellitus is a high research priority and would be feasible and ethical to undertake, since ACCORD BP did not prove that the lower goal was not beneficial due to the unexpected reduced power (from low event rates) and a wide confidence interval for the primary outcome that included a clinically important benefit.

Results from randomized clinical trials demonstrate that more intensive therapy of diastolic blood pressure to levels below that in the general population is of benefit in hypertension patients with diabetes. The strongest evidence is provided by the UK Prospective Diabetes Study Group. [134] Patients with a mean blood pressure of 160/94 mmHg at baseline were randomized to tight control (target blood pressure <150/85 mmHg) versus less tight control (target blood pressure <180/105 mmHg). Tight control was associated with reduced risk of important outcomes including death due to diabetes and stroke. While this was not a direct comparison of a target of 90 mmHg versus a lower goal, the achieved blood pressure was 144/82 mmHg in the tight control group versus an achieved blood pressure of 154/87 mmHg in the group with less tight control. The HOT study was a direct comparison study. [130] Diabetic and non-diabetic patients with DBPs between 100 and 115 mmHg were randomized to target DBPs of ≤90, ≤85 or ≤80 mmHg. Achieved blood pressures were 85.2, 83.2, and 81.1 mmHg respectively. Among patients with diabetes, intensive treatment was associated with significant declines in major cardiovascular events. The relatively small diabetes sub-sample, and the fact that the analysis of patients with diabetes was not pre-specified, limits the strength of this evidence. It should be noted that the VA/DoD Management of Diabetes Mellitus in Primary Care CPG recommends a DBP goal of 80 mmHg due to more weight being placed on the HOT study.[5]

Elderly Population

Particular uncertainty exists surrounding blood pressure treatment goals in very old patients with hypertension. Clinical trials such as SHEP and HYVET provide strong evidence for the benefits of treatment to guideline-recommended levels in at least some elderly hypertension patients. However, it is important to recognize that these clinical trials included relatively few people over age 85 and those elderly included in the study may have been healthier than "average." [135] This raises questions as to the generalizability of these results to broad segments of the elderly population. Moreover, extensive population-based data suggest that higher blood pressure is associated with enhanced survival in people over age 85. [136] While these conflicting results cannot be fully reconciled, recent observational studies suggest that frailty and comorbidity should perhaps be considered when setting treatment goals in the very old. Among elderly patients in the National Health and Nutrition Examination Survey (NHANES)

[5] See the VA/DoD Clinical Practice Guideline for the Management of Diabetes Mellitus in Primary Care. Available at: http://www.healthquality.va.gov/guidelines/CD/diabetes/

sample, higher SBP was associated with increased mortality in those with a fast gait speed, while in people with a slow gait speed there was no association between mortality and blood pressure. In those unable to do the walk test, higher SBP was associated with a lower risk of death. [137] Similarly, in the Leiden 85-Plus Study, higher SBP was associated with a lower risk of stroke in those subjects with physical and cognitive impairment. [138] Further guidance on treatment goals for frail, elderly hypertension patients will require additional clinical trials. For now, clinicians should exercise their judgment in setting treatment goals for these patients.

Hypertension Control and Follow-up

Control, Adherence, and Presence of Adverse Effects

Recommendation

33. We suggest that patients be seen within one month of initiation of lifestyle or pharmacological therapy to determine adequacy of hypertension control, degree of patient adherence, and presence of adverse effects. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*

Discussion

Some medications may have a rapid onset of blood lowering pressure, but the full antihypertensive effect may take a month or more. Seeing these patients within a month may help stress to these patients the importance of their diagnosis, and may help the clinical care team to assess how well the patient is adhering to his or her therapy. In addition, the provider can discuss with the patient any side effects he or she may be having from the medication or other challenges he or she may have with adherence to treatment.

Although the initiation of treatment belongs firmly in the hand of the credentialed provider, other members of the healthcare team can serve a valuable role in the follow-up of these newly diagnosed patients. Patient education, assessment of adherence and the assessment of potential adverse effects can easily be done by their skill set, freeing up the clinician to see the more resistant cases and the patients where titration of therapy is necessary. The implementation of the Patient Centered Medical Home (PCMH) model also supports the elevation of primary care staff to functioning at the top of their licensure.

Follow-up Once Hypertension is Controlled

Recommendation

34. Once the patient's blood pressure is controlled, we suggest follow-up at least annually, or more frequently as indicated, depending on patient preference. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*

Discussion

There is no definitive evidence on what duration between follow-up visits helps maintain optimal blood pressure, although a study by Birtwhistle et al. suggested that six month visits yielded similar control to three month visits. [139] However, in that study, because patients were free to visit their clinician at any

time, the number of visits over the approximately three-year study period was roughly similar (16.2 vs. 18.8 visits) although statistically significant. Hence, any interval within that timeframe would generally be appropriate; depending on clinical circumstances some patients may be seen earlier or later.

Without evidence to show that more frequent visits are beneficial to patients, our recommendation is that well-controlled, uncomplicated patients be seen at least annually. Patients should be instructed to contact their care providers in the interim if they experience any side effects or have any other challenges with continuing their therapy.

Cessation of hypertensive therapy

Decrease or cessation of antihypertensive drug therapy is possible in patients who are willing to do so, and whose BP is well below goal. These patients should be closely followed-up.

Although hypertension is frequently considered to be a life-long diagnosis, there is the potential to reduce the number or dosage of drugs for patients who have been under good control for an extended period of time, or if they have made new significant changes in their lifestyle or body weight. This reduction in medication is most likely to be successful if the BP control has been accompanied by one or more changes in the patient's weight, diet and/or activity level. If the medications were started in a stepwise manner, it is unlikely that a reduction in the dosage or number of medications will be successful without a change in some of the underlying lifestyle habits that are known to lead to increased blood pressure.

Regarding completely stopping hypertensive therapy, a review of observational data from the Second Australian National Blood Pressure Study (ANBP2) cohort suggests that those most likely to successfully withdraw from antihypertensive medication are patients whose blood pressures are controlled with monotherapy. [140] When withdrawal of therapy does occur, follow-up should generally be tailored to shorter durations at first to assure that blood pressure does not rise again.

Referrals to specialists

From a clinical perspective, referral to, or consultation with, hypertension specialists or those with particular expertise in the relevant clinical area should be considered if there is failure to achieve target blood pressure goals when the patient is on appropriate doses of three medications (one of which should typically be a thiazide-type diuretic and assuming that other remedial causes of inadequate response have been identified and addressed) or there is a suspected secondary cause for hypertension.

The vast majority of hypertensive patients can be successfully managed within DoD and VA primary care clinics. However, there are cases when patients will not reach their blood pressure target, even after having been prescribed three or more medications at recommended doses. If patient non-adherence and white coat effect have been ruled out, then further work-up should be done to determine if there is any treatable cause for this "resistant hypertension." Although a primary care provider can test for and treat a few of the causes of resistant secondary hypertension, others require specialist intervention. Referring a patient to, or consulting with, a hypertensive specialist can help direct the diagnostic work-up and treatment of these patients. Referral to a specialist need not wait until the patient is on three

antihypertensive agents at maximal doses if clear signs/symptoms of a cause of secondary hypertension are present.

Resistant and Secondary Hypertension

An early discussion or consultation with an appropriate specialist is encouraged when a patient has resistant hypertension or is suspected of having secondary hypertension due to such conditions as primary kidney disease, Cushing's, or pheochromocytoma. Refer to **Table 5** for a list of the most common causes of secondary hypertension.

Secondary forms of hypertension may be present in up to 10% of all cases of hypertension. [141-143] In cases of resistant hypertension, a contributing cause such as sleep apnea, [144] hyperaldosteronism, [145,146] Cushing's syndrome, [147] or kidney disease [148,149] is present in the majority of cases and a targeted evaluation based on the patient's risk factors and clinical history should be undertaken. Recent estimates suggest that more than 20% of hypertensive patients meet criteria for resistant hypertension in the US, [150] so evaluation for causes of secondary hypertension will become a more common practice, even in the primary care setting. Referral to appropriate experts, as needed, may lead to the most accurate and cost-effective evaluation for secondary hypertension.

Table 5. Recommended Testing for Patients Suspected of Having Secondary Hypertension

Disease	Features	Recommended Test/Referral
Obstructive Sleep apnea	Daytime somnolence Fatigue Obesity Snoring or observed apneic episodes	Referral for overnight polysomnagram (sleep study)
Drug or substance Induced	Nonsteroidal anti-inflammatory drugs (NSAIDs), including Cox-2 Inhibitors Sympathomimetics (e.g., decongestants, anorectics) Combined oral contraceptives Adrenal steroids Erythropoietin Cyclosporine, tacrolimus Cocaine, amphetamines Excessive alcohol use Licorice Selected dietary supplements (e.g., ma huang, ephedra, bitter orange)	History Urine toxicology as indicated
Primary hyperaldosteronism	Resistant Hypertension Hypokalemia	Plasma aldosterone and plasma renin activity

Disease	Features	Recommended Test/Referral
		Consider referral for an elevated aldosterone/renin ratio
Kidney disease	Elevated serum creatinine Proteinuria Hematuria on two occasions or structural renal abnormality (e.g., abdominal or flank masses) Abnormal urine sediment	Urinalysis; estimation of urinary protein excretion and creatinine clearance by using a single random urine test; renal ultrasound may also be considered Consider referral to nephrology
Renovascular disease	Abdominal bruits over the renal arteries Abrupt onset of severe hypertension Diastolic BP $\geq$115 mmHg Initial onset age <50 years Worsening BP control when previously stable Evidence of atherosclerotic vascular disease Hypertension	There are a variety of screening tests for renovascular hypertension, depending on equipment and expertise in institutions Renal Artery Doppler Ultrasound, Computerized tomography (CT) Angiography, Magnetic resonance Angiography, and post-captopril renograms are used However, there is no single best test for renovascular hypertension, and consultation with experts in your institution is recommended Intravenous pyelogram is relatively contraindicated in diabetes and no longer recommended as screening test for renovascular disease.
Cushing's syndrome and other glucocorticoid excess states including chronic steroid therapy	Amenorrhea Increased dorsal fat Diabetes mellitus Edema Hirsutism Moon facies Purple striae Truncal obesity	History 24-hour urine for free cortisol Dexamethasone suppression test Late night salivary cortisol Consider referral to a specialist
Hyperthyroidism	Anxiety Brisk reflexes Hyperdefecation Heat intolerance Tachycardia Tremor Weight loss	Thyroid Stimulating Hormone (TSH) Free T4

Disease	Features	Recommended Test/Referral
	Wide pulse pressure	
Aortic Coarctation	Weak or delayed femoral pulses	Echocardiogram Computerized tomography angiography
Pheochromocytoma	Labile BP Orthostatic hypotension Paroxysms (headaches, palpitations, sweating, pallor) Tachycardia	Plasma metanephrines or 24-hour urine for metanephrines and/or catecholamines Consider referral to specialist
Hyperparathyroidism	Hypercalcemia Polyuria/polydipsia Renal stones	Serum calcium and parathyroid hormone (PTH) level

Monotherapy or Combination Therapy

Recommendations

35. We suggest taking into consideration the patient's baseline blood pressure and presence of comorbidities, when deciding on either monotherapy or combination therapy (two drugs) when initiating drug therapy. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*
36. We suggest initiating combination therapy for patients with a baseline systolic blood pressure of >20 mmHg or diastolic blood pressure of >10 mmHg above the patient's goal. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*

Discussion

Different approaches to initial treatment of hypertension, either with a single agent or combination therapy, are appropriate as long as the goal blood pressure is achieved. Evidence is lacking to suggest a benefit in primary outcomes of interest to include mortality, cardiovascular events, stroke, or adverse effect profiles of one treatment approach compared to another. We recommend the provider consider each patient's comorbid conditions and degree of blood pressure lowering desired when selecting initial therapy.

Evidence from the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) confirms that combination therapy is safe and effective, [151] and evidence from ALLHAT confirms that combination therapy is required in a majority of patients to reach blood pressure goals. [152] Only 26% of participants reached goal blood pressure (<140/90 mmHg) with a single antihypertensive drug, even after adjustment in dosage. [153] Although evidence is lacking to recommend a firm threshold for initiating combination therapy, we observe that a desired reduction of blood pressure of 20/10 mmHg will often require at least two medications to achieve BP control, and that initiating therapy with two drugs appears to be well tolerated in most patients. Patients with a compelling indication for more than one class of antihypertensive agent may benefit from initial

combination therapy as well. Although the evidence review for this update did not include studies with primary outcomes of medication adherence, time to blood pressure control, or overall effectiveness of reaching goal blood pressure, the committee suggests that these measures may be improved with initial combination therapy.

In summary, the best outcomes result from achievement of goal blood pressure. As a majority of patients will require more than one medication to achieve goal, we suggest initial therapy with two medications of different classes for patients with an SBP of >20 mmHg or DBP of >10 mmHg or more above goal. However, no two renin-angiotensin system (RAS) blockers should be used together (Refer to **Recommendations 43 and 44**).

First-line Therapy

Recommendation

37. We recommend the use of thiazide-type diuretics for the treatment of hypertension.
38. We suggest the use of thiazide-type diuretics at recommended treatment doses as first-line therapy for drug treatment of hypertension either as monotherapy or in combination with other agents. *(Modified from 2004 VA/DoD HTN CPG)*

Discussion

Similar to past guidelines, evidence supporting initiating antihypertensive therapy with a thiazide-type diuretic is based primarily on many placebo-controlled outcome trials with thiazide-type diuretics as the basis of therapy and results from the ALLHAT trial, [154] which is especially pertinent to VA/DoD providers due to the >7,000 Veterans included in the study. New evidence has been published in the ACCOMPLISH study favoring ACEI/calcium channel blocker combination over an ACEI/thiazide-type diuretic combination. [151] While this evidence was considered for this recommendation, the dose of the thiazide-type diuretic in ACCOMPLISH (hydrochlorothiazide 12.5-25 mg/day) is lower than equipotent doses of chlorthalidone or indapamide. [151] Due to this finding, thiazide-type diuretics should be prescribed at the doses which demonstrated greatest clinical benefit from randomized controlled trials. While the cost differential between all initial therapies has closed significantly since the 2004 VA/DoD HTN CPG was published, thiazide-type diuretics remain a cost-effective first choice. Although ACCOMPLISH has weakened the strength of this recommendation, there remains strong evidence to support the use of thiazide-type diuretics as first-line therapy.

Thiazide-type Diuretics

Recommendations

39. To initiate treatment of hypertension with a thiazide-type diuretic, we suggest the use of chlorthalidone or indapamide over hydrochlorothiazide.
40. We do not suggest switching from hydrochlorothiazide to chlorthalidone or indapamide if the patient is adequately controlled on and tolerating hydrochlorothiazide.
41. We suggest considering a switch from hydrochlorothiazide to chlorthalidone for patients whose hypertension is inadequately controlled on 50mg/day of hydrochlorothiazide.

42. We recommend a dosage of 12.5-25mg/day of chlorthalidone, 25-50mg/day of hydrochlorothiazide, or a dosage of 2.5mg/day immediate-release or 1.5-2.5mg/day sustained-release (not currently available in the US) of indapamide.

Discussion

The justifications for these recommendations are based on the level of blood pressure reduction and the drugs doses which have reduced major outcomes in RCTs for hydrochlorothiazide (HCTZ), chlorthalidone and indapamide. For initial or add-on treatment of hypertension, chlorthalidone and indapamide result in greater decreases of blood pressure compared to current low doses (12.5-25mg/day) of HCTZ. [155-160] There is limited evidence which suggests that HCTZ at doses of 37.5-60mg/day provides similar BP as chlorthalidone 12.5-60mg/day. [160,161] Additionally, the effect of HCTZ only lasts about 16 to 24 hours, while the action of chlorthalidone is about 48 to 72 hours. This difference could have a more stable effect on blood pressure and partially explain the larger effect of chlorthalidone in preventing cardiovascular events. [162] In general, indapamide and chlorthalidone at recommended doses appear to provide additional reduction in SBP (4-5 mmHg) and DBP (2-3 mmHg) compared to low doses of HCTZ (12.5-25mg/day). There is limited evidence for direct comparisons of blood pressure reduction between chlorthalidone and indapamide; however, they appear to be similar at the doses we have recommended. [163] A variety of doses and formulations of indapamide have been used in studies. Indapamide immediate-release (IR) appears to provide the greatest blood pressure reduction at 2.5mg/day, but based on the differences in study designs, a specific dose of the sustained-release (SR) formation could not be recommended. Therefore we have listed a dose range of 1.5-2.5mg/day. It should be noted that the SR formulation of indapamide is not currently available in the US.

There are no randomized controlled trials comparing HCTZ, chlorthalidone, and indapamide to each other, or at different doses, on clinical outcomes such as overall mortality, cardiovascular mortality and stroke.

Changes in serum electrolytes, specifically potassium, were measured in several studies; there is no clear evidence of clinically significant differences between these three thiazide-type diuretics at comparable therapeutic doses based on the available evidence either in the general hypertensive population or in the elderly. [158,160,161]

Thiazide-type diuretics were found to be safe and effective for the treatment of hypertension in patients with mild chronic kidney disease. Thiazide-type diuretics may be less effective in patients with serum creatinine above 2mg/dL or creatinine clearance less than 30mL/min, as patients with moderate to severe kidney disease were largely excluded from these clinical studies.

We considered making a stronger recommendation for chlorthalidone or indapamide based on the evidence; however, when considering the values of patients and providers we recognized the reasons why it may be difficult to change therapy from HCTZ or to initiate therapy with another thiazide. HCTZ is well known to both patients and providers and is incorporated into a variety of combination products, especially those including ACEIs and angiotensin II receptor blockers (ARBs) that are commonly used in practice. In contrast, chlorthalidone and indapamide are only available in a limited number of

combination products. We also recognize that many providers may be hesitant to prescribe HCTZ in doses greater than 25mg/day based on their training or clinical experience; however, we point out the lack of positive outcome data for HCTZ at doses of 12.5-25mg/day when compared to other agents.

Given the proven safety and outcome benefits of thiazide-type diuretics and the low cost of select thiazide-type diuretics, specifically HCTZ and chlorthalidone, these agents should continue to be a major component of the treatment of hypertension; however, we currently have limited outcome data to compare the specific thiazide-type diuretics to each other. A research priority should be to provide comparative effectiveness data, preferably via randomized controlled trials focusing on the important patient outcomes of overall mortality and cardiovascular morbidity and mortality.

Alternative or Supplementary Therapies

Recommendation

43. We recommend using the following as alternative therapies for patients who cannot tolerate thiazide-type diuretics, as supplementary therapies for patients who do not reach their hypertensive goals, or for those starting on combination therapy:
    a. Angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers (but not together)
    b. Long-acting dihydropyridine calcium channel blockers

(Modified from 2004 VA/DoD HTN CPG)

Discussion

ACEIs and ARBs have shown benefit in reducing CVD morbidity in patients with hypertension, and either drug class is recommended. In addition, ACEIs have well-established benefits when used in patients with reduced ejection fraction heart failure, left ventricular systolic dysfunction, post MI, and in patients with diabetic and non-diabetic CKD.

In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) head-to-head trial of an ACEI (ramipril) vs. an ARB (telmisartan), no differences were reported in renal or cardiovascular (CV) outcomes (composite endpoint of CV death, myocardial infarction, stroke or heart failure hospitalization) in a population of patients with vascular disease, of whom 69% were hypertensive. [164] Other data support the use of ARBs. The composite of cardiovascular morbidity (including stroke) and mortality were reduced with losartan when compared to a beta blocker (atenolol). [165] Additionally, no difference in CV morbidity and mortality was seen with an ARB (valsartan) vs. a long-acting dihydropyridine calcium channel blocker (LA DHP CCB) (amlodipine) in patients at high risk for cardiovascular events. [166]

The largest study supporting efficacy of an ACEI or LA DHP CCB comes from the ALLHAT trial, where over 33,000 patients 55 years of age or older with hypertension were randomized to treatment with a thiazide-type diuretic (chlorthalidone), lisinopril or amlodipine. Neither the ACEI nor the LA DHP CCB were superior to chlorthalidone in preventing the primary endpoint of coronary heart disease or nonfatal MI, or all-cause mortality. For the secondary endpoints, higher rates of stroke were reported with the ACEI, and an increased risk of heart failure was seen with the ACEI and LA DHP CCB. [152]

Other supporting evidence for a LA DHP CCB includes the Intervention as a Goal in Hypertension Treatment (INSIGHT) trial, where there was no difference in cardiovascular events in a group of patients with hypertension and one additional cardiovascular risk factor who were randomized to either long acting nifedipine or amiloride/HCTZ. [167]

Patients often require multiple drugs to reduce elevated blood pressure. The systematic evidence base did not include studies evaluating combinations for antihypertensive drug classes. However, patients requiring a three drug regimen for managing hypertension should usually be on a RAS blocker, LA DHP CCB, and thiazide-type diuretic, before considering addition of other drug classes. Patients should not use combinations of two RAS blockers for the treatment of hypertension (e.g., ACEIs, ARBs, and/or direct renin inhibitors [DRIs]).

Recommendation

44. We recommend against the use of more than one of the following three drug classes together in the same patient: angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors.

Discussion

Despite the potential for additional blood pressure reduction with combination therapy of agents that act at the renin-angiotensin system (ACEIs, ARBs, and DRIs), data from recent clinical trials have reported an increased risk for harm (including hypotensive symptoms, renal dysfunction or acute kidney injury events, or hyperkalemia) without long-term cardiovascular or renal outcome benefit in patients treated with combination therapy with two or more of these three classes, compared to monotherapy. [164,168,169] Although these trials primarily studied high-risk patients with at least one of the following conditions including vascular disease, diabetes mellitus, kidney disease, or diabetic nephropathy, the majority of patients either had a diagnosis of hypertension or were being treated with antihypertensive medications. [164,168,169]

Recommendation

45. We recommend additional therapy in refractory hypertension (for those who do not tolerate or are not adequately controlled with triple therapy [i.e., thiazide-type diuretics, ACEI or ARB, and LA DHP CCBs] described in **Recommendation 43**) or as supplementary therapy in some clinical indications. Drug classes for consideration can include (not in priority order):
    a. Aldosterone/mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone)
    b. Other potassium-sparing diuretic (i.e., amiloride)
    c. Alpha adrenergic blockers
    d. Beta adrenergic blockers
    e. Non-dihydropyridine calcium channel blockers
    f. Combined alpha-beta adrenergic blockers
    g. Peripherally acting antiadrenergic agents (reserpine, pending availability)
    h. Direct acting vasodilators (e.g., hydralazine, minoxidil)
    i. Centrally acting antiadrenergic drugs (e.g., clonidine, methyldopa)

Discussion

Antihypertensive agents other than thiazide-type diuretics, ACEIs, ARBs, and LA DHP CCBs have a role in certain situations. Adequate treatment of high blood pressure to recommended goals frequently requires use of multiple antihypertensive agents. The alternative drugs are often used fourth- or fifth-line as add-on therapy when combination therapy with the preferred antihypertensive drug classes has failed to adequately control blood pressure, or in cases where there is intolerance to or contraindications to the preferred drug classes. Several of these drugs were used as add-on therapy in the pivotal randomized controlled trials used in the systematic evidence base.

