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Evidence for the Reaffirmation of the U.S. Preventive Services Task Force Recommendation on Screening for High Blood Pressure

Investigators:
Tracy Wolff, MD, MPH
Therese Miller, DrPH
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

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Structured Abstract

Background

High blood pressure is common, and screening is a well-established evidence-based standard of current medical practice.

Purpose

To perform a literature search for new, substantial evidence on screening for high blood pressure that would inform the reaffirmation of the U.S. Preventive Services Task Force recommendation on screening for high blood pressure.

Data Sources

The PubMed and Cochrane databases were searched. The searches were limited to English-language articles on studies of adult humans (age >18 years) that were published between 1 October 2001 and 31 March 2006 in core clinical journals.
Study Selection: For the literature on benefits, meta-analyses; systematic reviews; and randomized, controlled trials were included. For harms, meta-analyses; systematic reviews; randomized, controlled trials; cohort studies; case--control studies; and case series of large, multisite databases were included. Two reviewers independently reviewed titles, abstracts, and full articles for inclusion.

Data Extraction

No new evidence was found on benefits or harms of screening. Two reviewers extracted data from studies on the harms of early treatment, including adverse effects of drug therapy and adverse quality-of-life outcomes.

Data Synthesis

No new evidence was found for the benefits of screening for high blood pressure. New evidence on the harms of treatment of early hypertension shows that pharmacologic therapy is associated with common side effects; serious adverse events are uncommon.

Limitations

The nonsystematic search may have missed some smaller studies on the benefits and harms of screening and treatment for high blood pressure.

Conclusions

No new evidence was found on the benefits of screening. Pharmacotherapy for early hypertension is associated with common side effects.

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Introduction

Hypertension is usually defined in adults as systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher (1). Data from NHANES III (the Third National Health and Nutrition Examination Survey) suggest that an estimated 43 million U.S. adults older than 25 years have hypertension and that hypertension is more common in African American and elderly persons than in other groups. In the United States, hypertension is responsible for 35% of myocardial infarctions and strokes, 49% of episodes of heart failure, and 24% of premature deaths. Additional complications of hypertension include end-stage renal disease, retinopathy, and aortic aneurysm (2-4).

In 2006, the U.S. Preventive Services Task Force (USPSTF) decided to reexamine the evidence in order to reaffirm its 2003 recommendation on screening for high blood pressure (or hypertension). The Task Force issues a reaffirmation update for a topic that the USPSTF decides to keep current because the topic is one of its priorities, is within its scope, and is a topic for which there is a compelling reason to make a recommendation. Topics in this category are well-established evidence-based standards of current medical practice. The USPSTF decided to perform a reaffirmation update because the evidence base on hypertension is strong and only large, high-quality studies would overturn such a recommendation. Such recommendations would previously have been an A or D recommendation. Therefore, we performed a literature search for new, substantial evidence that would be sufficient to change the 2003 recommendation.

Methods

The USPSTF developed 2 key questions to be addressed: 1) What are the benefits of screening for high blood pressure in adults? 2) What are the harms of screening and/or early treatment of high blood pressure? To determine whether the benefits of screening for hypertension continue to outweigh the harms, the USPSTF included new information on the adverse effects of drug therapy for "early hypertension" as part of the question on harms.

Data Sources and Searches

We performed nonsystematic literature searches of PubMed and the Cochrane Library. We used the following search terms: *hypertension, mass screening, adverse effects,* and *false positive results.* We limited the searches to English-language studies of adult humans (age >18 years) that were published in core clinical journals between 1 October 2001 and 31 March 2006. "Core clinical journals" are a subset of 120 English language journals defined by the National Library of Medicine; it was previously known as the

Abridged Index Medicus. We also checked reference lists of systematic reviews and other studies for possibly relevant studies.

Study Selection

In this review, we included studies on benefits and harms of screening and treatment of "early hypertension." We understood "early hypertension" to be a blood pressure elevation that screening could reasonably identify. For this review, we defined "early hypertension" as prehypertension (systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg), hypertension detected through screening, or untreated or newly diagnosed mild to moderate hypertension (systolic blood pressure of 140 to 180 mm Hg or diastolic blood pressure of 90 to 110 mm Hg, when information was not given about how hypertension was detected). We excluded studies in very high-risk or special populations, including patients with preexisting cardiovascular disease\.