Overall, there was a lack of studies in the evidence base to provide specific recommendations for many of the drug classes listed above (e.g., combined alpha-beta adrenergic blockers, and centrally acting antiadrenergic drugs). Consideration should be given to the presence of comorbid conditions, risk of adverse events with a particular drug class, and the patient's willingness to adhere to multi-drug regimens.

Refer to other VA/DoD Clinical Practice Guidelines for treatment recommendations in patients with hypertension and chronic heart failure[6], CKD[7] (see also **Recommendation 47**), or ischemic heart disease[8]. General comments and available outcomes based on the evidence are included below for some of the drug classes.

- ***Aldosterone/mineralocorticoid receptor antagonists:*** Spironolactone is often added on to multi-drug regimens in patients with resistant hypertension, and for hyperaldosteronism. Eplerenone is an alternative for patients experiencing antiandrogen adverse effects with spironolactone.

- ***Other potassium sparing diuretics (i.e. amiloride):*** Amiloride is frequently combined with a thiazide-type diuretic (e.g., HCTZ) in patients with hypertension, due to its benefit of preserving potassium. In the INSIGHT trial, amiloride/HCTZ and nifedipine produced comparable results in reducing CV morbidity, and amiloride/HCTZ was significantly more effective in reducing HF. [167] Amiloride is also often added to a multidrug regimen in resistant hypertension when spironolactone is not tolerated or contraindicated.

- ***Beta blockers:*** Evidence for a clear benefit of beta blockers in reducing cardiovascular events is mixed. For the outcomes of CV morbidity and mortality, a beta blocker (atenolol) was inferior to ARB (losartan). [165] However, no difference was noted between propranolol and the thiazide bendrofluazide for all CV events, coronary events and all-cause death, with the exception of a lower stroke rate with the thiazide. [129] Other important indications for beta blockers

[6] See the VA/DoD Clinical Practice Guideline for the Management of Chronic Heart Failure. Available at: http://www.healthquality.va.gov/guidelines/cd/chf/index.asp
[7] See the VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease. Available at: http://www.healthquality.va.gov/guidelines/cd/ckd/index.asp
[8] See the VA/DoD Clinical Practice Guideline for the Management of Ischemic Heart Disease. Available at: http://www.healthquality.va.gov/guidelines/cd/ihd/index.asp

unrelated to hypertension include hypertensive patients with underlying coronary artery disease, following MI, and in low ejection-fraction heart failure. Beta blockers may be an alternative therapy in patients with contraindications or intolerance to an ACEI or ARB. The adverse event profile of beta blockers may limit their use.

- ***Non-dihydropyridine calcium channel blockers****:* Evidence supporting use of a non-DHP CCB comes from one large trial which reported no difference in CV endpoints (all-cause mortality, nonfatal stroke, MI) when verapamil SR (with ACEI) was compared with beta blocker (with HCTZ) in hypertensive patients with CAD. [170] A non-DHP CCB can be considered in hypertensive patients with atrial fibrillation when beta blockers are not tolerated.

- ***Reserpine (pending availability):*** Reserpine, if available, can also be used as supplemental therapy. In ALLHAT, reserpine, atenolol or clonidine were the options for step two drugs. [171] Reserpine combined with HCTZ and hydralazine was the active treatment arm in the Veterans Administration Cooperative Study Group on Antihypertensive Agents morbidity trial. [118] Limitations to the use of reserpine include adverse events and availability. As of August 2014, there are no commercially available reserpine products, due to a shortage of raw material. [172]

Recommendation

46. We recommend against the use of alpha-adrenergic blockers as monotherapy, but this class of agents may be used as supplemental therapy or if warranted by comorbid conditions (e.g., symptomatic prostatic hypertrophy). *(Modified from 2004 VA/DoD HTN CPG)*

Discussion

The evidence for this recommendation comes from the initial findings of the ALLHAT study. [171] The ALLHAT study was a randomized, double-blind, multicenter clinical trial sponsored by the NHLBI. It was designed to determine whether the occurrence of fatal coronary heart disease or nonfatal MI was lower for high-risk patients with hypertension treated with a CCB (represented by amlodipine), an ACEI (represented by lisinopril), or an alpha blocker (represented by doxazosin), each compared with diuretic treatment (represented by chlorthalidone). Chlorthalidone was found to be superior to doxazosin, leading to early termination of the doxazosin arm of the trial. In high-risk hypertensive patients, chlorthalidone significantly reduced the risk of total CVD events, particularly heart failure, compared with doxazosin. Furthermore, the doxazosin arm compared with the chlorthalidone arm had a higher risk of stroke and total CVD events. [154] The study population of interest was 55 years of age and older.

Specific Populations

Patients with Chronic Kidney Disease

Recommendation

47. In patients with hypertension and chronic kidney disease (reduced kidney function with albuminuria), we recommend treatment with an angiotensin-converting-enzyme inhibitor, or angiotensin II receptor blocker for improving kidney outcomes. *(Modified from 2004 VA/DoD HTN CPG)*

Discussion

The recommendation for selection of antihypertensive therapy in patients with CKD is based on the beneficial effect on kidney outcomes, as clinical trials in patients with CKD either did not evaluate cardiovascular endpoints as a primary outcome, or found no difference between treatment groups for cardiovascular outcomes evaluated as secondary endpoints or by subgroup analyses. [173-176]

The recommendation to use an ACEI or ARB as initial therapy in patients with hypertension and CKD with albuminuria is based on the beneficial effects on kidney outcomes, with evidence as outlined in the VA/DoD Clinical Practice Guideline on the Management of CKD.[9] The majority of data reviewed shows that treatment with an ACEI in patients with non-diabetic kidney disease slows the progression of CKD; with evidence for use of an ARB in this patient population based on limited data on surrogate outcomes. The ACEIs have also been shown to decrease the progression of kidney disease and reduce the combined risk of death, dialysis, or transplantation in patients with type 1 diabetes mellitus and albuminuria. [177] In patients with type 2 diabetes mellitus and albuminuria, treatment with an ACEI or an ARB decreased the progression of kidney disease. In two long-term trials in patients with nephropathy due to type 2 diabetes, the primary endpoint of composite all-cause mortality, doubling of serum creatinine, and end stage renal disease (ESRD) was significantly reduced with an ARB compared to placebo [173,178] or treatment with a DHP CCB. [173] When treatment with an ACEI was compared to an ARB in patients with type 2 diabetes and nephropathy, an ARB was not inferior to treatment with an ACEI for the primary endpoint of change in glomular filtration rate (GFR); and the secondary endpoints of annual change in GFR, level of serum creatinine, urinary albumin excretion rate, and blood pressure were not significantly different between treatment groups. [179]

The evidence review for this guideline is in agreement with the VA/DoD CKD guideline to use an ACEI or ARB in patients with hypertension and CKD with proteinuria. The clinical trials evaluating treatment comparisons found that an ACEI improved kidney outcomes compared to treatment with a DHP CCB, [180-183] as did treatment with an ARB compared to a DHP CCB. [173]

It is recommended that in patients with CKD, if either an ACEI or ARB is not tolerated, the other class should be used. As discussed in the VA/DoD CKD guideline,[9] use of an ACEI or ARB is commonly associated with an increase in serum creatinine and potassium. Patients with CKD prescribed an ACEI or ARB should be monitored closely for changes in electrolytes and kidney function, with dose adjustments, or modifications in treatment, as indicated. Potassium-sparing diuretics should be used with caution in patients with CKD, and may contribute to hyperkalemia if prescribed with an ACEI or ARB, or in patients with other risk factors for hyperkalemia. In one evaluation of patients with resistant hypertension being considered for treatment with spironolactone, predictors of hyperkalemia included an eGFR $\leq$45 ml/min/1.73m^2 in patients with a potassium >4.5 mEq/L. [184] Patients experiencing cough on an ACEI should be switched to an ARB. [185-187] An ARB should be used with caution in patients who have previously experienced angioedema with an ACEI. [188,189]

[9] See the VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease. Available at: http://www.healthquality.va.gov/guidelines/cd/ckd/index.asp

Add-on Antihypertensive Therapy

Most patients with CKD and hypertension will require more than one medication to achieve the recommended blood pressure target. [173,179-182] In the trials reviewed, the most frequently used add-on therapy to an ACEI or ARB was a diuretic, followed by a LA DHP CCB or beta blocker. A diuretic should be considered as add-on or concomitant initial therapy with an ACEI or ARB in patients with CKD, as a general recommendation to improve cardiovascular outcomes in patients with hypertension. It is generally recommended that thiazide-type diuretics be used if eGFR $\geq$30 ml/min/1.73 m^2, with loop diuretics added to or instead of thiazide-type diuretics for patients with more advanced kidney disease. [190-192] A LA DHP CCB may also be considered as add-on therapy as per a subgroup analysis of the ACCOMPLISH trial, [151] where a decrease in progression of CKD (doubling serum creatinine or ESRD) and combined cardiovascular events and CKD events were reported in patients receiving combination with an ACEI (benazepril) and LA DHP CCB (amlodipine) compared to treatment with benazepril and a thiazide-type diuretic (HCTZ), although the thiazide-type diuretic was dosed lower than what had been proven effective in CVD outcome trials. [193] Drug therapy selection should also take into account patient comorbidities and tolerability.[10]

Patients with a history of stroke

There is no evidence that the choice of drug should differ in patients with a history of stroke. In post-stroke patients, the addition of an ACEI may be considered, but should be paired with a diuretic. An ACEI may provide additional benefit to existing antihypertensive therapies or for patients who are not hypertensive for primary stroke protection. In the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) trial, the thiazide-type diuretic indapamide, when added on to ACEI therapy with perindopril, resulted in lower rates of CV morbidity and mortality, and stroke, over that seen with ACEI alone in patients with a history of TIA or minor stroke. There were no blood pressure entry criteria, although it was recommended that individuals with uncontrolled hypertension receive antihypertensive therapy with agents other than ACEIs before entry to the trial. [194]

African American Population

Recommendations

48. In African American patients with hypertension, we recommend against using an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker as monotherapy.
49. In African American patients with hypertension and stage 1-3 chronic kidney disease, we suggest a combination of a thiazide-type diuretic (for cardiovascular protection) with either an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker (for renal protection).

Discussion

Thiazide-type diuretics remain the drugs of choice in initial therapy for African Americans with hypertension. [195] The ALLHAT study included more than 15,000 African Americans and found that the

[10] See the VA/DoD Clinical Practice Guideline for the Management of Chronic Kidney Disease. Available at: http://www.healthquality.va.gov/guidelines/cd/ckd/index.asp

ACEI (lisinopril) was less effective in lowering blood pressure than the thiazide-type diuretic (chlorthalidone) or the LA DHP CCB (amlodipine). [195] The study population of interest was 55 years of age and older. The study found that those participants randomized to the ACEI (lisinopril) versus the thiazide-type diuretic (chlorthalidone) were at a 40% greater risk of stroke, 32% greater risk of heart failure, and 19% great risk of CVD. [152] There was no difference in major CVD outcomes between the thiazide-type diuretic and the LA DHP CCB, besides higher incidence of heart failure with the CCB. The ALLHAT study also found that African Americans randomized to the LA DHP CCB (amlodipine) had a greater adherence to the treatment and ended up needing fewer medications to reach the blood pressure goal than those randomly assigned to ACEI (lisinopril). [196] Additionally, the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) reported that African Americans on a beta-blocker (atenolol) had better cardiovascular outcomes than those on an ARB (losartan). [197]

Furthermore, in the African American Study of Kidney Disease and Hypertension (AASK), ACEIs were found to be more effective than beta blockers or LA DHP CCBs in slowing GFR decline among African American patients with proteinuria. [183] The AASK trial would suggest that African Americans with CKD should be placed on an ACEI, but the ALLHAT study reported that chlorthalidone was superior to lisinopril for CVD outcomes in African Americans. [176] Therefore for African American patients with CKD on monotherapy with an ACEI or an ARB, a thiazide-type diuretic should be added to augment the cardiovascular protection of diuretics to the renal protection of ACEIs or ARBs.

Women of reproductive age

The treatment of hypertension in women who have the potential to become pregnant requires special consideration due to potential adverse effects to a fetus. Women of reproductive age with hypertension should be counseled about the potential teratogenic effects of their medications. In addition, women should be counseled to alert their providers whenever they are planning to become, or realize that they already are, pregnant. Medications which act through the renin-angiotensin system (i.e., ACEIs and ARBs) should be avoided during pregnancy since they can lead to renal dysgenesis, pulmonary hypoplasia, intrauterine growth restriction, or death of the fetus. [198-203] Direct renin inhibitors may carry a similar risk and should also be avoided. Spironolactone and RAS blockers should be avoided in women of child-bearing potential due to their anti-androgenic effects during fetal development and concern for undervirilization of a male fetus. Providers should enter a discussion with women about their plans for pregnancy or birth control prior to the initiation of medications for the treatment of hypertension. For patients who are interested in becoming pregnant, or who are not on reliable birth control and at risk for pregnancy, alternative agents should be utilized such as labetalol, calcium channel blockers, or thiazide-like diuretics. Elevated blood pressure during pregnancy can be caused by a myriad of conditions such as acute illness, chronic hypertension, pregnancy in hypertension, or pre-eclampsia and should be managed by a provider with experience in caring for these conditions, such as an obstetrician.

Deployed Service Members: Considerations for treatment of hypertension in a deployed environment

Medical support

Deployed Service Members are instructed to seek healthcare on their Forward Operating Base (FOB)/Combined Operating Base (COB) while in a Theater of Operations. If more urgent care is required, Service Members are then air evacuated to a higher level of care. Routine healthcare for Service Members while deployed in a Theater of Operations may vary from a single provider and medic at a Battalion Aid Station (BAS) on a remote FOB, to a Troop Medical Clinic (TMC), or forward surgical team (FST) or Combat Support Hospital (CSH) on a COB. The ability to have routine basic labs drawn, such as blood chemistry or complete blood count (CBC), is found at CSHs and FSTs.

Harsh environmental conditions

It is not unusual for Service Members to be working outdoors (sun and/or shade) for an extensive time in temperatures greater than 120° F, and/or at altitudes greater than 5000 feet. Fluid loss due to work intensity, duration of heat exposure, and clothing/equipment worn, as well as medications taken, may also result in increased dehydration rates. Additionally, in these cases acclimatization to heat and/or altitude may cause additional fluid loss. Service Members who are deployed and have a preexisting diagnosis of hypertension may become prone to dehydration in austere/extreme climates as they engage in extreme physical activity. If not contraindicated, primary care providers should consider prescribing DHP CCBs, ACEIs or ARBs as the preferred antihypertensive. However, for patients who are newly diagnosed with hypertension while in a deployed environment, the primary care providers should consider using DHP CCBs as the preferred agents. These medications are available in once a day formulations, do not limit heart rate, and do not require electrolytes to be checked after initiation. Moreover, Service Members may also be deployed to cold weather environments and will also experience diuresis as part of their acclimatization process. Clinicians who care for Service Members who are in a deployable status should be cognizant of the Service Member's worldwide mission, and remember to ask the patient if and where they will be deploying. This will facilitate modifying the patient's current medications, if necessary, so as to diminish any serious side effects that may affect electrolyte balance because of the limited ability to monitor the patient. Moreover, providers should also be aware that certain antihypertensive medications (e.g., beta-blockers or non-DHP CCBs) may limit maximum heart rate. As many Service Members are involved in physically demanding work, limiting their ability to increase cardiovascular output may increase their risk of environmental injury and compromise their ability to respond to a tactical situation that requires running, jumping, carrying heavy objects, or other types of sustained heavy physical exertion. Additionally, primary care managers should be mindful of the varying formulations of medications. For example, gel caps can melt and should not be used in hot climates.

Nuclear, biological, and chemical (NBC) operations

In high operational tempo environments, Service Members may be operating in chemical protective/flame protective over garments and equipment, sometimes for several hours at a time (e.g., fire fighters, decontamination teams). The donning of chemical/fire resistant protective over garments dramatically increases the Service Member's heat load, in addition to the austere environmental conditions. Moreover, it is also more difficult to drink fluids, eat, or take oral medications while wearing

a protective mask. Depending on the tactical situation, Service Members may also be required to take medications for pretreatment against nerve agent poisoning (pyridostigmine bromide) or biological warfare agents (usually a fluoroquinolone). If a Service Member is exposed to a nerve agent, he or she will be treated intramuscularly with Atropine and 2-PAM Chloride. Clinicians who care for deployed members should also be cautious about any medication that would either decrease the Service Members ability to compensate for heat stress, make them more sensitive to nerve agent poisoning, or make resuscitation medication drugs less effective (if indicated).

Adherence

Operational tempo in a deployed environment is high-paced. If at all possible, clinicians should attempt to prescribe daily dosing of chronic medications to facilitate medication adherence in deployed Service Members. Likewise, meals are either frequently carried by the Service Member or are available only at irregular intervals. Thus, if possible, the provider should avoid/limit prescribing medications that must be taken with food or that are required to be added to food or beverages.

Nutrition

Service Members frequently do not get a choice regarding where they are going, what they are doing, or where they will eat in a deployed/training environment. Food sources may range from Meals Ready to Eat (MREs), items received in care packages, to training area or FOB/COB dining facilities. Depending upon what area of responsibility the Service Member is deployed to/training in, these rations may be high in sodium and fat. These nutritional factors may impact hypertension management and necessitate provider counseling related to diet.

Appendix A: Evidence Review Methodology

The Clinical Practice Guideline Champions were tasked with identifying key evidence questions to guide the systematic review of the literature on hypertension. These questions, which were developed in consultation with the Lewin team, addressed clinical topics of the highest priority for the Veterans Affairs and Department of Defense populations. The key questions follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 provides a brief overview of the PICOTS typology.

Table A-1. PICOTS [204]

P	Patients, Population or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-morbidities, and other patient characteristics or demographics.
I	Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
C	Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
O	Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
(T)	Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
(S)	Setting, of applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Table A-2 contains the final set of key questions (KQs) used to guide the systematic review for this CPG.

Conducting the Systematic Review

The methods guiding this systematic review are described below. In part, these methods follow the guidelines for conducting a systematic review set forth by AHRQ in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. [205] The methods also follow the guidance set forth by the VA/DoD in the *Guideline for Guidelines* document. [10]

The Lewin Group conducted a systematic review in support of this VA/DoD CPG. The target population considered in the systematic review was outpatient adults ages 18 years or older. The systematic review did not address pregnant women, peri-operative/inpatient adults, children or adolescent populations.

The review addressed various management strategies for patients with HTN. This included assessing the benefits and harms associated with antihypertensive pharmacologic therapies as well as the blood pressure thresholds to initiate therapy and appropriate blood pressure targets. In addition to physician-directed management strategies, the review assessed the impact of non-pharmacologic therapies (e.g., weight reduction, sodium reduction, physical activity) in reducing HTN. The review also evaluated what measurement techniques are the best indicators to initiate anti-hypertensive therapy. The target audience of the systematic review and CPG are VA/DoD and other primary care physicians and specialists who treat active and inactive military personnel.

Extensive literature searches identified 19,888 potentially relevant studies. Of those, 19,093 were excluded upon title and abstract review for not meeting the inclusion and exclusion criteria. A total of 799 full-text articles were reviewed of which an additional 649 articles were excluded. Articles excluded from the evidence base for a particular key question were removed for one or more of the following reasons: the article was published before 1966, the article was not in English, the study type did not qualify, the study population was not a relevant population of interest, the intervention was not relevant, the comparator was not relevant, the outcomes examined were not relevant, the study setting was not relevant, the sample size was <100, or the study follow-up period was less than one year.

Overall, 150 publications addressed one or more of the KQs and comprised the evidence base for this literature review. Table A-2 indicates the number of studies that addressed each of the questions. Figure A-1 displays a summary of the phases of the systematic review.

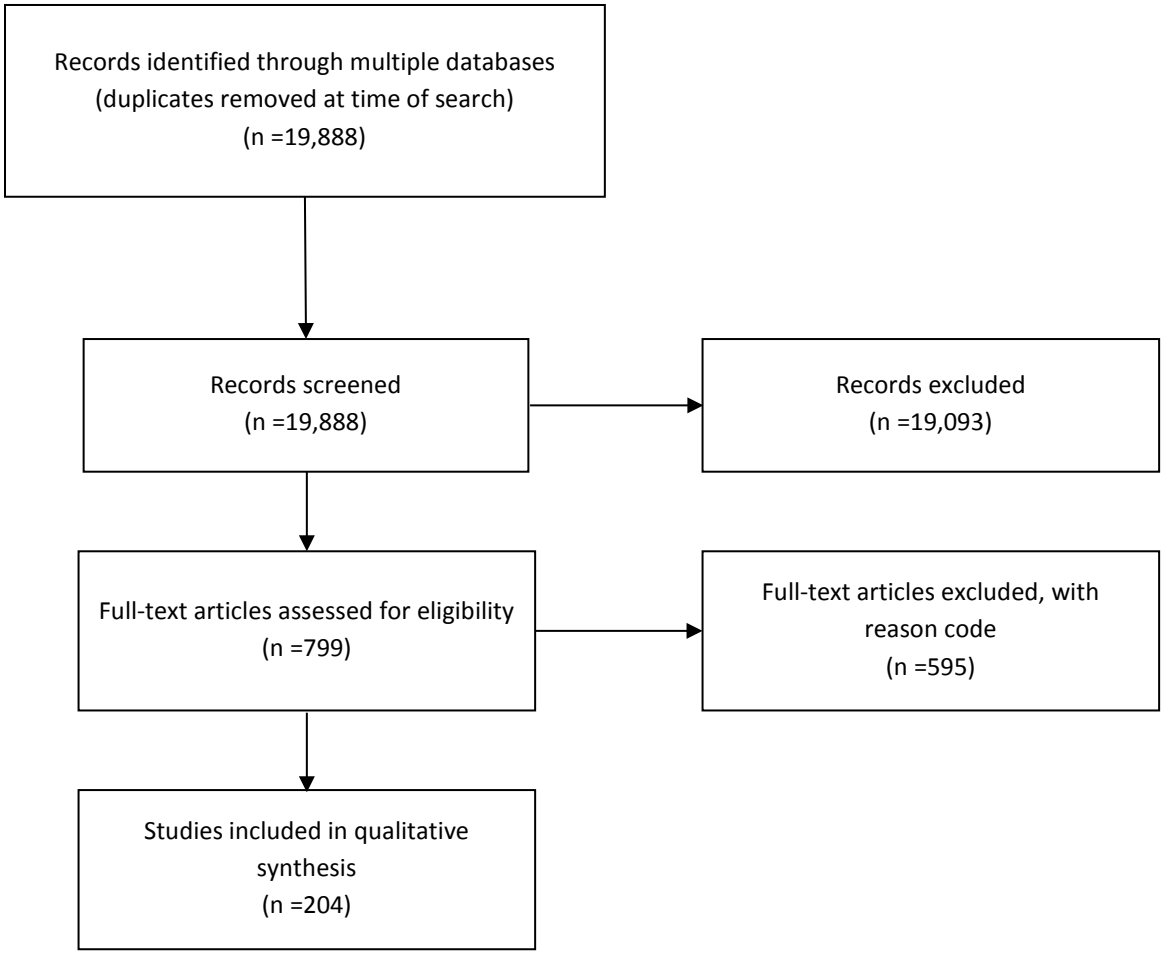
Table A-2. Evidence Base for Included Studies by Key Question

Number	Question	Number and type of included studies
1	In adult outpatients, at what systolic blood pressure threshold does initiating pharmacologic therapy for hypertension result in clinically improved outcomes? Does it differ based on the patient's age, gender, race, or history of prior stroke, LVH, diabetes, CKD (with and without proteinuria), CHF, CAD or combined CVD disease?	13 RCTs
2	In adult outpatients, at what diastolic blood pressure threshold does initiating pharmacologic therapy for hypertension result in clinically improved outcomes? Does it differ based on the patient's age, gender, race, or history of prior stroke, LVH, diabetes, CKD (with and without proteinuria), CHF, CAD or combined CVD disease?	12 RCTs
3	For adult outpatients being treated for hypertension, what is the systolic blood pressure goal that is associated with improved health outcomes? Does it differ based on the patient's age, gender, race, or history of prior stroke, LVH, diabetes, CKD (with and without proteinuria), CHF,	21 RCTs

Number	Question	Number and type of included studies
	CAD or combined CVD disease?	
4	For adult outpatients being treated for hypertension, what is the diastolic blood pressure goal that is associated with improved health outcomes? Does it differ based on the patient's age, gender, race, or history of prior stroke, LVH, diabetes, CKD (with and without proteinuria), CHF, CAD or combined CVD disease?	17 RCTs
5	In adult outpatients with an abnormal BP measurement, which measurement technique is the best indicator of whether hypertension therapy should be initiated and is more predictive of LVH, CKD, CVD, and end organ damage? • Office versus Home • Office versus 24 hour ambulatory blood pressure monitor • 24 hour ambulatory blood pressure monitor versus Home Does it differ based on the patient's age, gender, race, or history of prior stroke, LVH, diabetes, CKD (with and without proteinuria), CHF, CAD or combined CVD disease?	7 Observational Studies
6	In adult outpatients, how effective is non-pharmacologic therapy in reducing BP?	
	a. Weight reduction?	11 RCTs
	b. Reduced alcohol consumption?	1 RCT
	c. Sodium reduction?	2 RCTs
	d. Exercise/physical activity • Are certain types of exercise more effective?	6 RCTs
	e. Dietary and non-dietary potassium?	0 RCTs
	f. Combined dietary modification (two or more dietary changes)?	6 RCTs
	g. Mind-body therapy/behavioral therapy?	4 RCTs
	h. Improved adherence to treatment through self-monitoring, education interventions (patient and/or provider) and case management?	30 RCTs
7	In adults with hypertension on pharmacotherapy, what is the evidence that improved health outcomes vary by drug, within drug classes, or by drug class?	56 RCTs
8	In healthy adults with hypertension and no comorbidities, what is	2 RCTs

Number	Question	Number and type of included studies
	the evidence that initiation of pharmacotherapy as monotherapy, sequential therapy, or combination therapy (>2 drugs) produces the best results in improved blood pressure control, length of time to reach blood pressure goal, or health outcomes?	
9	In adults with hypertension, what is the evidence that there is a difference between thiazide-type diuretics for morbidity, mortality, or blood pressure reduction?	8 RCTs
	a. For each of these thiazide-type diuretics, how does the dose relate to the outcomes?	7 RCTs, 1 SR/MA

Figure A-1. Systematic Review Flow Diagram



Inclusion and Exclusion Criteria

To guide the collection of evidence, the team developed an initial set of inclusion and exclusion criteria that was discussed and agreed upon by the CPG Champions. While there are some overarching criteria for the review, the team also established individual sets of inclusion and exclusion criteria for each of the key questions, as necessary.

In some cases, the inclusion and exclusion criteria were influenced by recently published systematic evidence reviews or other publications. The utilization of previous publications as a starting point to address all or some of the key questions allowed the current literature search to be more efficient and effective.

Figure A-2 presents the overarching criteria that were applied to the literature searches and to the review of resulting literature identified through these searches.

A "best available evidence" approach was implemented to sort the evidence for the systematic review. [206] To be included in the systematic review, a study must be a prospective, randomized or nonrandomized (observational) controlled trial with an independent, concurrent control group. If no high quality intervention trials are available to address a particular key question, relevant observational studies were identified and included in the systematic review.

Figure A-2. General Inclusion and Exclusion Criteria

- Studies that enrolled adults (≥18 years) will be included. In studies with mixed adult and children populations, we will require that at least 85 percent of the enrolled patients are greater than age 18.
- Studies must be published in English.
- Publication must be a full clinical study or systematic review; abstracts alone will not be included. Similarly, letters, editorials, and other publications that are not full-length, clinical studies will not be included.
- Only human studies will be included.
- Studies that study acute hypertension/emergency treatment of hypertension will be excluded.
- Studies that look at only pulmonary hypertension will be excluded. If the study looks at regular and pulmonary hypertension, it will be included.
- Studies that look at pediatric hypertension will be excluded.

Outcomes

The patient outcomes of interest considered during the literature review for this CPG included:

- Blood pressure control
- Mortality: cardiovascular and all-cause
- Stroke: fatal and non-fatal
- CHF
- CAD, including MI and revascularization during an acute coronary syndrome
- Aortic events (e.g., aneurysm rupturing)

- LVH
- CKD: progression to ESRD, starting dialysis, kidney transplant, doubling of serum creatinine or reduction of GFR by 50%

Literature Search Strategies

Detailed search logic reflecting the PICOTS of interest were developed for each key question and used to identify relevant randomized controlled trials and other study design types as needed. The literature searches were conducted using the following bibliographic and other databases: PubMed/MEDLINE, EMBASE, and the Cochrane databases, including Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts of Reviews of Effects (DARE). The CPG Champions also contributed articles as part of the evidence generation step.

The literature search strategies incorporated key text terms identified from an initial review of relevant systematic reviews and primary research studies on related topics (including how they are indexed in their respective databases, e.g., use of medical subject headings [MeSH] in PubMed, EMTREE terms in EMBASE) and any terms identified by the CPG Champions or members of the evidence review team, including a clinical and research expert on the subject matter. Members of the evidence review team including a librarian, as needed, reviewed the search strategies developed to ensure comprehensiveness. Duplicates of studies were discarded during the search process so that each publication is represented only once in the resulting evidence base for each key question.

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) MeSH and EMTREE terms. Search sets were structured to address specific key questions and sub-questions. The strategies for PubMed are presented first, followed by the search strategies used in EMBASE and in Cochrane, including CENTRAL, CDSR and DARE. Searches of EMBASE and Cochrane were conducted in parallel with searches in PubMed.
For PubMed, two searches strategies were constructed for each key question. The first retrieved studies that are indexed in PubMed, and the second strategy captured any relevant studies which were in the process of being indexed or had not yet been indexed.

Key Questions 1 and 2

Date parameters ranged from 1966 to present in order to include seminal literature published in the late 1960s. We utilized the evidence base from a systematic review, Law et al., [207] which covered the years 1966-2007 and then conducted our own search from 2007 to present.

PubMed

1. Indexed Studies

	Concept(s)	Search Statement
#1	Blood pressure, hypertension, prehypertension	Blood Pressure[mh]/drug effects OR Hypertension[mh]/drug therapy OR Prehypertension[mh] OR Systole[mh] OR Diastole[mh] OR (hypertensive[tiab] OR prehypertensive[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab]) OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg)) OR (70 mmHg[tiab] OR 80 mmHg[tiab] OR 90 mmHg[tiab] OR 100 mmHg[tiab] OR 110 mmHg[tiab] OR 120*mmHg[tiab] OR 130*mmHg[tiab] OR 140*mmHg[tiab] OR 150*mmHg[tiab] OR 160*mmHg[tiab] OR 170*mmHg[tiab] OR

	Concept(s)	Search Statement
		180*mmHg[tiab])
#2	Outcomes of interest	(Mortality[mh] OR mortality[tiab] OR Death[mh] OR death*[tiab] OR Morbidity[mh] OR morbidity[tiab] OR Cause of Death[mh] OR Fatal Outcome[mh]) OR (Cardiovascular Diseases/prevention[mh] OR Cardiovascular Diseases/epidemiology[mh] OR Cardiovascular Diseases/etiology[mh] OR Cardiovascular Diseases/physiopathology[mh] OR Coronary Disease/prevention[mh] OR Coronary Disease/epidemiology[mh] AND Coronary Disease/etiology[mh] OR Coronary Disease/physiopathology[mh] OR Coronary Artery Disease/prevention[mh] OR Coronary Artery Disease/epidemiology[mh] OR Coronary Artery Disease/etiology[mh] OR Coronary Artery Disease/physiopathology[mh] OR Myocardial Infarction/prevention[mh] OR Myocardial Infarction/epidemiology[mh] OR Myocardial Infarction/etiology[mh] OR Myocardial Infarction/physiopathology[mh] OR Heart Failure/prevention[mh] OR Heart Failure/epidemiology[mh] OR Heart Failure/etiology[mh] OR Heart Failure/physiopathology[mh] OR Cerebrovascular Disorders/prevention[mh] OR Cerebrovascular Disorders/epidemiology[mh] OR Cerebrovascular Disorders/etiology[mh] OR Cerebrovascular Disorders/physiopathology[mh] OR Stroke/prevention[mh] OR Stroke/epidemiology[mh] OR Stroke/etiology[mh] OR Stroke/physiopathology[mh] OR Kidney/epidemiology[mh] OR Kidney/etiology[mh] OR Kidney/physiopathology[mh]) OR (myocardial infarction[tiab] OR heart failure[tiab] OR stroke[tiab] OR cerebrovascular disorder*[tiab] OR cerebrovascular event*[tiab] OR kidney failure[tiab] OR chronic kidney disease*[tiab] OR CKD[tiab]) OR (Myocardial Revascularization[mh] OR Myocardial Revascularization[tiab]) OR (Creatinine[mh] OR Creatinine[tiab]) OR (Glomerular Filtration Rate[mh] OR Glomerular Filtration Rate[tiab] OR GFR[tiab] OR eGFR[tiab] OR estGFR[tiab]) OR (hospitalization[tiab] OR coronary revascularization[tiab] OR angioplasty[tiab] OR stent*[tiab] OR peripheral revascularization[tiab] OR carotid[tiab] OR extremity revascularization[tiab] OR end stage renal disease[tiab] OR ESRD[tiab]) OR ((aggressive therapy[tiab] AND (goal*[tiab] OR target*[tiab]) AND (mmHg[tiab] OR mmHg[tiab])) OR morbidity[tiab])
#3	Antihypertensive treatment	Antihypertensive Agents/therapeutic use[mh] OR Hypertension/drug therapy[mh] OR ((antihypertensive OR anti-hypertensive) AND (drug therapy OR drug treatment)) OR (pharmacologic therapy OR pharmacologic lowering of blood pressure)
#4	Combine	#1 AND #2 AND #3
#5	Limit to RCTs	#4 AND Randomized Controlled Trial[PT]
#6	Apply date and language limit to RCTs	#5 AND ("1966/01/01"[PDAT] : "2013/12/16"[PDAT]) AND English[lang]

2. Indexed Studies for CKD Patients only

	Concept(s)	Search Statement
#1	Blood pressure, hypertension, prehypertension	Blood Pressure[mh]/drug effects OR Hypertension[mh]/drug therapy OR Prehypertension[mh] OR Systole[mh] OR Diastole[mh] OR (hypertensive[tiab] OR prehypertensive[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab]) OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg)) OR (70 mmHg[tiab] OR 80 mmHg[tiab] OR 90 mmHg[tiab] OR 100 mmHg[tiab] OR 110 mmHg[tiab] OR 120*mmHg[tiab] OR 130*mmHg[tiab] OR 140*mmHg[tiab] OR 150*mmHg[tiab] OR 160*mmHg[tiab] OR 170*mmHg[tiab] OR 180*mmHg[tiab])
#2	CKD population	renal insufficiency, chronic[majr] OR kidney failure, chronic[majr]
#3	Limit to RCTs	randomized controlled trial[pt]
#4	Combine	#1 AND #2 AND #3

#4	Apply date and language limit	#4 AND (#5 AND ("1966/01/01"[PDAT] : "2013/12/16"[PDAT]) AND English[lang]

3. Non-indexed Studies

	Concept(s)	Search Statement
#1	Blood pressure, hypertension, prehypertension	Blood Pressure[tiab] OR Prehypertension[tiab] OR Systole[tiab] OR Diastole[tiab] OR (hypertensive[tiab] OR prehypertensive[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab]) OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg)) OR (70 mmHg[tiab] OR 80 mmHg[tiab] OR 90 mmHg[tiab] OR 100 mmHg[tiab] OR 110 mmHg[tiab] OR 120*mmHg[tiab] OR 130*mmHg[tiab] OR 140*mmHg[tiab] OR 150*mmHg[tiab] OR 160*mmHg[tiab] OR 170*mmHg[tiab] OR 180*mmHg[tiab])
#2	Outcomes of interest	(Mortality[tiab] OR death*[tiab] OR morbidity[tiab] OR Cause of Death[tiab] OR Fatal Outcome[tiab]) OR (Cardiovascular Diseases [tiab] OR Coronary Disease [tiab] OR Coronary Artery Disease[tiab]) OR (myocardial infarction[tiab] OR heart failure[tiab] OR stroke[tiab] OR cerebrovascular disorder*[tiab] OR cerebrovascular event*[tiab] OR kidney failure[tiab] OR chronic kidney disease*[tiab] OR CKD[tiab]) OR Myocardial Revascularization[tiab] OR Creatinine[tiab] OR (Glomerular Filtration Rate[tiab] OR GFR[tiab] OR eGFR[tiab] OR estGFR[tiab]) OR (hospitalization[tiab] OR coronary revascularization[tiab] OR angioplasty[tiab] OR stent*[tiab] OR peripheral revascularization[tiab] OR carotid[tiab] OR extremity revascularization[tiab] OR end stage renal disease[tiab] OR ESRD[tiab]) OR ((aggressive therapy[tiab] AND (goal*[tiab] OR target*[tiab]) AND (mmHg[tiab] OR mmHg[tiab])) OR morbidity[tiab])
#3	Antihypertensive Treatment	Antihypertensive Agents[tiab] OR ((antihypertensive OR anti-hypertensive) AND (drug therapy OR drug treatment)) OR (pharmacologic therapy OR pharmacologic lowering of blood pressure)
#4	Combine	#1 AND #2 AND #3
#5	Limit to RCTs	#4 AND (randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#6	Apply language limit and limit to studies in the process of being indexed process of being indexed	#5 AND English[lang] AND inprocess[sb]

EMBASE

Set #	Searched for	Results
S1	EMB#("Blood Pressure") OR EMB#("Hypertension" LNK dt) OR EMB#("Systole") OR EMB#("Dystole")	515423*
S2	Mesh#("Blood Pressure" LNK de) OR Mesh# ("Hypertension" LNK dt) OR Mesh# ("Prehypertension") OR Mesh# ("Systole") OR Mesh# ("Dystole")	98328*
S3	S1 OR S2	613713*
S4	Mesh#("mortality") OR Mesh#("death") OR EMB#("Death") OR Mesh#("Cardiovascular Diseases" LNK pc) OR EMB#("Cardiovascular Disease" LNK pc)	1183047*
S5	Mesh#("Cardiovascular Diseases" LNK ep) OR EMB#("Cardiovascular Disease" LNK ep) OR Mesh#("Cardiovascular Diseases" LNK et) OR Mesh#("Cardiovascular Diseases" LNK pp) OR EMB#("Cardiovascular Disease" LNK et)	1142904*

Set #	Searched for	Results
S6	Mesh#("Kidney" LNK pc) OR Mesh#("Kidney" LNK ep) OR Mesh#("Kidney" LNK et) OR Mesh#("Kidney" LNK pp) OR EMB#(Kidney Failure)	269716*
S7	Mesh#("Myocardial revascularization") OR mesh#("creatinine") OR Mesh#("Glomerular filtration rate") OR EMB#("Heart Muscle revascularization") OR EMB#("Creatinine") OR EMB#("glomerulus filtration rate")	309623*
S8	S4 OR S5 OR S6 OR S7	2622712*
S9	EMB#("Heart Muscle revascularization") OR EMB#("Creatinine") OR EMB#("glomerulus filtration rate")	161775*
S10	S3 AND S8 AND S9	23141*
S11	S10 AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English") AND pd(>20061231))	7090*
S12	S11 AND (dtype("randomized controlled trial") OR emb#("randomized controlled trial"))	718°
S13	S11 AND (dtype("randomized controlled trial") OR emb#("randomized controlled trial"))	718°

* Duplicates are removed from your search, but included in your result count.
° Duplicates are removed from your search and from your result count.

A. *Cochrane CENTRAL*

ID	Search
#1	MeSH descriptor: [Blood Pressure] explode all trees and with qualifier(s): [Drug effects - DE]
#2	MeSH descriptor: [Hypertension] explode all trees and with qualifier(s): [Drug therapy - DT]
#3	MeSH descriptor: [Prehypertension] explode all trees
#4	MeSH descriptor: [Systole] explode all trees
#5	MeSH descriptor: [Diastole] explode all trees
#6	"hypertensive":ti,ab,kw (Word variations have been searched)
#7	prehypertensive:ti,ab,kw (Word variations have been searched)
#8	systolic pressure:ti,ab,kw (Word variations have been searched)
#9	diastolic pressure:ti,ab,kw (Word variations have been searched)
#10	arterial pressure:ti,ab,kw (Word variations have been searched)
#11	BP:ti,ab,kw (Word variations have been searched)
#12	systole (Word variations have been searched)
#13	diastole (Word variations have been searched)
#14	pressure (Word variations have been searched)
#15	mmHg (Word variations have been searched)
#16	mmHg (Word variations have been searched)
#17	#1 or #2 or #3 or #4 or #5 or (#6 or #7 or #8 or #9 or #10) or #11 or ((#12 or #13) and (#14 or #15 or #16))
#18	MeSH descriptor: [Mortality] explode all trees
#19	mortality:ti,ab,kw (Word variations have been searched)
#20	MeSH descriptor: [Death] explode all trees
#21	death:ti,ab,kw (Word variations have been searched)
#22	MeSH descriptor: [Morbidity] explode all trees
#23	morbidity:ti,ab,kw (Word variations have been searched)

ID	Search
#24	MeSH descriptor: [Cause of Death] explode all trees
#25	MeSH descriptor: [Fatal Outcome] explode all trees
#26	MeSH descriptor: [Cardiovascular Diseases] explode all trees and with qualifier(s): [Prevention & control - PC]
#27	MeSH descriptor: [Cardiovascular Diseases] explode all trees and with qualifier(s): [Epidemiology - EP]
#28	MeSH descriptor: [Cardiovascular Diseases] explode all trees and with qualifier(s): [Etiology - ET]
#29	MeSH descriptor: [Cardiovascular Diseases] explode all trees and with qualifier(s): [Physiopathology - PP]
#30	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Prevention & control - PC]
#31	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Epidemiology - EP]
#32	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Etiology - ET]
#33	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Physiopathology - PP]
#34	MeSH descriptor: [Coronary Artery Disease] explode all trees and with qualifier(s): [Prevention & control - PC]
#35	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Epidemiology - EP]
#36	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Etiology - ET]
#37	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Physiopathology - PP]
#38	MeSH descriptor: [Myocardial Infarction] explode all trees and with qualifier(s): [Prevention & control - PC]
#39	MeSH descriptor: [Myocardial Infarction] explode all trees and with qualifier(s): [Epidemiology - EP]
#40	MeSH descriptor: [Myocardial Infarction] explode all trees and with qualifier(s): [Etiology - ET]
#41	MeSH descriptor: [Myocardial Infarction] explode all trees and with qualifier(s): [Physiopathology - PP]
#42	MeSH descriptor: [Heart Failure] explode all trees and with qualifier(s): [Prevention & control - PC]
#43	MeSH descriptor: [Heart Failure] explode all trees and with qualifier(s): [Epidemiology - EP]
#44	MeSH descriptor: [Heart Failure] explode all trees and with qualifier(s): [Etiology - ET]
#45	MeSH descriptor: [Heart Failure] explode all trees and with qualifier(s): [Physiopathology - PP]
#46	MeSH descriptor: [Cerebrovascular Disorders] explode all trees and with qualifier(s): [Prevention & control - PC]
#47	MeSH descriptor: [Cerebrovascular Disorders] explode all trees and with qualifier(s): [Epidemiology - EP]
#48	MeSH descriptor: [Cerebrovascular Disorders] explode all trees and with qualifier(s): [Etiology - ET]
#49	MeSH descriptor: [Cerebrovascular Disorders] explode all trees and with qualifier(s): [Physiopathology - PP]
#50	MeSH descriptor: [Stroke] explode all trees and with qualifier(s): [Prevention & control - PC]
#51	MeSH descriptor: [Stroke] explode all trees and with qualifier(s): [Epidemiology - EP]
#52	MeSH descriptor: [Stroke] explode all trees and with qualifier(s): [Etiology - ET]
#53	MeSH descriptor: [Stroke] explode all trees and with qualifier(s): [Physiopathology - PP]
#54	MeSH descriptor: [Kidney] explode all trees and with qualifier(s): [Physiopathology - PP]
#55	"myocardial infarction":ti,ab,kw (Word variations have been searched)
#56	"heart failure":ti,ab,kw (Word variations have been searched)
#57	"stroke":ti,ab,kw (Word variations have been searched)
#58	cerebrovascular disorder:ti,ab,kw (Word variations have been searched)
#59	cerebrovascular event:ti,ab,kw (Word variations have been searched)
#60	"kidney failure":ti,ab,kw (Word variations have been searched)
#61	chronic kidney disease:ti,ab,kw (Word variations have been searched)
#62	CKD:ti,ab,kw (Word variations have been searched)
#63	MeSH descriptor: [Myocardial Revascularization] explode all trees

ID	Search
#64	"myocardial revascularization":ti,ab,kw (Word variations have been searched)
#65	MeSH descriptor: [Creatinine] explode all trees
#66	creatinine:ti,ab,kw (Word variations have been searched)
#67	MeSH descriptor: [Glomerular Filtration Rate] explode all trees
#68	"Glomerular Filtration Rate":ti,ab,kw (Word variations have been searched)
#69	"GFR":ti,ab,kw (Word variations have been searched)
#70	"eGFR":ti,ab,kw (Word variations have been searched)
#71	"estGFR":ti,ab,kw (Word variations have been searched)
#72	"hospitalization":ti,ab,kw (Word variations have been searched)
#73	"Coronary Revascularization":ti,ab,kw (Word variations have been searched)
#74	"angioplasty":ti,ab,kw (Word variations have been searched)
#75	stent:ti,ab,kw (Word variations have been searched)
#76	"peripheral revascularization":ti,ab,kw (Word variations have been searched)
#77	"carotid":ti,ab,kw (Word variations have been searched)
#78	"extremity revascularization":ti,ab,kw (Word variations have been searched)
#79	"end stage renal disease":ti,ab,kw (Word variations have been searched)
#80	"ESRD":ti,ab,kw (Word variations have been searched)
#81	"aggressive therapy":ti,ab,kw (Word variations have been searched)
#82	goal:ti,ab,kw (Word variations have been searched)
#83	target:ti,ab,kw (Word variations have been searched)
#84	"mmHg":ti,ab,kw (Word variations have been searched)
#85	"mmHg":ti,ab,kw (Word variations have been searched)
#86	"morbidity":ti,ab,kw (Word variations have been searched)
#87	(#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25) or (#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54) or (#55 or #56 or #57 or #58 or #59 or #60 or #61 or #62) or (#63 or #64) or (#65 or #66) or (#67 or #68 or #69 or #70 or #71) or (#72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80) or ((#81 and (#82 or #83) and (#84 or #85)) or #86)
#88	MeSH descriptor: [Antihypertensive Agents] explode all trees and with qualifier(s): [Therapeutic use - TU]
#89	MeSH descriptor: [Hypertension] explode all trees and with qualifier(s): [Drug therapy - DT]
#90	"antihypertensive" (Word variations have been searched)
#91	anti-hypertensive:ti,ab,kw (Word variations have been searched)

Key Questions 3 and 4

Date parameters ranged from 1966 to present. This was the date range used by the Eighth Joint National Committee (JNC 8) for the 2014 Evidence-based guideline for the management of high blood pressure in adults.[11] Since KQ 3-4 was identical to one of the questions addressed in the JNC 8 guideline, we utilized the evidence base from the JNC 8 evidence report which covered the years 1966-2010 and then conducted our own search from 2010 to present.

[11] James P, Oparil S, Carter B, Cushman W, 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2013; 311(5):507-20.

PubMed

1. Indexed Studies

	Concept(s)	Search Statement
#1	Outcomes of interest	(Mortality[mh] OR mortality[tiab] OR Death[mh] OR death*[tiab] OR Morbidity[mh] OR morbidity[tiab] OR Cause of Death[mh] OR Fatal Outcome[mh])
#2		(Cardiovascular Diseases/prevention[mh] OR Cardiovascular Diseases/epidemiology[mh] OR Cardiovascular Diseases/etiology[mh] OR Cardiovascular Diseases/physiopathology[mh] OR Coronary Disease/prevention[mh] OR Coronary Disease/epidemiology[mh] Coronary Disease/etiology[mh] OR Coronary Disease/physiopathology[mh] OR Coronary Artery Disease/prevention[mh] OR Coronary Artery Disease/epidemiology[mh] OR Coronary Artery Disease/etiology[mh] OR Coronary Artery Disease/physiopathology[mh] OR Myocardial Infarction/prevention[mh] OR Myocardial Infarction/epidemiology[mh] OR Myocardial Infarction/etiology[mh] OR Myocardial Infarction/physiopathology[mh] OR Heart Failure/prevention[mh] OR Heart Failure/epidemiology[mh] OR Heart Failure/etiology[mh] OR Heart Failure/physiopathology[mh] OR Cerebrovascular Disorders/prevention[mh] OR Cerebrovascular Disorders/epidemiology[mh] OR Cerebrovascular Disorders/etiology[mh] OR Cerebrovascular Disorders/physiopathology[mh] OR Stroke/prevention[mh] OR Stroke/epidemiology[mh] OR Stroke/etiology[mh] OR Stroke/physiopathology[mh] OR Kidney/epidemiology[mh] OR Kidney/etiology[mh] OR Kidney/physiopathology[mh])
#3		(myocardial infarction[tiab] OR heart failure[tiab] OR stroke[tiab] OR cerebrovascular disorder*[tiab] OR cerebrovascular event*[tiab] OR kidney failure[tiab] OR chronic kidney disease*[tiab] OR CKD[tiab])
#4		(Myocardial Revascularization [mh] OR Myocardial Revascularization[tiab])
#5		(Creatinine[mh] OR Creatinine[tiab])
#6		(Glomerular Filtration Rate[mh] OR Glomerular Filtration Rate[tiab] OR GFR[tiab] OR eGFR[tiab] OR estGFR[tiab])
#7		(hospitalization[tiab] OR coronary revascularization[tiab] OR angioplasty[tiab] OR stent*[tiab] OR peripheral revascularization[tiab] OR carotid[tiab] OR extremity revascularization[tiab] OR end stage renal disease[tiab] OR ESRD[tiab])
#8		(aggressive therapy[tiab] AND (goal*[tiab] OR target*[tiab]) AND (mmHg[tiab] OR mmHg[tiab])) OR morbidity[tiab]
#9	Antihypertensive treatment	((Antihypertensive Agents/therapeutic use [mh] OR Antihypertensive Agents/administration and dosage [mh]) OR (Hypertension/drug therapy [mh]) OR ((antihypertensive[tiab] OR anti-hypertensive[tiab]) AND drug therapy[tiab] OR drug treatment[tiab] OR dose[tiab] OR dosage[tiab]))
#10	Combine	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) AND #9
#11	Exclusion	((angioplasty[mh] OR angioplasty[tiab]) AND (renal artery obstruction [tiab] OR renal artery obstruction [mh] OR renal artery stenosis [tiab] OR renal artery stenosis[mh]))
#12	Exclusion	Ocular Hypertension[mh]
#13	Combine	#10 NOT (#11 OR #12)
#14	Limit to RCTs	#13 AND Randomized Controlled Trial[PT]
#15	Apply date and language limit	#14 AND ("1966/01/01"[PDAT] : "2013/12/14"[PDAT]) AND English[lang]

2. Non-indexed Studies

	Concept(s)	Search Statement
#1	Outcomes of interest	mortality[tiab] OR death*[tiab] OR morbidity[tiab] OR Cause of Death[tiab] OR Fatal Outcome[tiab]

#2		Cardiovascular Diseases [tiab] OR Coronary Disease [tiab] OR Coronary Artery Disease[tiab]
#3		myocardial infarction[tiab] OR heart failure[tiab] OR stroke[tiab] OR cerebrovascular disorder*[tiab] OR cerebrovascular event*[tiab] OR kidney failure[tiab] OR chronic kidney disease*[tiab] OR CKD[tiab]
#4		Myocardial Revascularization[tiab]
#5		Creatinine[tiab]
#6		Glomerular Filtration Rate[tiab] OR GFR[tiab] OR eGFR[tiab] OR estGFR[tiab]
#7		hospitalization[tiab] OR coronary revascularization[tiab] OR angioplasty[tiab] OR stent*[tiab] OR peripheral revascularization[tiab] OR carotid[tiab] OR extremity revascularization[tiab] OR end stage renal disease[tiab] OR ESRD[tiab]
#8		((aggressive therapy[tiab] AND (goal*[tiab] OR target*[tiab]) AND (mmHg[tiab] OR mmHg[tiab])) OR morbidity[tiab])
#9	Antihypertensive Treatment	(antihypertensive[tiab] OR anti-hypertensive[tiab]) AND (drug therapy[tiab] OR drug treatment[tiab] OR dose[tiab] OR dosage[tiab])
#10	Combine	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) AND #9
#11	Exclusion	(angioplasty[tiab] AND (renal artery obstruction [tiab] OR renal artery stenosis [tiab]))
#12	Exclusion	Ocular Hypertension[tiab]
#13	Combine	#10 NOT (#11 OR #12)
#14	Limit to RCTs	#13 AND (randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#15	Apply language limit and limit to studies in the process of being indexed	#14 AND English[lang] AND inprocess[sb]

EMBASE

Set #	Searched for	Results
S1	EMB.EXACT.EXPLODE("death") AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English")) AND pd(20100101-20141231)	44719*
S2	(Mesh.exact.explode("mortality") OR mesh.exact.explode("death")) AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English")) AND pd(20100101-20141231)	52875*
S3	(S1 OR S2) AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English")) AND pd(20100101-20141231)	97594*
S4	(EMB.EXACT.EXPLODE("cardiovascular disease -- prevention") OR EMB.EXACT.EXPLODE("cardiovascular disease -- epidemiology") OR EMB.EXACT.EXPLODE("cardiovascular disease -- etiology")) AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English")) AND pd(20100101-20141231)	38813*
S5	(Mesh.exact.explode("Cardiovascular Diseases" LNK pc) OR Mesh.exact.explode("Cardiovascular Diseases" LNK ep) OR Mesh.exact.explode("Cardiovascular Diseases" LNK et) OR Mesh.exact.explode("Cardiovascular Diseases" LNK pp)) AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English")) AND pd(20100101-20141231)	97489*
S6	(S4 OR S5) AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English")) AND pd(20100101-20141231)	136302*

Set #	Searched for	Results
S7	((Mesh.exact.explode("Kidney" LNK ep) OR Mesh.exact.explode("Kidney" LNK et) OR Mesh.exact.explode("Kidney" LNK pp)) OR EMB.exact.explode("Kidney Failure")) AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English")) AND pd(20100101-20141231)	26203*
S8	(EMB.EXACT("heart muscle revascularization") OR emb.exact("Creatinine") OR emb.exact("glomerulus filtration rate")) AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English")) AND pd(20100101-20141231)	29129*
S9	Mesh#(”Myocardial revascularization”) OR Mesh#(“creatinine”) OR Mesh#(“glomerular Filtration Rate”) ?	147873*
S10	S8 OR S9	177002*
S11	emb.exact("antihypertensive agent" LNK dt) OR (Mesh#(“antihypertensive agents” LNK tu) OR Mesh#(“antihypertensive agents” LNK dt)) OR (Mesh#("Hypertension" LNK dt))	135520*
S12	(S2 OR S6 OR S7 OR S9) AND S11	8013*
S13	emb.exact("angioplasty") OR emb.exact("kidney artery stenosis") OR emb.exact("intraocular hypertension")	39083*
S14	(Mesh#("Angioplasty") OR Mesh#("Renal Artery Obstruction")) OR (Mesh#("Renal Artery Stenosis") OR Mesh#("Ocular Hypertension"))	104251*
S15	S13 OR S14	143334*
S16	S12 NOT S15	7610*
S17	S16 AND (dtype("randomized controlled trial") OR emb#("randomized controlled trial"))	1396°
S18	S17 AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English") AND pd(>20091231))	724°
S19	(S3 OR S6 OR S7 OR S9) AND S11	8083*
S20	S19 NOT S15	7680*
S21	S20 AND (dtype("randomized controlled trial") OR emb#("randomized controlled trial"))	1399°
S22	S21 AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English") AND pd(>20091231))	727°
S23	S22 NOT S16	4°

* Duplicates are removed from your search, but included in your result count.
° Duplicates are removed from your search and from your result count.

Cochrane CENTRAL

ID	Search
#1	MeSH descriptor: [Mortality] explode all trees
#2	"mortality":ti,ab,kw (Word variations have been searched)
#3	MeSH descriptor: [Death] explode all trees
#4	death:ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Morbidity] explode all trees
#6	"morbidity":ti,ab,kw (Word variations have been searched)
#7	MeSH descriptor: [Cause of Death] explode all trees

ID	Search
#8	MeSH descriptor: [Fatal Outcome] explode all trees
#9	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)
#10	MeSH descriptor: [Cardiovascular Diseases] explode all trees and with qualifier(s): [Prevention & control - PC]
#11	MeSH descriptor: [Cardiovascular Diseases] explode all trees and with qualifier(s): [Epidemiology - EP]
#12	MeSH descriptor: [Cardiovascular Diseases] explode all trees and with qualifier(s): [Etiology - ET]
#13	MeSH descriptor: [Cardiovascular Diseases] explode all trees and with qualifier(s): [Physiopathology - PP]
#14	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Prevention & control - PC]
#15	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Epidemiology - EP]
#16	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Etiology - ET]
#17	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Physiopathology - PP]
#18	MeSH descriptor: [Coronary Artery Disease] explode all trees and with qualifier(s): [Prevention & control - PC]
#19	MeSH descriptor: [Coronary Artery Disease] explode all trees and with qualifier(s): [Epidemiology - EP]
#20	MeSH descriptor: [Coronary Artery Disease] explode all trees and with qualifier(s): [Etiology - ET]
#21	MeSH descriptor: [Coronary Artery Disease] explode all trees and with qualifier(s): [Physiopathology - PP]
#22	MeSH descriptor: [Myocardial Infarction] explode all trees and with qualifier(s): [Prevention & control - PC]
#23	MeSH descriptor: [Myocardial Infarction] explode all trees and with qualifier(s): [Epidemiology - EP]
#24	MeSH descriptor: [Myocardial Infarction] explode all trees and with qualifier(s): [Etiology - ET]
#25	MeSH descriptor: [Myocardial Infarction] explode all trees and with qualifier(s): [Physiopathology - PP]
#26	MeSH descriptor: [Heart Failure] explode all trees and with qualifier(s): [Prevention & control - PC]
#27	MeSH descriptor: [Heart Failure] explode all trees and with qualifier(s): [Epidemiology - EP]
#28	MeSH descriptor: [Heart Failure] explode all trees and with qualifier(s): [Etiology - ET]
#29	MeSH descriptor: [Heart Failure] explode all trees and with qualifier(s): [Physiopathology - PP]
#30	MeSH descriptor: [Cerebrovascular Disorders] explode all trees and with qualifier(s): [Prevention & control - PC]
#31	MeSH descriptor: [Cerebrovascular Disorders] explode all trees and with qualifier(s): [Epidemiology - EP]
#32	MeSH descriptor: [Cerebrovascular Disorders] explode all trees and with qualifier(s): [Etiology - ET]
#33	MeSH descriptor: [Cerebrovascular Disorders] explode all trees and with qualifier(s): [Physiopathology - PP]
#34	MeSH descriptor: [Stroke] explode all trees and with qualifier(s): [Prevention & control - PC]
#35	MeSH descriptor: [Stroke] explode all trees and with qualifier(s): [Epidemiology - EP]
#36	MeSH descriptor: [Stroke] explode all trees and with qualifier(s): [Etiology - ET]
#37	MeSH descriptor: [Stroke] explode all trees and with qualifier(s): [Physiopathology - PP]
#38	MeSH descriptor: [Kidney] explode all trees
#39	MeSH descriptor: [Kidney] explode all trees and with qualifier(s): [Physiopathology - PP]
#40	(#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39)
#41	"myocardial infarction":ti,ab,kw (Word variations have been searched)
#42	heart failure:ti,ab,kw (Word variations have been searched)
#43	stroke:ti,ab,kw (Word variations have been searched)
#44	cerebrovascular disorder:ti,ab,kw (Word variations have been searched)
#45	cerebrovascular event:ti,ab,kw (Word variations have been searched)
#46	"kidney failure":ti,ab,kw (Word variations have been searched)

ID	Search
#47	chronic kidney disease:ti,ab,kw (Word variations have been searched)
#48	CKD:ti,ab,kw (Word variations have been searched)
#49	(#41 or #42 or #43 or #44 or #45 or #46 or #47 or #48)
#50	MeSH descriptor: [Myocardial Infarction] explode all trees
#51	"myocardial revascularization":ti,ab,kw (Word variations have been searched)
#52	(#50 or #51)
#53	MeSH descriptor: [Creatinine] explode all trees
#54	creatinine:ti,ab,kw (Word variations have been searched)
#55	(#53 or #54)
#56	MeSH descriptor: [Glomerular Filtration Rate] explode all trees
#57	"glomerular filtration rate":ti,ab,kw (Word variations have been searched)
#58	GFR:ti,ab,kw (Word variations have been searched)
#59	eGFR:ti,ab,kw (Word variations have been searched)
#60	estGFR:ti,ab,kw (Word variations have been searched)
#61	(#56 or #57 or #58 or #59 or #60)
#62	"hospitalization":ti,ab,kw (Word variations have been searched)
#63	"coronary revascularization":ti,ab,kw (Word variations have been searched)
#64	angioplasty:ti,ab,kw (Word variations have been searched)
#65	"stent":ti,ab,kw (Word variations have been searched)
#66	"peripheral revascularization":ti,ab,kw (Word variations have been searched)
#67	"carotid":ti,ab,kw (Word variations have been searched)
#68	"extremity revascularization":ti,ab,kw (Word variations have been searched)
#69	"end stage renal disease":ti,ab,kw (Word variations have been searched)
#70	ESRD:ti,ab,kw (Word variations have been searched)
#71	(#62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70)
#72	aggressive therapy:ti,ab,kw (Word variations have been searched)
#73	goal:ti,ab,kw (Word variations have been searched)
#74	target:ti,ab,kw (Word variations have been searched)
#75	mmHg:ti,ab,kw (Word variations have been searched)
#76	mmHg:ti,ab,kw (Word variations have been searched)
#77	"morbidity":ti,ab,kw (Word variations have been searched)
#78	(#72 and (#73 or #74) and (#75 or #76)) or #77
#79	MeSH descriptor: [Antihypertensive Agents] explode all trees and with qualifier(s): [Therapeutic use - TU]
#80	MeSH descriptor: [Antihypertensive Agents] explode all trees and with qualifier(s): [Administration & dosage - AD]
#81	MeSH descriptor: [Hypertension] explode all trees and with qualifier(s): [Drug therapy - DT]
#82	"antihypertensive":ti,ab,kw (Word variations have been searched)
#83	"anti-hypertensive":ti,ab,kw (Word variations have been searched)
#84	"drug therapy":ti,ab,kw (Word variations have been searched)
#85	"drug treatment":ti,ab,kw (Word variations have been searched)
#86	dose:ti,ab,kw (Word variations have been searched)
#87	"dosage":ti,ab,kw (Word variations have been searched)

ID	Search
#88	((#79 or #80) or (#81) or ((#82 or #83) and #84 or #85 or #86 or #87))
#89	MeSH descriptor: [Angioplasty] explode all trees
#90	"angioplasty":ti,ab,kw (Word variations have been searched)
#91	"renal artery obstruction":ti,ab,kw (Word variations have been searched)
#92	MeSH descriptor: [Renal Artery Obstruction] explode all trees
#93	"renal artery stenosis":ti,ab,kw (Word variations have been searched)
#94	MeSH descriptor: [Ocular Hypertension] explode all trees
#95	((#89 or #90) and (#91 or #92 or #93))
#96	((#9 or #40 or #49 or #52 or #55 or #61 or #71 or #78) and #88) not (#95 or #94)
#97	#96 not pubmed:an
#98	"randomized controlled trial":pt (Word variations have been searched)
#99	#97 and #98 from 2010 to 2013
#100	#99 not pubmed:an

Key Question 5

It was determined that date parameters would range from 1983 to present as seminal literature on this topic began to be published in the mid-1980s.

PubMed

1. Indexed Studies

	Concept(s)	Search Statement
#1	Blood pressure monitoring	Blood Pressure Determination[mh] OR Blood Pressure Monitoring, Ambulatory[mh]
#2	Test characteristics	Predictive Value of Tests[mh] OR Prognosis[mh] OR Sensitivity[mh] OR Specificity[mh] OR Hypertension/diagnosis[mh] OR prognos*[tiab] OR predictive value[tiab]
#3	Combine	#1 AND #2
#4	Limit to clinical trial and observational study types	#3 AND Clinical Trial[PT] OR Epidemiologic Studies[mh] OR Comparative Study[PT]
#5	Apply date and language limit to clinical trials and observational studies	#4 AND ("1983/01/01"[PDAT] : "2014/01/09"[PDAT]) AND English[lang]

2. Non-indexed Studies

	Concept(s)	Search Statement
#1	Blood pressure monitoring	Blood Pressure Determination[tiab] OR Blood Pressure Monitoring[tiab] OR ((ambulatory OR office [tiab] OR home[tiab]) AND (blood pressure[tiab]))
#2	Test characterisics	Predictive Value[tiab] OR Prognos*[tiab] OR Sensitivity[tiab] OR Specificity[tiab] OR (Hypertension[tiab] AND diagnosis[tiab])

#3	Apply language limit and limit to studies in the process of being indexed	English[lang] AND inprocess[sb]

EMBASE

Set #	Searched for	Results
S1	MJEMB.EXACT("blood pressure monitoring") OR EMB.EXACT("blood pressure measurement")	40191*
S2	mesh#("Blood Pressure Determination") OR mesh#("Blood Pressure Monitoring, Ambulatory")	23421*
S3	S1 OR S2	63612*
S4	EMB.EXACT("predictive value") OR EMB.EXACT("prognosis") OR EMB.EXACT("sensitivity and specificity")	692031*
S5	mesh#("Predictive Value of Tests") OR mesh#("Prognosis") OR mesh#("Sensitivity") OR mesh#("Specificity")	1142189*
S6	S4 OR S5	1834220*
S7	emb#("Clinical Study") OR (EMB.EXACT.EXPLODE("comparative study") OR EMB.EXACT("meta analysis") OR EMB.EXACT("systematic review")) OR (EMB.EXACT.EXPLODE("controlled study") OR EMB.EXACT("cohort analysis") OR EMB.EXACT("cross-sectional study"))	10151018*
S8	(dtype("Clinical Trial") OR dtype("Meta-Analysis") OR Mesh#("Epidemiologic Studies") OR dtype("Comparative Study"))	3253809*
S9	dtype("Review") AND ti,ab(method* OR systematic OR comprehensive)	592496*
S10	S3 AND S6	5085*
S11	S10 AND (S7 OR S8 OR S9)	3063°
S12	EMB.EXACT.EXPLODE("clinical trial") OR EMB.EXACT("longitudinal study") OR EMB.EXACT("retrospective study") OR EMB.EXACT("case control study")	1505398*
S13	(EMB.EXACT.EXPLODE("comparative study") OR EMB.EXACT("meta analysis") OR EMB.EXACT("systematic review") OR EMB.EXACT("cohort analysis") OR EMB.EXACT("cross-sectional study"))	1468404*
S14	S10 AND (S12 OR S13 OR S9 OR S8)	2534°
S15	S14 AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English"))	2006°
S16	(S14 AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English"))) AND pd(19830101-20141231)	2002°
S17	S16 NOT SU("Medline")	1921°
S18	(EMB.EXACT.EXPLODE("comparative study") OR EMB.EXACT("meta analysis") OR EMB.EXACT("systematic review") OR EMB.EXACT("cross-sectional study"))	1322093*
S19	S10 AND (S18 OR S12 OR S8 OR S9)	2490°
S20	S19 NOT SU(Medline)	2343°
S21	S20 AND abany(yes)	2173°

S22	(S20 AND abany(yes)) AND rtype.exact("Journal Article")	1817°
S23	(S20 AND abany(yes)) AND (rtype.exact("Journal Article") AND la.exact("ENG"))	1673°
S24	(S20 AND abany(yes)) AND (rtype.exact("Journal Article") AND la.exact("ENG") AND pd(19830101-20141231))	1669°
S25	(S14 AND (abany(yes) AND pstype("Journal") AND at.exact("Article") AND la.exact("English"))) AND rtype.exact("Journal Article")	1673°
S26	(S10 AND (S12 OR S13 OR S9 OR S8)) AND at.exact("Article")	2325°
S27	(S10 AND (S12 OR S13 OR S9 OR S8)) AND (at.exact("Article") AND la.exact("ENG"))	2102°
S28	S27 NOT SU("Medline")	2012°
S29	(S27 NOT SU("Medline")) AND rtype.exact("Journal Article")	1713°
S30	S27 NOT SU("Medline")	2012°
S31	(S27 NOT SU("Medline")) AND at.exact("Article")	2012°

* Duplicates are removed from your search, but included in your result count.
° Duplicates are removed from your search and from your result count.

Cochrane CENTRAL

ID	Search	Hits
#1	MeSH descriptor: [Blood Pressure Determination] explode all trees	1802
#2	MeSH descriptor: [Blood Pressure Monitoring, Ambulatory] explode all trees	1029
#3	MeSH descriptor: [Predictive Value of Tests] explode all trees	5651
#4	MeSH descriptor: [Blood Pressure Determination] explode all trees	1802
#5	MeSH descriptor: [Hypertension] explode all trees and with qualifier(s): [Diagnosis - DI]	637
#6	MeSH descriptor: [Prognosis] explode all trees	102019
#7	MeSH descriptor: [Sensitivity and Specificity] explode all trees	14938
#8	(#1 or #2) and (#3 or #4 or #5 or #6 or #7) from 1983 to 2014	1710
#9	Pubmed:an	421700
#10	#8 not #9	101

Key Question 6

Date parameters ranged from 2002 to present as the interventions addressed in KQ 6 were also addressed in the 2004 HTN CPG. The evidence report for the previous version of the hypertension guideline reviewed evidence through May 2002.

A. *Weight Reduction*

1. PubMed Indexed Studies

	Concept(s)	Search Statement
#1	Weight reduction	("Obesity/diet therapy"[Mesh] OR "Obesity/prevention and control"[Mesh] OR "Obesity/therapy"[Mesh]) OR ("Overweight/diet therapy"[Mesh] OR "Overweight/prevention and control"[Mesh] OR "Overweight/therapy"[Mesh]) OR "Weight Loss"[Mesh] OR "Diet, Reducing"[Mesh] OR "Weight Reduction Programs"[Mesh] OR obesity treatment*[tiab] OR weight loss*[tiab] OR weight management*[tiab]

#2	Blood pressure	Blood Pressure[mesh] OR "Hypertension"[Mesh] OR Prehypertension[mh] OR Systole[mh] OR Diastole[mh] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND Randomized Controlled Trial[PT]
#5	Apply date and language limit to RCTs	#4 AND ("2002/05/01"[PDAT] : "2014/01/26"[PDAT]) AND English[lang]

2. PubMed Non-indexed Studies

	Concept(s)	**Search Statement**
#1	Weight reduction	Obesity[tiab] OR Overweight[tiab] OR Weight Reduc*[tiab] OR obesity treatment*[tiab] OR overweight treatment*[tiab] OR weight loss*[tiab] OR weight management*[tiab]
#2	Blood pressure	Blood Pressure[tiab] OR Hypertension[tiab] OR Prehypertension[tiab] OR Systole[tiab] OR Diastole[tiab] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND (randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#5	Apply language limit and limit to studies in the process of being indexed	#4 AND English[lang] AND inprocess[sb]

3. EMBASE

Set #	**Searched For**	**Results**
S1	mesh#("Blood Pressure") OR mesh#("Hypertension") OR mesh#("Prehypertension") OR Mesh#("Systole") OR Mesh#("Diastole")	426964*
S2	emb#("Blood Pressure") OR emb#("Hypertension") OR emb#("Systole") OR emb#("Diastole")	844407*
S3	S1 OR S2	1271371*
S4	dtype("Randomized Controlled Trial") OR emb#("Randomized Controlled Trial")	725446*
S5	(Mesh#("Obesity" LNK DT)) OR (Mesh#("Obesity" LNK PC)) OR (Mesh#("Obesity" LNK TH)) OR (Mesh#("Overweight" LNK DT)) OR (Mesh#("Overweight" LNK PC)) OR (Mesh#("Overweight" LNK TH))	29899*
S6	Mesh#("Weight Loss") OR Mesh#("Diet, Reducing") OR Mesh#("Weight Loss Reduction Programs")	33383*
S7	EMB.EXACT.EXPLODE("obesity -- therapy") OR EMB.EXACT("obesity -- prevention")	25891*
S8	EMB.EXACT("obesity") AND EMB.EXACT.EXPLODE("diet therapy")	29936*
S9	EMB.EXACT.EXPLODE("weight reduction") OR EMB.EXACT.EXPLODE("diet restriction")	188196*
S10	S5 OR S6 OR S7 OR S8 OR S9	268686*

Set #	Searched For	Results
S11	S3 AND S4 AND S10	2393°
S12	(S3 AND S4 AND S10) AND rtype.exact("Journal Article")	625°
S13	(S3 AND S4 AND S10) AND (rtype.exact("Journal Article") AND la.exact("ENG"))	612°
S14	(S3 AND S4 AND S10) AND (rtype.exact("Journal Article") AND la.exact("ENG") AND pd(20020501-20140207))	399°

* Duplicates are removed from your search, but included in your result count.
° Duplicates are removed from your search and from your result count.

4. *Cochrane CENTRAL*

ID	Search	Hits
#1	MeSH descriptor: [Blood Pressure] explode all trees	22608
#2	MeSH descriptor: [Hypertension] explode all trees	13629
#3	MeSH descriptor: [Prehypertension] explode all trees	29
#4	MeSH descriptor: [Systole] explode all trees	1153
#5	MeSH descriptor: [Diastole] explode all trees	909
#6	hypertens*:ti,ab or prehypertens*:ti,ab or "systolic pressure" *:ti,ab or "diastolic pressure" *:ti,ab or "arterial pressure" *:ti,ab or "blood pressure":ti,ab or BP;ti,ab	51569
#7	((systol*:ti,ab or diastol*:ti,ab) and (pressure*;ti,ab or mm*Hg;ti,ab))	7
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7	58762
#9	[mh obesity/DH] or [mh obesity/PC] or [mh obesity/TH] or [mh overweight/DH] or [mh overweight/PC] or [mh overweight/TH] or [mh "weight loss"] or [mh "diet, reducing"] or [mh "weight reduction programs"] or "obesity treatment" *:ti,ab or "weight loss" *:ti,ab or "weight management" *:ti,ab	9115
#10	#8 and #9 and randomized controlled trial:pt from 2002 to 2014, in Trials	676
#11	#10 not Pubmed:an	308

B. *Alcohol Intake*

1. *PubMed Indexed Studies*

	Concept(s)	Search Statement
#1	Alcohol intake	("Alcoholism/diet therapy"[Mesh] OR "Alcoholism/education"[Mesh] OR "Alcoholism/prevention and control"[Mesh] OR "Alcoholism/therapy"[Mesh]) OR "Ethanol"[Mesh] OR "Alcoholic Beverages"[Mesh] OR "Drinking Behavior"[Mesh] OR ethanol*[tiab] OR alcohol*[tiab]
#2	Blood pressure	Blood Pressure[mesh] OR "Hypertension"[Mesh] OR Prehypertension[mh] OR Systole[mh] OR Diastole[mh] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND Randomized Controlled Trial[PT]
#5	Apply date and language limit to RCTs	#4 AND ("2002/05/01"[PDAT] : "2014/01/26"[PDAT]) AND English[lang]

2. *PubMed Non-indexed Studies*

	Concept(s)	Search Statement
#1	Alcohol intake	Alcoholism[tiab] OR Alcoholic Beverages[tiab] OR Drinking Behavior[tiab] OR ethanol*[tiab] OR alcohol*[tiab]
#2	Blood pressure	Blood Pressure[tiab] OR Hypertension[tiab] OR Prehypertension[tiab] OR Systole[tiab] OR Diastole[tiab] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND (randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#5	Apply language limit and limit to studies in the process of being indexed	#4 AND English[lang] AND inprocess[sb]

3. *EMBASE*

Set #	Searched for	Results
S1	mesh#("Blood Pressure") OR mesh#("Hypertension") OR mesh#("Prehypertension") OR Mesh#("Systole") OR Mesh#("Diastole")	426939*
S2	emb#("Blood Pressure") OR emb#("Hypertension") OR emb#("Systole") OR emb#("Diastole")	844264*
S3	S1 OR S2	1271203*
S10	dtype("Randomized Controlled Trial") OR emb#("Randomized Controlled Trial")	725294*
S12	(mesh#("alcoholism" LNK DT)) OR (mesh#("alcoholism" LNK ED)) OR (mesh#("Alcoholism" LNK PC)) OR (mesh#("alcoholism" LNK TH)) OR mesh#("Ethanol") OR mesh#("Alcoholic Beverages") OR mesh#("Drinking Behavior")	353821*
S13	EMB.EXACT("alcoholism -- prevention") OR EMB.EXACT("alcoholism -- therapy")	10786*
S14	EMB.EXACT.EXPLODE("alcoholic beverage") AND EMB.EXACT.EXPLODE("drinking behavior")	2139°
S15	(EMB.EXACT.EXPLODE("education") OR EMB#("Diet Therapy")) AND EMB#("alcoholism")	7854*
S16	S12 OR S13 OR S14 OR S15	372939*
S17	S3 AND S10 AND S16	1969°
S18	(S3 AND S10 AND S16) AND la.exact("ENG")	1871°
S19	(S3 AND S10 AND S16) AND (la.exact("ENG") AND pd(20020501-20140206))	524°
S20	(S3 AND S10 AND S16) AND (rtype.exact("Journal Article") AND la.exact("ENG") AND pd(20020501-20140206))	512°
S21	EM	266968*
S22	emb#("drinking behavior") OR emb#("alcoholic beverage")	55924*
S23	S12 OR S13 OR S22 OR S15	423914*

S24	S23 AND S3 AND S10	1992°
S25	(S23 AND S3 AND S10) AND rtype.exact("Journal Article")	1951°
S26	(S23 AND S3 AND S10) AND (rtype.exact("Journal Article") AND pd(20020501-20140206))	523°
S27	(S23 AND S3 AND S10) AND (rtype.exact("Journal Article") AND la.exact("ENG") AND pd(20020501-20140206))	512°
S28	(S23 AND S3 AND S10) AND (rtype.exact("Journal Article") AND la.exact("ENG") AND subt.exact("humans") AND pd(20020501-20140206))	506°

* Duplicates are removed from your search, but included in your result count.
° Duplicates are removed from your search and from your result count.

4. *Cochrane CENTRAL*

ID	Search	Hits
#1	[mh "blood pressure"] or [mh hypertension] or [mh prehypertension] or [mh systole] or [mh diastole] or (hypertens*:ti,ab or prehypertens*:ti,ab or "systolic pressure" *:ti,ab or "diastolic pressure" *:ti,ab or "arterial pressure" *:ti,ab or "blood pressure":ti,ab or BP;ti,ab) or ((systol*:ti,ab or diastol*:ti,ab) and (pressure*;ti,ab or mm*Hg;ti,ab))	58762
#2	[mh alcoholism/DH] or [mh alcoholism/ED] or [mh alcoholism/PC] or [mh alcoholism/TH] or [mh ethanol] or [mh "alcoholic beverages"] or [mh "drinking behavior"] or ethanol*:ti,ab or alcohol*:ti,ab	14022
#3	#1 and #2 and randomized controlled trial:pt from 2002 to 2014, in Trials	290
#4	#3 not Pubmed:an	86

C. *Sodium Reduction*

1. *PubMed Indexed Studies*

	Concept(s)	Search Statement
#1	Sodium intake	"Diet, Sodium-Restricted"[Mesh] OR "Sodium, Dietary"[Mesh] OR "Sodium Chloride, Dietary"[Mesh] OR sodium*[tiab] OR salt*[tiab]
#2	Blood pressure	Blood Pressure[mesh] OR "Hypertension"[Mesh] OR Prehypertension[mh] OR Systole[mh] OR Diastole[mh] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND Randomized Controlled Trial[PT]
#5	Apply date and language limit to RCTs	#4 AND ("2002/05/01"[PDAT] : "2014/01/26"[PDAT]) AND English[lang]

2. *PubMed Non-indexed Studies*

	Concept(s)	Search Statement
#1	Sodium intake	Sodium intake[tiab] OR dietary sodium[tiab] OR (dietary[tiab] AND sodium[tiab]) OR sodium*[tiab] OR salt*[tiab]
#2	Blood pressure	Blood Pressure[tiab] OR Hypertension[tiab] OR Prehypertension[tiab] OR Systole[tiab] OR Diastole[tiab] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2

#4	Limit to RCTs	#3 AND (randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#5	Apply language limit and limit to studies in the process of being indexed	#4 AND English[lang] AND inprocess[sb]

3. *EMBASE*

Set #	Searched for	Results
S1	mesh#("Blood Pressure") OR mesh#("Hypertension") OR mesh#("Prehypertension") OR Mesh#("Systole") OR Mesh#("Diastole")	426821*
S2	emb#("Blood Pressure") OR emb#("Hypertension") OR emb#("Systole") OR emb#("Diastole")	843597*
S3	S1 OR S2	1270421*
S7	dtype("Randomized Controlled Trial") OR emb#("Randomized Controlled Trial")	724777*
S8	mesh#("Mind-Body Therapies") OR mesh#("Mind-Body Relations, Metaphysical") OR mesh#("Behavior Therapy")	864123*
S9	EMB.EXACT.EXPLODE("alternative medicine") OR EMB.EXACT.EXPLODE("behavior therapy")	71569*
S10	S3 AND (S8 OR S9)	30722*
S11	S10 AND S7	2796°
S12	S11 AND (pstype("Journal") AND at.exact("Article") AND la.exact("English") AND pd(20020501-20140204))	1142°
S13	mesh#("Diet, Sodium-Restricted") OR mesh#("Sodiium, Dietary") OR mesh#("Sodium Chloride, Dietary")	8979*
S14	EMB.EXACT.EXPLODE("sodium intake") OR EMB.EXACT.EXPLODE("sodium restriction") OR EMB.EXACT.EXPLODE("salt intake")	20517*
S15	S13 OR S14	29496*
S16	S3 AND S15 AND S7	657°
S17	S16 AND (pstype("Journal") AND at.exact("Article") AND la.exact("English") AND pd(20020501-20140204))	237°

4. *Cochrane CENTRAL*

ID	Search	Hits
#1	[mh "blood pressure"] or [mh hypertension] or [mh prehypertension] or [mh systole] or [mh diastole] or (hypertens*:ti,ab or prehypertens*:ti,ab or "systolic pressure" *:ti,ab or "diastolic pressure" *:ti,ab or "arterial pressure" *:ti,ab or "blood pressure":ti,ab or BP;ti,ab) or ((systol*:ti,ab or diastol*:ti,ab) and (pressure*;ti,ab or mm*Hg;ti,ab))	58762
#2	[mh "diet, sodium-restricted"] or [mh "sodium, dietary"] or [mh "sodium chloride, dietary"] or sodium*:ti,ab or salt*:ti,ab	17004
#3	#1 and #2 and randomized controlled trial:pt from 2002 to 2014, in Trials	660
#4	#3 not Pubmed:an	180

D. *Dietary and Non-Dietary Potassium*

1. *PubMed Indexed Studies*

	Concept(s)	Search Statement
#1	Potassium intake	("Potassium/administration and dosage"[Mesh] OR "Potassium/drug effects"[Mesh] OR "Potassium/pharmacology"[Mesh] OR "Potassium/therapeutic use"[Mesh] OR "Potassium/therapy"[Mesh]) OR "Potassium, Dietary"[Mesh] OR "Potassium Chloride"[Mesh] OR potassium*[tiab]
#2	Blood pressure	Blood Pressure[mesh] OR "Hypertension"[Mesh] OR Prehypertension[mh] OR Systole[mh] OR Diastole[mh] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND Randomized Controlled Trial[PT]
#5	Apply date and language limit to RCTs	#4 AND ("2002/05/01"[PDAT] : "2014/01/26"[PDAT]) AND English[lang]

2. *PubMed Non-indexed Studies*

	Concept(s)	Search Statement
#1	Potassium intake	Potassium intake[tiab] OR dietary potassium[tiab] OR (dietary[tiab] AND potassium[tiab])
#2	Blood pressure	Blood Pressure[tiab] OR Hypertension[tiab] OR Prehypertension[tiab] OR Systole[tiab] OR Diastole[tiab] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND (randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#5	Apply language limit and limit to studies in the process of being indexed	#4 AND English[lang] AND inprocess[sb]

3. *EMBASE*

Set #	Searched for	Results
S1	mesh#("Blood Pressure") OR mesh#("Hypertension") OR mesh#("Prehypertension") OR Mesh#("Systole") OR Mesh#("Diastole")	426939*
S2	emb#("Blood Pressure") OR emb#("Hypertension") OR emb#("Systole") OR emb#("Diastole")	844264*
S3	S1 OR S2	1271203*
S4	(Mesh#("Potassium" LNK AD)) OR (Mesh#("Potassium" LNK DE)) OR (Mesh#("Potassium" LNK PD)) OR (Mesh#("Potassium" LNK TU)) OR (Mesh#("Potassium" LNK TH)) OR Mesh#("Potassium, Dietary") OR Mesh#("Potassium Chloride")	40392*

S5	EMB.EXACT("potassium -- drug dose") OR EMB.EXACT("potassium -- drug administration")	1142°
S6	EMB.EXACT("potassium -- pharmacology") OR EMB.EXACT("potassium -- therapy")	7132*
S7	EMB.EXACT("potassium") AND EMB.EXACT("Drug Effect")	13731*
S8	S4 OR S5 OR S6 OR S7	57480*
S9	S3 AND S8	3342°
S10	dtype("Randomized Controlled Trial") OR emb#("Randomized Controlled Trial")	725294*
S11	S10 AND S9	313°
S12	(S10 AND S9) AND at.exact("Article")	302°
S13	(S10 AND S9) AND (at.exact("Article") AND rtype.exact("Journal Article"))	165°
S14	(S10 AND S9) AND (at.exact("Article") AND rtype.exact("Journal Article") AND pd(20020501-20140206))	42°
S15	EMB.EXACT.EXPLODE("potassium intake") OR EMB.EXACT("potassium chloride")	31731*
S16	S8 OR S15	88789*
S17	S16 AND S3 AND S10	367°
S18	(S16 AND S3 AND S10) AND rtype.exact("Journal Article")	165°

4. *Cochrane CENTRAL*

ID	Search	Hits
#1	[mh "blood pressure"] or [mh hypertension] or [mh prehypertension] or [mh systole] or [mh diastole] or (hypertens*:ti,ab or prehypertens*:ti,ab or "systolic pressure" *:ti,ab or "diastolic pressure" *:ti,ab or "arterial pressure" *:ti,ab or "blood pressure":ti,ab or BP;ti,ab) or ((systol*:ti,ab or diastol*:ti,ab) and (pressure*;ti,ab or mm*Hg;ti,ab))	58762
#2	[mh potassium/AD] or [mh potassium/DE] or [mh potassium/PD] or [mh potassium/TU] or [mh potassium/TH] or [mh "potassium, dietary"] or [mh "potassium chloride"] or potassium*:ti,ab	5575
#3	#1 and #2 and randomized controlled trial:pt from 2002 to 2014, in Trials	344
#4	#3 NOT Pubmed:an	0

E. *Combined Dietary Modification*

1. *PubMed Indexed Studies*

	Concept(s)	Search Statement
#1	Dietary changes	"Diet"[Mesh] OR "Food Habits"[Mesh] OR "Hypertension/diet therapy"[Mesh] OR dietary [tiab]
#2	Blood pressure	Blood Pressure[mesh] OR "Hypertension"[Mesh] OR Prehypertension[mh] OR Systole[mh] OR Diastole[mh] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND Randomized Controlled Trial[PT]
#5	Apply date and language limit to RCTs	#4 AND ("2002/05/01"[PDAT] : "2014/01/26"[PDAT]) AND English[lang]

2. *PubMed Non-indexed Studies*

	Concept(s)	Search Statement
#1	Dietary changes	Diet[tiab] OR food habits[tiab] OR dietary[tiab]
#2	Blood pressure	Blood Pressure[tiab] OR Hypertension[tiab] OR Prehypertension[tiab] OR Systole[tiab] OR Diastole[tiab] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND (randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#5	Apply language limit and limit to studies in the process of being indexed	#4 AND English[lang] AND inprocess[sb]

3. *EMBASE*

Set #	Searched for	Results
S1	mesh#("Blood Pressure") OR mesh#("Hypertension") OR mesh#("Prehypertension") OR Mesh#("Systole") OR Mesh#("Diastole")	426939*
S2	emb#("Blood Pressure") OR emb#("Hypertension") OR emb#("Systole") OR emb#("Diastole")	844264*
S3	S1 OR S2	1271203*
S10	dtype("Randomized Controlled Trial") OR emb#("Randomized Controlled Trial")	725294*
S11	mesh#("Diet") OR mesh#("Food Habits") OR (Mesh#("Hypertension" LNK DH))	311694*
S12	(EMB.EXACT.EXPLODE("diet") OR EMB.EXACT.EXPLODE("diet therapy")) OR EMB.EXACT.EXPLODE("feeding behavior")	554282*
S13	S11 OR S12	865976*
S14	S3 AND S10 AND S13	3760°
S15	(S3 AND S10 AND S13) AND pd(20020501-20140206)	2510°
S16	(S3 AND S10 AND S13) AND (rtype.exact("Journal Article") AND pd(20020501-20140206))	771°

4. *Cochrane CENTRAL*

ID	Search	Hits
#1	[mh "blood pressure"] or [mh hypertension] or [mh prehypertension] or [mh systole] or [mh diastole] or (hypertens*:ti,ab or prehypertens*:ti,ab or "systolic pressure" *:ti,ab or "diastolic pressure" *:ti,ab or "arterial pressure" *:ti,ab or "blood pressure":ti,ab or BP;ti,ab) or ((systol*:ti,ab or diastol*:ti,ab) and (pressure*;ti,ab or mm*Hg;ti,ab))	58762
#2	[mh diet] or [mh "food habits"] or [mh hypertension/DH] or dietary:ti,ab	25846
#3	#1 and #2 and randomized controlled trial:pt from 2002 to 2014, in Trials	1239
#4	#3 not Pubmed:an	215

F. *Exercise/Physical Activity*

1. *PubMed Indexed Studies*

	Concept(s)	Search Statement
#1	Exercise/ physical activity	"Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Motor Activity"[Mesh] OR physical activ*[tiab]
#2	Blood pressure	Blood Pressure[mesh] OR "Hypertension"[Mesh] OR Prehypertension[mh] OR Systole[mh] OR Diastole[mh] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND Randomized Controlled Trial[PT]
#5	Apply date and language limit to RCTs	#4 AND ("2002/05/01"[PDAT] : "2014/01/26"[PDAT]) AND English[lang]

2. *PubMed Non-indexed Studies*

	Concept(s)	Search Statement
#1	Exercise/ physical activity	Exercise[tiab] OR motor activity[tiab] OR physical activ*[tiab] OR physically active[tiab]
#2	Blood pressure	Blood Pressure[tiab] OR Hypertension[tiab] OR Prehypertension[tiab] OR Systole[tiab] OR Diastole[tiab] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND (randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#5	Apply language limit and limit to studies in the process of being indexed	#4 AND English[lang] AND inprocess[sb]

3. *EMBASE*

Set #	Searched for	Results
S1	mesh#("Blood Pressure") OR mesh#("Hypertension") OR mesh#("Prehypertension") OR Mesh#("Systole") OR Mesh#("Diastole")	426821*
S2	emb#("Blood Pressure") OR emb#("Hypertension") OR emb#("Systole") OR emb#("Diastole")	843597*
S3	S1 OR S2	1270421*
S4	mesh#("Exercise") OR mesh#("Exercise Therapy") OR Mesh#("Motor Activity")	212122*
S5	EMB.EXACT.EXPLODE("exercise") OR EMB.EXACT.EXPLODE("kinesiotherapy") OR EMB.EXACT.EXPLODE("motor activity")	629073*
S6	S3 AND (S4 OR S5)	47352*

S7	dtype("Randomized Controlled Trial") OR emb#("Randomized Controlled Trial")	724777*

4. *Cochrane CENTRAL*

ID	Search	Hits
#1	[mh "blood pressure"] or [mh hypertension] or [mh prehypertension] or [mh systole] or [mh diastole] or (hypertens*:ti,ab or prehypertens*:ti,ab or "systolic pressure" *:ti,ab or "diastolic pressure" *:ti,ab or "arterial pressure" *:ti,ab or "blood pressure":ti,ab or BP;ti,ab) or ((systol*:ti,ab or diastol*:ti,ab) and (pressure*;ti,ab or mm*Hg;ti,ab))	58762
#2	[mh exercise] or [mh "exercise therapy"] or [mh "motor activity"] or "physical activ" *:ti,ab	18585
#3	#1 and #2 and randomized controlled trial:pt from 2002 to 2014, in Trials	1034
#4	#3 not Pubmed:an	228

G. *Mind-Body Therapy*

1. *PubMed Indexed Studies*

	Concept(s)	Search Statement
#1	Mind- body interventions	"Mind-Body Therapies"[Mesh] OR "Mind-Body Relations, Metaphysical"[Mesh] OR "Behavior Therapy"[Mesh] OR biofeedback[tiab] OR meditat*[tiab] OR yog*[tiab] OR tai ji[tiab] OR t'ai chi[tiab] OR hypnosis[tiab] OR relax*[tiab] OR breath*[tiab] OR stress management[tiab] OR cognitive therapy[tiab] OR autogen*[tiab]
#2	Blood pressure	Blood Pressure[mesh] OR "Hypertension"[Mesh] OR Prehypertension[mh] OR Systole[mh] OR Diastole[mh] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND Randomized Controlled Trial[PT]
#5	Apply date and language limit to RCTs	#4 AND ("2002/05/01"[PDAT] : "2014/01/26"[PDAT]) AND English[lang]

2. *PubMed Non-indexed Studies*

	Concept(s)	Search Statement
#1	Mind- body interventions	Mind body[tiab] OR behavior therapy[tiab] OR biofeedback[tiab] OR meditat*[tiab] OR yog*[tiab] OR tai ji[tiab] OR t'ai chi[tiab] OR hypnosis[tiab] OR relax*[tiab] OR breath*[tiab] OR stress management[tiab] OR cognitive therapy[tiab] OR autogen*[tiab]
#2	Blood pressure	Blood Pressure[tiab] OR Hypertension[tiab] OR Prehypertension[tiab] OR Systole[tiab] OR Diastole[tiab] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND (randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#5	Limit to studies in the process of being indexed and english	#4 AND English[lang] AND inprocess[sb]

3. *EMBASE*

Set #	Searched for	Results
S1	mesh#("Blood Pressure") OR mesh#("Hypertension") OR mesh#("Prehypertension") OR Mesh#("Systole") OR Mesh#("Diastole")	426821*
S2	emb#("Blood Pressure") OR emb#("Hypertension") OR emb#("Systole") OR emb#("Diastole")	843597*
S3	S1 OR S2	1270421*
S7	dtype("Randomized Controlled Trial") OR emb#("Randomized Controlled Trial")	724777*
S8	mesh#("Mind-Body Therapies") OR mesh#("Mind-Body Relations, Metaphysical") OR mesh#("Behavior Therapy")	864123*
S9	EMB.EXACT.EXPLODE("alternative medicine") OR EMB.EXACT.EXPLODE("behavior therapy")	71569*
S10	S3 AND (S8 OR S9)	30722*
S11	S10 AND S7	2796°
S12	S11 AND (pstype("Journal") AND at.exact("Article") AND la.exact("English") AND pd(20020501-20140204))	1142°

4. *Cochrane CENTRAL*

ID	Search	Hits
#1	[mh "blood pressure"] or [mh hypertension] or [mh prehypertension] or [mh systole] or [mh diastole] or (hypertens*:ti,ab or prehypertens*:ti,ab or "systolic pressure" *:ti,ab or "diastolic pressure" *:ti,ab or "arterial pressure" *:ti,ab or "blood pressure":ti,ab or BP;ti,ab) or ((systol*:ti,ab or diastol*:ti,ab) and (pressure*;ti,ab or mm*Hg;ti,ab))	58762
#2	[mh "mind-body therapies"] or [mh "mind-body relations, metaphysical"] or [mh "behavior therapy"] or biofeedback:ti,ab or meditat*:ti,ab or yog*:ti,ab or "tai ji":ti,ab or "t'ai chi":ti,ab or hypnosis:ti,ab or relax*:ti,ab or breath*:ti,ab or "stress management":ti,ab or "cognitive therapy":ti,ab or autogen*:ti,ab	28279
#3	#1 and #2 and randomized controlled trial:pt from 2002 to 2014, in Trials	751
#4	#3 not Pubmed:an	105

H. *Improved Adherence*

1. *PubMed Indexed Studies*

	Concept(s)	Search Statement
#1	Adherence interventions	"Patient Compliance"[Mesh] OR "Patient Education as Topic"[Mesh] OR "Health Education"[Mesh] OR "Case Management"[Mesh] OR "Disease Management"[MeSH Terms] OR "Patient Care Management"[Mesh] OR "Patient Care Planning"[Mesh] OR "Patient Participation"[Mesh] OR "Reminder Systems"[Mesh] OR "Self Care"[Mesh] OR complian*[tiab] OR adheren*[tiab] OR self monitor*[tiab] OR self-monitor*[tiab] OR educat*[tiab] OR case management[tiab]
#2	Blood pressure	Blood Pressure[mesh] OR "Hypertension"[Mesh] OR Prehypertension[mh] OR Systole[mh] OR Diastole[mh] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND Randomized Controlled Trial[PT]
#5	Apply date and language limit to RCTs	#4 AND ("2002/05/01"[PDAT] : "2014/01/26"[PDAT]) AND English[lang]

2. *PubMed Non-indexed Studies*

	Concept(s)	Search Statement
#1	Adherence interventions	patient[tiab] AND (complian*[tiab] OR adheren*[tiab] OR self monitor*[tiab] OR self-monitor*[tiab] OR educat*[tiab] OR case management[tiab] OR management[tiab] OR reminder system*[tiab] OR self care[tiab] OR care planning[tiab])
#2	Blood pressure	Blood Pressure[tiab] OR Hypertension[tiab] OR Prehypertension[tiab] OR Systole[tiab] OR Diastole[tiab] OR hypertens*[tiab] OR prehypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#3	Combine	#1 AND #2
#4	Limit to RCTs	#3 AND (randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#5	Apply language limit and limit to studies in the process of being indexed	#4 AND English[lang] AND inprocess[sb]

3. *EMBASE*

Set #	Searched for	Results
S1	Mesh#("Patient Compliance") OR Mesh#("Patient Education as Topic") OR Mesh#("Health Education") OR Mesh#("Case Management") OR Mesh#("Disease Management")	209459*
S2	Mesh#("Patient Care Management") OR Mesh#("Patient Care Planning") OR Mesh#("Patient Participation") OR Mesh#("Reminder Systems") OR Mesh#("Self Care")	1026946*
S3	EMB.EXACT("patient compliance") OR EMB.EXACT.EXPLODE("health education") OR EMB.EXACT("patient care planning") OR EMB.EXACT.EXPLODE("patient care") OR EMB.EXACT.EXPLODE("disease management")	2356085*
S4	EMB.EXACT.EXPLODE("reminder system") OR EMB.EXACT.EXPLODE("self care") OR EMB.EXACT.EXPLODE("patient satisfaction")	134928*
S5	mesh#("Blood Pressure") OR mesh#("Hypertension") OR mesh#("Prehypertension") OR Mesh#("Systole") OR Mesh#("Diastole")	426821*
S6	emb#("Blood Pressure") OR emb#("Hypertension") OR emb#("Systole") OR emb#("Diastole")	843569*
S7	S1 OR S2 OR S3 OR S4	3518090*
S8	S7 AND (S5 OR S6)	130997*
S9	EMB.EXACT.EXPLODE("randomized controlled trial") OR dtype("Randomized Controlled Trial")	724754*
S10	S8 AND S9	12498*
S11	(S8 AND S9) AND rtype.exact("Journal Article")	1593°
S12	pstype("Journal") AND at.exact("Article") AND la.exact("English")	35988942*
S13	(S11 AND S12) AND (pstype("Journal") AND at.exact("Article") AND la.exact("English"))	1540°
S14	(S11 AND S12) AND (pstype("Journal") AND at.exact("Article") AND la.exact("English"))	1000°

S15	(S11 AND S12) AND (pstype("Journal") AND at.exact("Article") AND la.exact("English") AND pd(20020501-20140204))	950°
S16	(S11 AND S12) AND (pstype("Journal") AND at.exact("Article") AND la.exact("English") AND pd(20020501-20140204))	950°

4. *Cochrane CENTRAL*

ID	Search	Hits
#1	[mh "blood pressure"] or [mh hypertension] or [mh prehypertension] or [mh systole] or [mh diastole] or (hypertens*:ti,ab or prehypertens*:ti,ab or "systolic pressure" *:ti,ab or "diastolic pressure" *:ti,ab or "arterial pressure" *:ti,ab or "blood pressure":ti,ab or BP;ti,ab) or ((systol*:ti,ab or diastol*:ti,ab) and (pressure*;ti,ab or mm*Hg;ti,ab))	58762
#2	[mh "patient compliance"] or [mh "patient educaton as topic"] or [mh "health education"] or [mh "case management"] or [mh "disease management"] or [mh "patient care management"] or [mh "patient care planning"] or [mh "patient participation"] or [mh "reminder systems"] or [mh "self care"] or complian*:ti,ab or adheren*:ti,ab or "self monitor" *:ti,ab or "self monitor" *:ti,ab or educat*:ti,ab or "case management":ti,ab	55610
#3	#1 and #2 and randomized controlled trial:pt from 2002 to 2014, in Trials	1717
#4	#3 not Pubmed:an	560

Key Question 7

Date parameters ranged from 1966 to present. This was the date range used by the Eighth Joint National Committee (JNC 8) for the 2014 evidence-based guideline for the management of high blood pressure in adults.[12] Since KQ 7 was indentical to one of the questions addressed in the JNC 8 guideline, we utilized the evidence base from the JNC 8 evidence report which covered the years 1966-2010 and then conducted our own search from 2010 to present.

PubMed

1. *Indexed Studies*

	Concept	Search Statement
#1	Hypertension	Hypertension[mh] OR hypertension[tiab] OR hypertensive*[tiab]
#2	Outcomes	(Mortality[mh] OR mortality[tiab] OR Death[mh] OR death*[tiab] OR Morbidity[mh] OR morbidity[tiab] OR Cause of Death[mh] OR Fatal Outcome[mh] OR Survival Rate[mh])

[12] James P, Oparil S, Carter B, Cushman W, 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2013; 311(5):507-20.

	Concept	Search Statement
#3		(Cardiovascular Diseases/prevention[mh] OR Cardiovascular Diseases/epidemiology[mh] OR Cardiovascular Diseases/etiology[mh] OR Cardiovascular Diseases/physiopathology[mh] OR Coronary Disease/prevention[mh] OR Coronary Disease/epidemiology[mh] Coronary Disease/etiology[mh] OR Coronary Disease/physiopathology[mh] OR Coronary Artery Disease/prevention[mh] OR Coronary Artery Disease/epidemiology[mh] OR Coronary Artery Disease/etiology[mh] OR Coronary Artery Disease/physiopathology[mh] OR Myocardial Infarction/prevention[mh] OR Myocardial Infarction/epidemiology[mh] OR Myocardial Infarction/etiology[mh] OR Myocardial Infarction/physiopathology[mh] OR Heart Failure/prevention[mh] OR Heart Failure/epidemiology[mh] OR Heart Failure/etiology[mh] OR Heart Failure/physiopathology[mh] OR Cerebrovascular Disorders/prevention[mh] OR Cerebrovascular Disorders/epidemiology[mh] OR Cerebrovascular Disorders/etiology[mh] OR Cerebrovascular Disorders/physiopathology[mh] OR Stroke/prevention[mh] OR Stroke/epidemiology[mh] OR Stroke/etiology[mh] OR Stroke/physiopathology[mh] OR Kidney/epidemiology[mh] OR Kidney/etiology[mh] OR Kidney/physiopathology[mh])
#4		(myocardial infarction[tiab] OR heart failure[tiab] OR stroke[tiab] OR cerebrovascular disorder*[tiab] OR cerebrovascular event*[tiab] OR kidney failure[tiab] OR chronic kidney disease*[tiab] OR CKD[tiab])
#5		(Myocardial Revascularization [mh] OR Myocardial Revascularization[tiab])
#6		(Creatinine[mh] OR Creatinine[tiab])
#7		(Glomerular Filtration Rate[mh] OR Glomerular Filtration Rate[tiab] OR GFR[tiab] OR eGFR[tiab] OR estGFR[tiab])
#8	Treatment	((Antihypertensive Agents/therapeutic use[mh] OR Antihypertensive Agents/adverse effects[mh]) OR (Hypertension/drug therapy[mh] OR Hypertension/adverse effects) OR (Drug Therapy, Combination[mh]) OR ((antihypertensive[tiab] OR anti-hypertensive[tiab]) AND (drug therapy[tiab] OR drug treatment[tiab] OR adverse effects[tiab] OR harm*[tiab] OR drug*[tiab] OR safety[tiab] OR efficacy[tiab])) OR (pharmacologic therapy[tiab] OR pharmacologic lowering of blood pressure[tiab])
#9	Limit to RCTs	Randomized Controlled Trial[PT]
#10	Apply date and language parameters	("2010/01/01"[PDAT] : "2014/02/11"[PDAT]) AND English[lang]

2. *Non-indexed Studies*

	Concept	Search Statement
#1	Hypertension	hypertension[tiab] OR hypertensive*[tiab]
#2	Outcomes	(mortality[tiab] OR death*[tiab] OR morbidity[tiab] OR Cause of Death[tiab] OR Fatal Outcome[tiab] OR Survival Rate[tiab])
#3		(Cardiovascular Disease*[tiab] OR Coronary Disease*[tiab] OR Coronary Artery Disease*[tiab])
#4		(myocardial infarction[tiab] OR heart failure[tiab] OR stroke[tiab] OR cerebrovascular disorder*[tiab] OR cerebrovascular event*[tiab] OR kidney failure[tiab] OR chronic kidney disease*[tiab] OR CKD[tiab])
#5		Myocardial Revascularization[tiab]
#6		Creatinine[tiab]
#7		(Glomerular Filtration Rate[tiab] OR GFR[tiab] OR eGFR[tiab] OR estGFR[tiab])

	Concept	Search Statement
#8	Treatment	((antihypertensive[tiab] OR anti-hypertensive[tiab] OR hypertension[tiab]) AND (drug therapy[tiab] OR drug treatment[tiab] OR adverse effects[tiab] OR harm*[tiab] OR drug*[tiab] OR safety[tiab] OR efficacy[tiab])) OR (pharmacologic therapy[tiab] OR pharmacologic lowering of blood pressure[tiab])
#9	Limit to RCTs	(randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#10	Apply date and language parameters	English[lang] AND inprocess[sb]

EMBASE

Set #	Searched for	Results
S1	mesh#("Hypertension") OR emb#("Hypertension")	746211*
S2	Mesh#(“mortality”) OR Mesh#(“death”) OR Mesh#("morbidity") OR Mesh#("cause of death") OR Mesh#("Fatal Outcome") OR Mesh#("Survival Rate")	700514*
S3	EMB.EXACT.EXPLODE("death") OR EMB.EXACT.EXPLODE("mortality") OR EMB.EXACT.EXPLODE("morbidity") OR EMB.EXACT.EXPLODE("fatality") OR EMB.EXACT.EXPLODE("survival rate")	1304971*
S6	Mesh.exact.explode("Kidney" LNK ep) OR Mesh.exact.explode("Kidney" LNK et) OR Mesh.exact.explode("Kidney" LNK pp)	24150*
S7	(Mesh#(“Cardiovascular Diseases” LNK ep)) OR (Mesh#(“Cardiovascular Diseases” LNK et)) OR (Mesh#(“Cardiovascular Diseases” LNK pc)) OR (Mesh#(“Cardiovascular Diseases” LNK pp))	816897*
S9	EMB.EXACT("kidney -- epidemiology") OR EMB.EXACT("kidney -- etiology")	0°
S10	EMB.EXACT("kidney") AND EMB.EXACT.EXPLODE("pathophysiology")	11720*
S11	S6 OR S7 OR S9 OR S10	846920*
S12	EMB.EXACT.EXPLODE("chronic kidney disease") OR EMB.EXACT.EXPLODE("kidney failure") OR Mesh#("Renal Insuffiencieny, Chronic")	268126*
S13	S11 OR S12	1113072*
S14	Mesh#(“Myocardial revascularization”) OR mesh#(“creatinine”) OR Mesh#(“Glomerular filtration rate”) OR EMB#(“Heart Muscle revascularization”) OR EMB#(“Creatinine”) OR EMB#(“glomerulus filtration rate”)	310529*
S15	(Mesh#("Antihypertensive Agents" LNK TU)) OR (Mesh#("Antihypertensive Agents" LNK AE)) OR (Mesh#("Hypertension" LNK DT)) OR (Mesh#("Hypertension" LNK AE)) OR Mesh#("Drug Therapy, Combination")	344698*
S16	(EMB.EXACT("antihypertensive agent -- adverse drug reaction") OR EMB.EXACT("antihypertensive agent -- drug therapy")) OR (EMB.EXACT("hypertension -- drug therapy") OR EMB.EXACT("hypertension -- adverse drug reaction")) OR EMB.EXACT.EXPLODE("drug combination")	284864*
S17	S14 OR S15 OR S16	925541*
S18	S1 AND (S2 OR S13) AND S17	47295*
S19	S18 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))	4621°

S20	(S18 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))) AND rtype.exact("Journal Article")	4070°
S21	(S18 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))) AND (rtype.exact("Journal Article") AND la.exact("ENG"))	3767°
S22	(S18 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))) AND (rtype.exact("Journal Article") AND la.exact("ENG") AND pd(20100101-20140212))	575°

Cochrane CENTRAL

ID	Search	Hits
#1	[mh Hypertension] or hypertension:ti,ab or hypertensiv*:ti,ab	28430
#2	[mh Mortality] or mortality:ti,ab or [mh Death] or death:ti,ab or [mh Morbidity] or morbidity:ti,ab or [mh "Cause of Death"] or [mh "Fatal Outcome"] or [mh "Survival Rate"]	57424
#3	([mh "Cardiovascular Diseases"/PC] or [mh "Cardiovascular Diseases"/EP] or [mh "Cardiovascular Diseases"/ET] or [mh "Cardiovascular Diseases"/PP] or [mh "Coronary Disease"/PC] or [mh "Coronary Disease"/EP] or [mh "Coronary Disease"/ET] or [mh "Coronary Disease"/PP] or [mh "Coronary Artery Disease"/PC] or [mh "Coronary Artery Disease"/EP] or [mh "Coronary Artery Disease"/ET] or [mh "Coronary Artery Disease"/PP] or [mh "Myocardial Infarction"/PC] or [mh "Myocardial Infarction"/EP] or [mh "Myocardial Infarction"/ET] or [mh "Myocardial Infarction"/PP] or [mh "Heart Failure"/PC] or [mh "Heart Failure"/EP] or [mh "Heart Failure"/ET] or [mh "Heart Failure"/PP] or [mh "Cerebrovascular Disorders"/PC] or [mh "Cerebrovascular Disorders"/EP] or [mh "Cerebrovascular Disorders"/ET] or [mh "Cerebrovascular Disorders"/PP] or [mh Stroke/PC] or [mh Stroke/EP] or [mh Stroke/ET] or [mh Stroke/PP] or [mh Kidney/EP] or [mh Kidney/ET] or [mh Kidney/PP])	38439
#4	(myocardial infarction:ti,ab or heart failure:ti,ab or stroke:ti,ab or "cerebrovascular disorder" *:ti,ab or "cerebrovascular event" *:ti,ab or "kidney failure":ti,ab or "chronic kidney disease" *:ti,ab or CKD:ti,ab)	41207
#5	([mh "Myocardial Revascularization"] or "Myocardial Revascularization":ti,ab)	8528
#6	([mh Creatinine] or Creatinine:ti,ab)	8954
#7	([mh "Glomerular Filtration Rate"] or "Glomerular Filtration Rate":ti,ab or GFR:ti,ab or eGFR:ti,ab or estGFR:ti,ab)	3783
#8	[mh "Antihypertensive Agents"/TU] or [mh "Antihypertensive Agents"/AE] or [mh Hypertension/DT] or [mh Hypertension/AE] or [mh "Drug Therapy, Combination"] or ((antihypertensive:ti,ab or anti-hypertensive:ti,ab) and ("drug therapy":ti,ab or "drug treatment":ti,ab or "adverse effects":ti,ab or harm*:ti,ab or drug*:ti,ab or safety:ti,ab or efficacy:ti,ab)) or ("pharmacologic therapy":ti,ab or "pharmacologic lowering of blood pressure":ti,ab)	50823
#9	#2 or #3 or #4 or #5 or #6 or #7	119748
#10	#1 and #9 and #8	8476
#11	#10 and randomized controlled trial:pt from 2010 to 2014, in Trials	881
#12	#11 not pubmed:an	426

Key Question 8

Date parameters ranged from 1966 to present.

PubMed

1. *Indexed Studies*

	Concept	Search Statement
#1	Initiation strategy	"Drug Therapy, Combination"[Mesh] OR "Drug Combinations"[Mesh] OR combination therapy[tiab] OR combined therapy[tiab] OR monotherap*[tiab] OR sequential*[tiab] OR step*[tiab]

	Concept	Search Statement
#2	Blood pressure treatment	"Hypertension/drug effects"[Mesh] OR "Hypertension/drug therapy"[Mesh] OR "Hypertension/pharmacology"[Mesh] OR "Hypertension/prevention and control"[Mesh] OR "Hypertension/therapeutic use"[Mesh] OR "Hypertension/therapy"[Mesh]
#3	Blood pressure outcome	Blood Pressure[mh] OR "Hypertension"[Mesh] OR hypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#4	Limit to RCTs	"Randomized Controlled Trial"[pt]
#5	Apply date and language parameters	("1966/01/01"[PDAT] : "2014/02/20"[PDAT]) AND English[lang]

2. *Non-indexed Randomized Controlled Trials*

	Concept	Search Statement
#1	Initiation strategy	(drug[tiab] OR pharmacologic*[tiab]) AND (combination therapy[tiab] OR combined therapy[tiab] OR monotherap*[tiab] OR sequential*[tiab] OR step*[tiab] OR combination*[tiab])
#2	Blood pressure treatment	hypertension[tiab] AND (drug effect*[tiab] OR drug therapy[tiab] OR pharmacology[tiab] OR prevention[tiab] OR therapeutic use[tiab] OR therapy[tiab])
#3	Blood pressure outcome	hypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#4	Combine	#1 AND #2 AND #3
#5	Limit to RCTs	#4 AND (randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab])
#5	Apply language limit and limit to studies in the process of being indexed	#5 AND English[lang] AND inprocess[sb]

3. *Non-indexed Systematic Reviews and Meta-analyses*

	Concept	Search Statement
#1	Initiation strategy	(drug[tiab] OR pharmacologic*[tiab]) AND (combination therapy[tiab] OR combined therapy[tiab] OR monotherap*[tiab] OR sequential*[tiab] OR step*[tiab] OR combination*[tiab])
#2	Blood pressure treatment	hypertension[tiab] AND (drug effect*[tiab] OR drug therapy[tiab] OR pharmacology[tiab] OR prevention[tiab] OR therapeutic use[tiab] OR therapy[tiab])
#3	Blood pressure outcome	hypertens*[tiab] OR systolic pressure*[tiab] OR diastolic pressure*[tiab] OR arterial pressure*[tiab] OR blood pressure [tiab] OR BP[tiab] OR ((systol* OR diastol*) AND (pressure* OR mmHg OR mmHg))
#4	Combine	#1 AND #2 AND #3
#5	Limit to MAs and SRs	#4 AND (meta-analysis[tiab] OR systematic[sb])

	Concept	Search Statement
#5	Apply language limit and limit to studies in the process of being indexed	#5 AND English[lang] AND inprocess[sb]

EMBASE

Set #	Searched for	Results
S1	Mesh#("Drug Therapy, Combination") OR Mesh#("Drug Combinations")	304057*
S2	EMB.EXACT.EXPLODE("drug combination")	190061*
S3	S1 OR S2	494118*
S4	(Mesh#("Hypertension" LNK DE)) OR (Mesh#("Hypertension" LNK TH)) OR (Mesh#("Hypertension" LNK TU)) OR (Mesh#("Hypertension" LNK PD)) OR (Mesh#("Hypertension" LNK DT)) OR (Mesh#("Hypertension" LNK PC))	80802*
S5	EMB.EXACT.EXPLODE("hypertension -- therapy") OR EMB.EXACT.EXPLODE("hypertension -- adverse drug reaction") OR EMB.EXACT.EXPLODE("hypertension -- drug therapy") OR EMB.EXACT.EXPLODE("hypertension -- drug administration") OR EMB.EXACT.EXPLODE("hypertension -- prevention")	120017*
S6	EMB#("hypertension") AND EMB#("Drug Effect")	25230*
S7	S4 OR S5 OR S6	211265*
S8	Mesh#("Blood Pressure") OR EMB.EXACT.EXPLODE("blood pressure") OR Mesh#("Hypertension") OR EMB#("Hypertension")	1243969*
S9	S3 AND S7 AND S8	12393*
S10	(dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))	727583*
S11	S9 AND S10	2156°
S12	(S9 AND S10) AND rtype.exact("Journal Article")	1826°
S13	(S9 AND S10) AND (rtype.exact("Journal Article") AND la.exact("ENG"))	1627°
S14	(S9 AND S10) AND (rtype.exact("Journal Article") AND la.exact("ENG") AND pd(19660101-20140224))	1627°

Cochrane CENTRAL, CDSR, DARE

ID	Search	Hits
#1	[mh "Drug Therapy, Combination"] or [mh "Drug Combinations"] or "combination therapy":ti,ab or "combined therapy":ti,ab or monotherap*:ti,ab or sequential*:ti,ab or step*:ti,ab	66283
#2	[mh Hypertension/DT] or [mh Hypertension/PC] or [mh Hypertension/TH] or ([mh hypertension] and ("drug effects":ti,ab or "therapeutic use":ti,ab))	36
#3	[mh "Blood Pressure"] or [mh Hypertension] or hypertens*:ti,ab or "systolic pressure" *:ti,ab or "diastolic pressure" *:ti,ab or "arterial pressure" *:ti,ab or "blood pressure" *:ti,ab or BP:ti,ab or ((systol*:ti,ab or diastol*:ti,ab) and (pressure*:ti,ab or mmHg:ti,ab or "mmHg":ti,ab))	63106
#4	#1 and #2 and #3	4
#5	#4 from 1966 to 2014, in Cochrane Reviews (Reviews and Protocols), Other Reviews and Trials	4

Key Question 9

Date parameters ranged from 1966 to present.

A. *Thiazides*

PubMed Indexed Studies

	Concept	Search Statement
#1	Thiazide Treatment	("Hydrochlorothiazide"[nm] AND "Chlorthalidone"[nm]) OR ("Hydrochlorothiazide"[nm] AND "Indapamide"[nm]) OR ("Chlorthalidone"[nm] AND "Indapamide"[nm])
#2	Limit to RCTs	"Randomized Controlled Trial"[pt]
#3	Apply date and language parameters	("1966/01/01"[PDAT] : "2014/02/03"[PDAT]) AND English[lang]

PubMed Non-indexed Studies

	Concept	Search Statement
#1	Thiazide Treatment	("Hydrochlorothiazide"[tw] AND "Chlorthalidone"[tw]) OR ("Hydrochlorothiazide"[tw] AND "Indapamide"[tw]) OR ("Chlorthalidone"[tw] AND "Indapamide"[tw])
#2	Limit to RCTs	randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab]
#3	Apply date and language parameters	English[lang] AND inprocess[sb]

EMBASE

Set #	Searched for	Results
S1	Mesh#("Hydrochlorothiazide")	5839*
S2	Mesh.exact.explode("chlorthalidone")	1319°
S3	Mesh.exact.explode("indapamide")	850°
S4	(S1 AND S2) OR (S1 AND S3) OR (S2 AND S3)	281°
S5	EMB.EXACT.EXPLODE("hydrochlorothiazide")	23372*
S6	EMB.EXACT.EXPLODE("chlortalidone")	7228*
S7	EMB.EXACT.EXPLODE("indapamide")	4031°
S8	(S5 AND S6) OR (S5 AND S7) OR (S6 AND S7)	3693°
S9	S4 OR S8	3748°
S10	S9 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))	193°
S11	(S9 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))) AND la.exact("ENG")	172°
S12	(S9 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))) AND (rtype.exact("Journal Article") AND la.exact("ENG"))	43°

S13	(S9 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))) AND la.exact("ENG")	172°
S14	(S9 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))) AND (rtype.exact("Article") AND la.exact("ENG"))	77°
S15	(S9 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))) AND (rtype.exact("Article") AND la.exact("ENG") AND pd(19660101-20140226))	77°

Cochrane CENTRAL

ID	Search	Hits
#1	([mh Hydrochlorothiazide] and [mh Chlorthalidone]) or ([mh Hydrochlorothiazide] and [mh Indapamide]) or ([mh Chlorthalidone] and [mh Indapamide])	69
#2	randomized controlled trial:pt	336485
#3	#1 and #2 from 1966 to 2014, in Trials	49

A. *Thiazide Dose Response*

1. Systematic reviews or meta-analyses with dose comparisons of any of the three thiazides of interest.

PubMed Indexed Studies

	Concept	Search Statement
#1	Thiazide treatment	“Hydrochlorothiazide/administration and dosage"[Mesh] OR "Chlorthalidone/administration and dosage"[Mesh] OR "Indapamide/administration and dosage"[Mesh]
#2		"Hypertension/drug effects"[Mesh] OR "Hypertension/drug therapy"[Mesh] OR "Hypertension/pharmacology"[Mesh] OR "Hypertension/prevention and control"[Mesh] OR "Hypertension/therapeutic use"[Mesh] OR "Hypertension/therapy"[Mesh]
#3	Limit to systematic reviews	“systematic”[sb]
#4	Apply date and language parameters	("1966/01/01"[PDAT] : "2014/02/03"[PDAT]) AND English[lang]

PubMed Non-indexed Studies

	Concept	Search Statement
#1	Thiazide treatment	Hydrochlorothiazide[tw] OR Chlorthalidone[tw] OR Indapamide[tw]
#2		Hypertension[tiab] AND (drug[tiab] OR pharmacology[tiab] OR prevention[tiab] OR therapeutic use[tiab] OR therapy[tiab])
#3	Limit to systematic reviews	systematic[sb]
#4	Apply language parameters and identify nonindexed studies	English[lang] and inprocess[tsb]

Cochrane CENTRAL

	Concept	Search Statement
#1	Thiazide treatment	[mh Hydrochlorothiazide/AD] OR [mh Chlorthalidone/AD] OR [mh Indapamide/AD]
#2		[mh hypertension/DT] OR [mh hypertension/TH] OR [mh hypertension/PC] OR ([mh hypertension] AND (drug*:ti,ab OR pharmacology:ti,ab OR "therapeutic use":ti,ab))
#3	Apply date limits	Limit to reviews databases and 1966-2014

2. ***RCTs with dose comparisons for indapamide as there were no relevant systematic reviews that looked at indapamide dosage.***

PubMed Indexed Studies

	Concept	Search Statement
#1	Thiazide treatment	"Indapamide/administration and dosage"[Mesh]
#2		"Hypertension/drug effects"[Mesh] OR "Hypertension/drug therapy"[Mesh] OR "Hypertension/pharmacology"[Mesh] OR "Hypertension/prevention and control"[Mesh] OR "Hypertension/therapeutic use"[Mesh] OR "Hypertension/therapy"[Mesh]
#3	Limit to RCTs	"Randomized Controlled Trial"[pt]
#4	Apply date and language parameters	("1966/01/01"[PDAT] : "2014/02/03"[PDAT]) AND English[lang]

PubMed Non-Indexed Studies

	Concept	Search Statement
#1	Thiazide treatment	Indapamide[tw]
#2		Hypertension[tiab] AND (drug[tiab] OR pharmacology[tiab] OR prevention[tiab] OR therapeutic use[tiab] OR therapy[tiab])
#3	Limit to RCTs	randomized controlled trial* [tiab] OR randomized control trial*[tiab] OR random*[tiab] OR single blind*[tiab] OR double blind* [tiab]
#4	Apply language parameters and identify nonindexed studies	English[lang] AND inprocess[sb]

Cochrane CENTRAL

	Concept	Search Statement
#1	Thiazide treatment	[mh Indapamide/AD]
#2		[mh hypertension/DT] OR [mh hypertension/TH] OR [mh hypertension/PC] OR ([mh hypertension] AND (drug*;ti,ab OR pharmacology:ti,ab OR "therapeutic use":ti,ab))
#3	Limit to RCTs and apply date parameters	Limit to Randomized Controlled Trial:pt and 1966-2014

3. ***EMBASE search strategy for systematic reviews, meta-analyses, and RCTs, for three thiazide drugs dose comparisons.***

EMBASE

Set #	Searched for	Results
S1	(mesh#("Hydrochlorothiazide" LNK ad)) OR (mesh#("Chlorthalidone" LNK ad)) OR (mesh#("Indapamide" LNK ad))	1732°
S2	EMB.EXACT.EXPLODE("hydrochlorothiazide -- drug administration") OR EMB.EXACT.EXPLODE("hydrochlorothiazide -- drug dose") OR EMB.EXACT.EXPLODE("hydrochlorothiazide -- drug concentration")	1807°
S3	EMB.EXACT.EXPLODE("Chlortalidone -- drug administration") OR EMB.EXACT.EXPLODE("chlortalidone-- drug dose") OR EMB.EXACT.EXPLODE("chlortalidone -- drug concentration")	451°
S4	EMB.EXACT.EXPLODE("Indapamide -- drug administration") OR EMB.EXACT.EXPLODE("indapamide-- drug dose") OR EMB.EXACT.EXPLODE("indapamide -- drug concentration")	408°
S5	S1 OR S2 OR S3 OR S4	3382°
S6	(Mesh#("Hypertension" LNK DE)) OR (Mesh#("Hypertension" LNK TH)) OR (Mesh#("Hypertension" LNK TU)) OR (Mesh#("Hypertension" LNK PD)) OR (Mesh#("Hypertension" LNK DT)) OR (Mesh#("Hypertension" LNK PC))	80847*
S7	EMB.EXACT.EXPLODE("hypertension -- therapy") OR EMB.EXACT.EXPLODE("hypertension -- adverse drug reaction") OR EMB.EXACT.EXPLODE("hypertension -- drug therapy") OR EMB.EXACT.EXPLODE("hypertension -- drug administration") OR EMB.EXACT.EXPLODE("hypertension -- prevention")	120142*
S8	(EMB#("hypertension") AND EMB#("Drug Effect")) OR EMB.EXACT.EXPLODE("hypertension -- pharmacology")	25256*
S9	S6 OR S7 OR S8	211452*
S10	S5 AND S9	2485°
S11	S10 AND (dtype("meta analysis") OR EMB.EXACT.EXPLODE("meta analysis") OR EMB.EXACT.EXPLODE("systematic review"))	90°
S12	S10 AND (dtype("review") AND AB(review n/10 (comprehensive OR system* OR method*)))	14°
S13	S11 OR S12	99°
S14	(S11 OR S12) AND la.exact("ENG")	94°
S15	S14 AND pstype("Journal")	92°
S16	S14 AND (pstype("Journal") AND fdb(10000134))	85°
S17	S14 AND pstype("Journal")	92°
S18	S14 AND (pstype("Journal") AND la.exact("ENG"))	92°
S19	(S4 AND S9) AND pstype("Journal")	285°
S20	(S19 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))) AND pstype("Journal")	73°

S21	(S19 AND (dtype(“randomized controlled trial”) OR emb#(“randomized controlled trial”))) AND (pstype("Journal") AND la.exact("ENG"))	49°

Convening the Face-to-Face Meeting

In consultation with the Contracting Officer Representative, the Champions, and the Work Group, the Lewin Team convened a three and a half day face-to-face meeting of the CPG Champions and Work Group members on April 8-11, 2014. These experts were gathered to develop and draft the clinical recommendations for an update to the 2004 HTN CPG. Lewin presented findings from the evidence review of the key questions in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review, and asked to retain, revise, or reject each recommendation from the 2004 HTN CPG. The members also developed new clinical practice recommendations, not presented in the 2004 HTN CPG, based on the 2014 evidence review. The subject matter experts were divided into two smaller subgroups at this meeting.

Following the drafting of clinical practice recommendations, the Work Group assigned a grade for each recommendation based on GRADE methodology.

Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation: [208]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate, e.g.,:
    - Resource Use
    - Equity
    - Acceptability
    - Feasibility
    - Subgroup considerations

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved quality of life (QoL), decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review used for the development of recommendations for the HTN CPG assessed the confidence in the quality of the evidence base and assigned a rate of "High," "Moderate," "Low" or "Very Low."

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term "values" has the closest connotation to these processes. For others, the connotation of "preferences" best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having "similar values", "some variation", or "large variation" in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient's values and preferences?
- Are the assumed or identified relative values similar across the target population?

Other implications consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example, statin use in the frail elderly and others with multiple comorbidities may not be effective and depending on the societal benchmark

for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility and subgroup considerations require similar judgments around the practically of the recommendation.

The framework below was used by the Work Group to guide discussions on each domain.

Table A-3. Evidence to Recommendation Framework

Decision Domain	Judgment
Balance of desirable and undesirable outcomes	
Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? Are the desirable anticipated effects large? Are the undesirable anticipated effects small? Are the desirable effects large relative to undesirable effects?	Benefits outweigh harms/burden Benefits slightly outweigh harms/burden Benefits and harms/burden are balanced Harms/burden slightly outweigh benefits Harms/burden outweigh benefits
Confidence in the quality of the evidence	
Is there high or moderate quality evidence that answers this question? What is the overall certainty of this evidence?	High Moderate Low Very low
Values and preferences	
Are you confident about the typical values and preferences and are they similar across the target population? What are the patient's values and preferences? Are the assumed or identified relative values similar across the target population?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations):	
Are the resources worth the expected net benefit from the recommendation? What are the costs per resource unit? Is this intervention generally available? Is this intervention and its effects worth withdrawing or not allocating resources from other interventions Is there lots of variability in resource requirements across settings?	Various considerations

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains. [208] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low. [209] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "We recommend offering this option …")
- Weak For (or "We suggest offering this option …")
- Weak Against (or "We suggest not offering this option …")
- Strong Against (or "We recommend against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified". Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

Drafting and Submitting the Final CPG

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments for the update of specific sections of the 2004 HTN CPG that would form the narrative text for the 2014 HTN CPG. During this time, the Champions also revised the 2004 HTN algorithms and identified the content for the guideline summary and pocket card, as part of the provider toolkits that will be developed by the Office of Evidence-Based Practice, HQ MEDCOM following the publication of the 2014 HTN CPG. The algorithms will be included as part of this HTN CPG so as to provide a clear description of the flow of patient care. The final 2014 HTN CPG was submitted to the EBPWG in October 2014.

Appendix B: Evidence Table

Recommendation	2004 Grade[13]	2014 Evidence[14]	2014 Strength of Recommendation[15]
Screening and Diagnosis of Hypertension			
Screening			
1. We recommend screening adults for elevated blood pressure occur periodically, preferably annually. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	B →	**Additional evidence:** [14]	→ Strong for
2. We suggest that screening occur at the time of routine preventive care or routine health assessment. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	I →		→ Weak for
Diagnosis			
3. We recommend the diagnosis of hypertension be determined based on at least two blood pressure readings on two separate patient visits. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	N/A →	**Additional evidence:** [14] [24]	→ Strong for
Measurement Techniques			
4. We recommend that blood pressure be measured with a technique recommended for the measurement of blood pressure in adults using a properly calibrated and validated sphygmomanometer. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	A →	**Additional evidence:** [24]	→ Strong for

[13] The 2004 VA/DoD HTN CPG used the U.S. Preventive Services Task Force (USPSTF) evidence grading system. http://www.uspreventiveservicestaskforce.org

[14] The evidence column indicates studies that support each recommendation. For new recommendations, developed by the 2014 guideline Work Group, the literature cited corresponds directly to the 2014 evidence review. For recommendations that have been carried over from the 2004 VA/DoD HTN CPG, slight modifications were made to the language in order to better reflect the current evidence and/or the change in grading system used for assigning the strength of each recommendation (USPSTF to GRADE). For these "modified" recommendations, the evidence column indicates "additional evidence," which can refer to either 1) studies that support the recommendation and which were identified through the 2014 evidence review, or 2) relevant studies that support the recommendation, but which were not systematically identified through a literature review.

[15] Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

Recommendation	2004 Grade[13]	2014 Evidence[14]	2014 Strength of Recommendation[15]
5. For patients whose diagnosis of hypertension remains uncertain, we recommend offering home blood pressure monitoring to confirm diagnosis prior to beginning pharmacologic treatment. (Two to three times a day for seven consecutive days, disregard the first day and take the average of measurements.)	--	[27] [210] [211] [31] [30]	Strong for
6. For patients whose diagnosis of hypertension remains uncertain, we suggest offering 24 hour ambulatory blood pressure monitoring as an alternative to home blood pressure monitoring to confirm diagnosis prior to beginning pharmacologic treatment.	--	[212] [34]	Weak for
Adherence to Therapy			
7. We suggest offering a multi-modal approach to adherence interventions, which could include telemonitoring, multi-disciplinary group medical appointments, (e.g., shared medical appointments), case management (by pharmacists, nurses, social workers), patient and provider education, behavioral therapy, etc.	--	[54] [55] [56] [57] [58] [59]	Weak for
Lifestyle Modification Therapies			
8. We recommend offering lifestyle modification interventions for patients with prehypertension or hypertension based on patient indications and preferences as well as assessment of available local resources. *(Modified from 2004 VA/DoD HTN CPG)*	A →	→	Strong for
Weight Reduction			
9. We recommend discussing healthy weight range and advising overweight or obese hypertensive patients to reduce their body mass index to below 25. *(Modified from 2004 VA/DoD HTN CPG)*	B →	**Additional evidence:** [64]	Strong for
10. If a normal body mass index (<25) cannot be achieved, we suggest advising patients that a weight reduction of at least 10 pounds can achieve a decrease in blood pressure.	--	[67] [68]	Weak for
Exercise/Physical Activity			

Recommendation	2004 Grade[13]	2014 Evidence[14]	2014 Strength of Recommendation[15]
11. We recommend a target for aerobic exercise of 30 to 45 minutes per session, at least four times per week. *(Modified from 2004 VA/DoD HTN CPG)*	B →	**Additional evidence:** [75] [76]	→ Strong for
12. We suggest the use of a self-monitoring device (e.g., pedometer, mobile apps, etc.) to increase adherence to physical activity.	--	[73] [74]	Weak for
Mind-body/Alternative Therapies			
13. For patients interested in complementary and alternative medicine, we suggest considering mind-body therapies such as transcendental meditation or yoga.	--	[77] [78] [79]	Weak for
14. We suggest not offering Tai Chi for the treatment of hypertension as there is a moderate body of evidence that shows this intervention does not reduce blood pressure.	--	[80]	Weak against
Dietary Modification			
15. We recommend a dietitian-led Dietary Approaches to Stop Hypertension (DASH) Diet for the treatment and/or prevention of hypertension for patients with hypertension and/or interested patients with prehypertension and other cardiovascular risk factors. *(Modified from 2004 VA/DoD HTN CPG)*	B →	**Additional evidence:** [213]	→ Strong for
16. In patients with additional cardiovascular risk factors, such as dyslipidemia, we suggest considering a dietitian-led Mediterranean Diet as an alternative to the DASH Diet.	--	[85]	Weak for
17. We recommend against the use of soy protein supplements for the treatment of hypertension.	--	[88]	Strong against
Sodium Reduction			
18. In patients with hypertension or prehypertension, we recommend that sodium intake be limited to no more than 2300mg/day (100mmol/day), with referral to a dietitian or other support as appropriate. *(Modified from 2004 VA/DoD HTN CPG)*	B →	**Additional evidence:** [90] [91]	→ Strong for

Recommendation	2004	2014	
	Grade[13]	Evidence[14]	Strength of Recommendation[15]
		[92]	
Alcohol Reduction			
19. We recommend advising hypertensive and prehypertensive patients to limit alcohol intake to no more than 1 oz per day for men or 0.5 oz of alcohol per day for women. (This is approximately 2 drinks/day in men and 1 drink/day in women, where a drink is 1.5 oz 80-proof liquor, 12 oz beer, or 5 oz wine [all 14g]). *(Modified from 2004 VA/DoD HTN CPG)*	B →	**Additional evidence:** [103]	→ Strong for
Pharmacological Therapy			
Initiation of Pharmacotherapy			
20. We recommend offering pharmacologic treatment for hypertensive patients 60 years and older with a systolic blood pressure ≥ 160 mmHg.	--	[110] [111] [112]	Strong for
21. We suggest considering pharmacologic treatment using a shared decision-making model for hypertensive patients 60 years and older with systolic blood pressure <160 mmHg.	--	[113]	Weak for
22. We suggest offering pharmacologic treatment to patients with a history of cerebrovascular disease (stroke, transient ischemic attack, or asymptomatic carotid artery disease) and a systolic blood pressure ≥140 mmHg.	--	[106] [107] [108] [109]	Weak for
23. We suggest pharmacologic treatment for hypertensive patients younger than 60 with a systolic blood pressure ≥160 mmHg, regardless of diastolic blood pressure.	--	[114]	Weak for
24. We recommend offering pharmacologic treatment for patients 30 years and older with a diastolic blood pressure ≥90 mmHg.	--	[117] [118] [111] [107] [116] [120] [121]	Strong for

Recommendation	2004	2014	
	Grade[13]	Evidence[14]	Strength of Recommendation[15]
25. We suggest offering pharmacologic treatment for patients age 18 to 29 with a diastolic blood pressure ≥90 mmHg.	--	[123] [122]	Weak for
Blood Pressure Goals			
26. For patients 60 years and over, we recommend treating to a systolic blood pressure goal of <150 mmHg.	--	[109] [124] [110]	Strong for
27. For patients below 60 years of age, we suggest treating to a systolic blood pressure goal of <150 mmHg.	--	[109] [124] [110]	Weak for
28. We recommend treating to a diastolic blood pressure goal <90mmHg in patients 30 years and older.	--	[117] [118] [120] [122] [129]	Strong for
29. We suggest treating to a diastolic blood pressure goal <90mmHg in patients age 18 to 29.	--	[117] [118] [120] [122] [129]	Weak for
30. For patients with diabetes (all age groups), we recommend treating to a systolic blood pressure goal of <150 mmHg.	--	[109] [124] [131]	Strong for
31. For patients with diabetes (all age groups) who tolerate antihypertensive drugs, we suggest treating to a systolic blood pressure goal of <140 mmHg.	--	[132]	Weak for
32. For patients with diabetes, we recommend treating to a diastolic blood pressure goal <85 mmHg.	--	[134] [130]	Strong for
Hypertension Control and Follow-up			
33. We suggest that patients be seen within one month of initiation of lifestyle or pharmacological therapy to determine adequacy of hypertension control, degree of patient adherence, and presence of adverse effects. *(Modified from*	N/A →	→	Weak for

Recommendation	2004 Grade[13]	2014 Evidence[14]	2014 Strength of Recommendation[15]
2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)			
34. Once the patient's blood pressure is controlled, we suggest follow-up at least annually or more frequently as indicated, depending on patient preference. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	N/A →		→ Weak for
Monotherapy or Combination Therapy			
35. We suggest taking into consideration the patient's baseline blood pressure and presence of comorbidities, when deciding on either monotherapy or combination therapy (two drugs) when initiating drug therapy. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	N/A →	**Additional evidence:** [151] [152] [153]	→ Weak for
36. We suggest initiating combination therapy for patients with a baseline systolic blood pressure of >20 mmHg or diastolic blood pressure of >10 mmHg above the patient's goal. *(Modified from 2004 VA/DoD HTN CPG without an updated systematic review of the evidence.)*	N/A →	**Additional evidence:** [151] [152] [153]	→ Weak for
First-line Therapy			
37. We recommend the use of thiazide-type diuretics for the treatment of hypertension.	--	[151] [154]	Strong for
38. We suggest the use of thiazide-type diuretics at recommended treatment doses as first-line therapy for drug treatment of hypertension either as monotherapy or in combination with other agents. *(Modified from 2004 VA/DoD HTN CPG)*	A →	**Additional evidence:** [151] [154]	→ Weak for
39. To initiate treatment of hypertension with a thiazide-type diuretic, we suggest the use of chlorthalidone or indapamide over hydrochlorothiazide.	--	[159] [155] [156] [157] [158] [160] [161]	Weak for

Recommendation	2004	2014	
	Grade[13]	Evidence[14]	Strength of Recommendation[15]
40. We do not suggest switching from hydrochlorothiazide to chlorthalidone or indapamide if the patient is adequately controlled on and tolerating hydrochlorothiazide.	--	[163]	Weak against
41. We suggest considering a switch from hydrochlorothiazide to chlorthalidone for patients whose hypertension is inadequately controlled on 50mg/day of hydrochlorothiazide.	--	[163]	Weak for
42. We recommend a dosage of 12.5-25mg/day of chlorthalidone, 25-50mg/day of hydrochlorothiazide, or a dosage of 2.5mg/day immediate-release or 1.5-2.5mg/day sustained-release (not currently available in the US) of indapamide.	--	[159] [155] [156] [157] [158] [160] [161]	Strong for
Alternative or Supplementary Therapies			
43. We recommend using the following as alternative therapies for patients who cannot tolerate thiazide-type diuretics, as supplementary therapies for patients who do not reach their hypertensive goals, or for those starting on combination therapy: a. Angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers (but not together) b. Long-acting dihydropyridine calcium channel blockers *(Modified from 2004 VA/DoD HTN CPG)*	A →	**Additional evidence:** [164] [166]	→ Strong for
44. We recommend against the use of more than one of the following three drug classes together in the same patient: angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors.	--	[164] [168] [169]	Strong against
45. We recommend additional therapy in refractory hypertension (for those who do not tolerate or are not adequately controlled with triple therapy [i.e., thiazide-type diuretics, ACEI or ARB, and CCBs] described in Recommendation 43) or as supplementary therapy in some clinical indications. Drug classes for	--	[129] [167] [165] [170]	Strong for

Recommendation	2004 Grade[13]	2014 Evidence[14]	2014 Strength of Recommendation[15]
consideration can include (not in priority order): a. Aldosterone/mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone) b. Other potassium-sparing diuretic (i.e., amiloride) c. Alpha adrenergic blockers d. Beta adrenergic blockers e. Non-dihydropyridine calcium channel blockers f. Combined alpha-beta adrenergic blockers g. Peripherally acting antiadrenergic agents (reserpine, pending availability) h. Direct acting vasodilators (e.g., hydralazine, minoxidil) i. Centrally acting antiadrenergic drugs (e.g., clonidine, methyldopa)		[171]	
46. We recommend against the use of alpha-adrenergic blockers as monotherapy, but this class of agents may be used as supplemental therapy or if warranted by comorbid conditions (e.g., symptomatic prostatic hypertrophy). *(Modified from 2004 VA/DoD HTN CPG)*	A →	**Additional evidence:** [154] [171]	→ Strong against
Specific Populations			
47. In patients with hypertension and chronic kidney disease (reduced kidney function with albuminuria), we recommend treatment with an angiotensin-converting-enzyme inhibitor, or angiotensin II receptor blocker for improving kidney outcomes. *(Modified from 2004 VA/DoD HTN CPG)*	A →	**Additional evidence:** [176] [174] [175]	→ Strong for
48. In African American patients with hypertension, we recommend against using an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker as monotherapy.	--	[195] [152]	Strong against
49. We suggest African American patients with hypertension and stage 1-3 chronic kidney disease, we suggest a combination of a thiazide-type diuretic (for cardiovascular protection) with either an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker (for renal protection).	--	[195] [152]	Weak for

Appendix C: Dietary Information

Table D-1. Nutrient Composition of the Dietary Approaches to Stop Hypertension (DASH) Diet* [213]

Nutrient	Recommended Intake
Saturated Fat	6% of total calories
Total Fat	27% of total calories
Carbohydrate	55% of total calories
Fiber	30 grams/day
Protein	18% of total calories
Cholesterol	150 mg/day
Total calories (energy)†	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain.
†Daily calorie expenditure should include at least 30 minutes of moderate physical activity/day. To avoid weight gain, the total should be approximately 60 minutes per day.	

* Additional information on the DASH diet is available at: http://www.nhlbi.nih.gov/health/health-topics/topics/dash/. [213]

Table D-2. Summary of Dietary Recommendations in the Mediterranean Diet* [85,214]

Food	Goal
Recommended	
Olive Oil	≥ 4 tbsp. per day
Tree nuts and peanuts	≥ 3 servings per week
Fresh fruits including natural fruit juices	≥ 3 servings per day
Vegetables	≥ 2 servings per day
Seafood (primarily fatty fish)	≥ 3 servings per week
Legumes	≥ 3 servings per week
Sofrito†	≥ 2 servings per week
White Meat	In place of red meat
Wine with meals	≥ 7 glasses per week, for those who drink
Discouraged	
Soda drinks	< 1 drink per day
Commercial baked goods, sweets, pastries‡	< 3 servings per week
Spread fats	< 1 serving per day
Red and processed meats	< 1 serving per day

*Dietary patterns vary both within and among countries in the Mediterranean region, precluding a single standardized definition of the Mediterranean diet, though certain characteristic features are generally agreed upon by those studying its potential health effects. The table above represents the specific dietary recommendations used in the research study constituting our evidence base for this section of the guideline.

† Sofrito is a sauce made with tomato and onion, and often includes garlic, herbs, and olive oil.

‡ Commercial bakery goods, sweets, and pastries included cakes, cookies, biscuits, and custard, and did not include those that are homemade.

Appendix D: Blood Pressure Thresholds to Initiate Pharmacologic Therapy and Treatment Goals

Table D-1. Blood Pressure Thresholds to Initiate Pharmacologic Treatment and Treatment Goals by Patient Category and Age

			Category of Patient		
Patient Age		**Blood Pressure (mm Hg)[a]**	**General Population**	**Diabetic Population**	**History of cerebrovascular disease**
18-29 years	**Initiate**	**SBP**	≥160 (Suggested)	≥160 (Suggested)[b]	≥140 (Suggested)
		DBP	≥90 (Suggested)	≥90 (Suggested)[b]	≥90 (Suggested)[b]
	Goals	**SBP**	<150 (Suggested)	<150 (Recommended) <140 (Suggested for those who tolerate medication)	<150 (Suggested)[b]
		DBP	<90 (Suggested)	<85 (Recommended)	<90 (Suggested)[b]
30-59 years	**Initiate**	**SBP**	≥160 (Suggested)	≥160 (Suggested)[b]	≥140 (Suggested)
		DBP	≥90 (Recommended)	≥90 (Recommended)[b]	≥90 (Recommended)[b]
	Goals	**SBP**	<150 (Suggested)	<150 (Recommended) <140 (Suggested for those who tolerate medication)	<150 (Suggested)[b]
		DBP	<90 (Recommended)	<85 (Recommended)	<90 (Recommended)[b]
≥60 years	**Initiate**	**SBP**	≥160 (Recommended) 160 > SBP ≥ 140 (Suggested; using shared decision making)	≥160 (Recommended)[b] 160 > SBP ≥ 140 (Suggested; using shared decision making)[b]	≥140 (Suggested)
		DBP	≥90 (Recommended)	≥90 (Recommended)[b]	≥90 (Recommended)[b]
	Goals	**SBP**	<150 (Recommended)	<150 (Recommended) <140 (Suggested for those who tolerate medication)	<150 (Recommended)[b]
		DBP	<90 (Recommended)	<85 (Recommended)	<90 (Recommended)[b]

[a] Initiate pharmacologic treatment at SBP OR DBP threshold; once pharmacologic treatment is initiated, treat to SBP AND DBP goals.

[b] Evidence was not reviewed which indicated the blood pressure value should be different from the general population.

Appendix E: Drug Dosage Table

Table E-1. Recommended Dosage for Selected Hypertension Drug Therapy

Drug[a]	Usual Dose Range	Comments[h]
Thiazide-type Diuretics		
Chlorthalidone[b]	12.5-25 mg daily	May cause hyperuricemia/gout.
HCTZ[b]	12.5-50 mg daily[f]	Monitor K+ levels.
		May cause photosensitivity (rare).
Indapamide	IR: 2.5 mg daily	
	SR[g]: 1.25 – 2.5 mg daily	
Angiotensin-Converting Enzyme Inhibitors		
Benazepril	10-40 mg/day (daily or divided bid)	When pregnancy is detected, discontinue as soon as possible, due to potential for fetal and neonatal morbidity and death. Patients of child-bearing potential should also be educated about the risks. Do not use if history of angioedema. Avoid concomitant use of ACEI with ARB or direct renin inhibitor due to increased risk of hypotension, syncope, increased K+, and changes in renal function (See recommendation #44). Monitor K+ and kidney function; use caution if combined with, K+ sparing diuretic, or K+ supplement. Consider interruption or discontinuation in patients who develop clinically significant decline in kidney function after initiation of therapy, until further work-up, as indicated (e.g., renal artery stenosis).
Enalapril	5-40 mg/day (daily or divided bid)	
Fosinopril	10-40 mg daily	
Lisinopril[b]	10-40 mg daily	
Ramipril[b,c]	2.5-20 mg/day (daily or divided bid) (10 mg daily for CV risk prevention)	
Angiotensin II Receptor Blockers		
Azilsartan[c]	40-80 mg daily	When pregnancy is detected, discontinue as soon as possible. Drugs that act directly on the renin angiotensin system can cause injury and death to the developing fetus. Patients of child-bearing potential should also be educated about the risks. Avoid concomitant use of ACEI with angiotensin II receptor blocker or direct renin inhibitor due to increased risk of hypotension, syncope, increased K+, and changes in renal function (See recommendation #44). Monitor K+ and kidney function; use caution if combined with, K+ sparing diuretic, or K+ supplement.
Candesartan[c]	8-32 mg daily	
Eprosartan[c]	400-800 mg/daily (daily or divided bid)	
Irbesartan[c]	150-300 mg daily	
Losartan[b]	25-100 mg/day (daily or divided bid)	
Olmesartan[c]	20-40 mg daily	
Telmisartan[c]	20-80 mg daily	
Valsartan[b,d]	80-320 mg daily	

		Consider interruption or discontinuation in patients who develop clinically significant decline in kidney function after initiation of therapy, until further work-up, as indicated (e.g., renal artery stenosis).
Long-Acting Dihydropyridine Calcium Channel Blockers		
Amlodipine[b] Felodipine Nifedipine SR[b]	2.5-10 mg daily 2.5-10 mg daily 30-120 mg daily	Monitor adverse effects (DHP CCBs may cause ankle edema, dizziness, flushing, headache). Use with caution in patients with hepatic or renal dysfunction.
Aldosterone/mineralocorticoid Receptor Antagonists		
Eplerenone[c] Spironolactone[b]	50-100 mg/day (daily or divided bid) 25-50 mg/daily	Avoid use if hyperkalemia or severe kidney dysfunction. Monitor K+ and kidney function; consider risk vs. benefit if combined with ACEI, ARB, K+ sparing diuretic, or K+ supplement. Higher risk of gynecomastia with spironolactone than eplerenone.
Other Potassium-Sparing Diuretics		
Amiloride[c]	5-10 mg daily	Avoid use if hyperkalemia or severe kidney dysfunction. Helpful in reducing hypokalemia caused by thiazide diuretics.
Alpha-Adrenergic Blockers		
Doxazosin Prazosin Terazosin[b]	1-16 mg daily 2-20 mg/day (divided bid or tid) 1-20 mg daily	Initiate at low doses (1 mg). Administer 1st dose at bedtime to avoid syncope. Avoid use as monotherapy (See recommendation #46).
Beta-Adrenergic Blockers		
Noncardioselective Propranolol *Cardioselective* Atenolol[b] Metoprolol tartrate[b] Metoprolol succinate (XL)[b,d]	IR: 80-160 mg/day (divided bid) SR: 80-160 mg daily 25-100 mg daily (adjust dose in CKD) IR: 50-300 mg/day (daily or divided bid) SR: 25-200 mg/day	Discontinue with slow taper over one week. Avoid combination with non-DHP CCB due to increased risk of bradycardia. As doses increase, cardioselectivity decreases. Beta-blockers should be used cautiously in asthma.
Long-Acting Non-Dihydropyridine Calcium Channel Blockers		
Verapamil SR[b]	120-480 mg divided daily-bid	Verapamil may cause constipation; verapamil is contraindicated in AV node dysfunction (2nd or 3rd degree heart block), systolic HF and ↓ LV function.
Diltiazem SR[b]	120-540 mg daily	Diltiazem may ↓ sinus rate and cause heart

		block. Use CCBs with caution in patients with liver or kidney dysfunction.
Combined Alpha-beta adrenergic blockers		
Carvedilol	IR[b]: 12.5-50 mg/day (divided bid) SR[c]: 20-80 mg/day	Precautions for beta-blockers apply.
Labetalol[c]	200-800 mg/day (divided bid)	
Peripherally Acting Adrenergic Agents		
Reserpine[e]	0.1-0.25 mg daily	Monitor for sedation, and nasal congestion.
Direct Acting Vasodilators		
Minoxidil Hydralazine[b]	2.5-100 mg/day (daily or divided bid) 50-200 mg/day (divided bid)	Direct acting vasodilators often need concomitant use of diuretic and beta-blocker to reduce edema and reflex tachycardia. Monitor for hypertrichosis and pericardial effusions with minoxidil. Monitor for headache and SLE (dose-related) with hydralazine.
Centrally Acting Antiadrenergic Drugs		
Clonidine Tablet[b]	0.1-0.8 mg/day (divided bid)	Monitor for somnolence and dry mouth. Taper dose to discontinue.
Clonidine Patch	0.1-0.3 mg patch weekly	Clonidine patches may be useful in select patients.
Methyldopa	500-2,000 mg/day (divided bid)	

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; AV=atrioventricular; bid=twice daily; CCB=calcium channel blockers; CKD=chronic kidney disease; CV=cardiovascular; DHP: dihydropyridine; HCTZ=hydrochlorothiazide; HF=heart failure; IR=immediate-release; K+=potassium; LV=left ventricular; SLE=systemic lupus erythematosus; SR=sustained-release

[a] Partial list; refer to http://www.pbm.va.gov/nationalformulary.asp for items available on the VA National Formulary (VANF) and refer to http://pec.ha.osd.mil/formulary_search.php?submenuheader=1 for items available on the DoD Uniform Formulary. All drugs listed are on the DoD Uniform Formulary.

[b] DoD Basic Core Formulary (BCF) item.

[c] Item not on VANF

[d] Restricted to patients with chronic heart failure in VA.

[e] Reserpine not currently available in the U.S. due to changes in requirements for raw materials (re-verified 10/15/2014; next available supply estimated March 2015). Refer to FDA Drug Shortages for current information.

[f] 12.5 mg may be considered as an initial dose with titration recommended to 25 to 50mg daily; refer to Recommendation #42 and associated discussion for further information.

[g] Indapamide SR not currently available in the US.

[h] For complete drug information, review the manufacturer's prescribing information

Appendix F: Participant List

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Appendix G: Acronyms List

AASK	African American Study of Kidney Disease and Hypertension
ABPM	Ambulatory Blood Pressure Monitoring
ACCOMPLISH	Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACEI	Angiotensin-Converting-Enzyme Inhibitor
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ANBP2	Second Australian National Blood Pressure Study
ARB	Angiotensin-II Receptor Blockers
BAS	Battalion Aid Station
BP	Blood Pressure
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CBP	Clinic Blood Pressure
CCB	Calcium Channel Blockers
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHD	Coronary Heart Disease
CHF	Chronic Heart Failure
CKD	Chronic Kidney Disease
CNS	Central Nervous System
COB	Combined Operating Base
COR	Contracting Officer's Representative
CPG	Clinical Practice Guideline
CSH	Combat Support Hospital
CT	Computerized Tomography
CVA	Cerebrovascular Accident
CV	Cardiovascular
CVD	Cardiovascular Disease
DARE	Database of Abstracts of Reviews of Effects
DASH	Dietary Approaches to Stop Hypertension

DBP	Diastolic Blood Pressure
DHP	Dihydropiridine
DM	Diabetes Mellitus
DoD	Department of Defense
DRI	Direct Renin Inhibitor
EBPWG	Evidence-Based Practice Working Group
ECG	Electrocardiography
ESRD	End Stage Renal Disease
FOB	Forward Operating Base
FST	Forward Surgical Team
GFR	Glomular Filtration Rate
GMC	Group Medical Clinic
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBPM	Home Blood Pressure Monitoring
HCTZ	hydrochlorothiazide
HDFP	Hypertension Detection and Follow-up Program
HF	Heart Failure
HINTS	Hypertension Intervention Nurse Telemedicine Study
HOT	Hypertension Optimal Treatment Trial
HTN	Hypertension
HYVET	Hypertension in the Very Elderly Trial
IHD	Ischemic Heart Disease
ILI	Intensive Lifestyle Interventions
INSIGHT	Intervention as a Goal in Hypertension Treatment trial
IOM	Institute of Medicine
IR	Immediate-Release
JNC7	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
JNC8	Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LA	Long-acting
LEARN	Lifestyle Exercise Attitudes Relationships Nutrition
LSM	Lifestyle Modification
LVH	Left Ventricular Hypertrophy
KQ	Key Question
MeSH	Medical Subject Headings
MI	Myocardial Infarction
MRC	Medical Research Council
MRE	Meals Ready to Eat
NHANES	National Health and Nutrition Examination Survey

NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NSAID	Nonsteroidal Anti-Inflammatory Drug
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
PICOTS	Population, Intervention, Comparison, Outcome, Timing and Setting
PROGRESS	Perindopril pROtection aGainst REcurrent Stroke Study
RAS	Renin-Angiotensin System
RCT	Randomized Controlled Trial
RF	Risk Factors
SBP	Systolic Blood Pressure
SDM	Shared Decision-making
SHEP	Systolic Hypertension in Elderly Patients Trial
SPRINT	Systolic Blood Pressure Intervention Trial
SR	Sustained-Release
Syst-Eur	Systolic Hypertension in Europe Trial
TIA	Transient Ischemic Attack
TMC	Troop Medical Clinic
TOD	Target Organ Damage
TOHP II	Trials of Hypertension Prevention Phase II
TONE	Trial of Nonpharmacologic Interventions in the Elderly
UA	Urinalysis
US	United States
USPSTF	United States Preventive Services Task Force
VA	Department of Veterans Affairs
VAMC	Veterans Affairs Medical Center
VHA	Veterans Health Administration

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