We included studies of non-pregnant adults older than 18 years. We included studies from the United States and from countries with patient populations that are generalizable to the United States. For the literature on benefits, we included meta-analyses; systematic reviews; and randomized, controlled trials. For harms, we included meta-analyses; systematic reviews; randomized, controlled trials; cohorts; case--control studies; and case series of large, multisite databases. We excluded editorials, case reports, nonsystematic reviews, and guideline reports.

Data Extraction

No studies were included for data abstraction on the benefits or harms of screening. For harms of early treatment, 2 reviewers abstracted information on sample size, entry criteria, demographic characteristics, comorbid conditions, study design, treatment group allocation, reports of adverse effects of drug therapy, and quality-of-life outcomes.

Data Synthesis and Analysis

Data from the included studies were synthesized qualitatively in tabular and narrative formats.

Role of the Funding Source

The work of the USPSTF is supported by the Agency for Healthcare Research and Quality. No separate funding was used specifically for this study.

Results

The search returned 378 potentially relevant titles, which we entered into a reference database. A total of 341 studies were excluded after title review, 19 studies were excluded after abstract review, and 13 were excluded after full article review. We

excluded 253 studies that were not on hypertension, 62 that included a high-risk population, 31 that did not meet study design criteria, 12 that were not from a U.S. population, 8 that were not done in adults, and 7 that had no relevant outcomes.
No new studies on the benefits or harms of screening for high blood pressure met our inclusion criteria. Five studies evaluated the harms of early treatment of hypertension and met our inclusion criteria (**Table**); these are discussed below.

Three studies presented data on adverse effects related to antihypertensive drugs. These studies compared outcomes from treatment of one type of drug versus another type of drug or placebo. In general, they were multicenter studies in the United States, Canada, and United Kingdom; included a predominantly white, male patient sample; and excluded persons with multiple comorbid conditions or manifest cardiovascular disease. In addition, two studies examined the effects of antihypertensive medications on quality of life. In these 2 studies, participants with untreated hypertension were randomly allocated to different treatment regimens (the second study also included a placebo group) and followed for effects on quality of life: sexual dysfunction in one study, and "symptom distress" in the other study. The study on sexual dysfunction included men 40 to 49 years of age, and the study on symptom distress included men and women 50 years of age or older.

In 1 study that gathered data on adverse effects, White and colleagues studied the effect of bedtime dosing on early morning blood pressure in 261 persons who were randomly allocated to 10 weeks of extended-release diltiazem or ramipril (5). Adverse effects were reported in 50% of the diltiazem group and 40% of the ramipril group. Serious adverse effects were uncommon, and 2 of the 3 reported events were probably not related to the drug: 1 event occurred during placebo run-in, and 1 was associated with infection. The most common reasons for withdrawal from the study were lower-extremity edema associated with diltiazem (3%) and cough associated with ramipril (2%). Headache was commonly reported in both groups. The main finding of the study was that diltiazem at bedtime reduced early morning blood pressure to a greater extent than ramipril.

Julius and colleagues compared candesartan with placebo in participants with systolic blood pressure of 130 to 139 mm Hg and diastolic blood pressure of 89 mm Hg or less**"** (6). Serious adverse effects were uncommon: 3.5% of candesartan recipients and 5.9% of placebo recipients. However, other, less serious adverse effects were very common, occurring in approximately 89% of participants in both the candesartan and placebo groups. Commonly reported adverse effects in the candesartan group were headache (22%), upper respiratory infection (14%), nasopharyngitis (10%), and dizziness (10%).

A third study evaluated the effectiveness in reducing clinic-measured and ambulatory blood pressure of 4 antihypertensive agents (doxazosin, amlodipine, enalapril, and bendrofluazide) in 204 persons with diastolic blood pressure of 95 to 110 mm Hg (7). The authors reported that clinic-measured and ambulatory blood pressure decreased in all groups, with no significant differences among the 4 groups; the authors did not report data that allowed us to determine the statistical significance of this comparison. Adverse effects were very common and did not statistically significantly differ among treatment

groups (overall rate, 74%; range among groups, 68% to 81%). Serious adverse effects were uncommon (overall rate, 11%; range, 6% to 14%), and the rate of withdrawals due to adverse events was 11%. The most commonly reported adverse effect was headache (overall rate, 20%; range, 16% to 25%).

In 1 study with quality-of-life outcomes, Fogari and colleagues followed 160 married men 40 to 49 years of age with newly diagnosed hypertension (diastolic blood pressure of 95 to 110 mm Hg) who had never been treated for hypertension and had no symptoms of sexual dysfunction (8). One hundred twenty men were randomly assigned to receive an angiotensin II receptor antagonist (valsartan) or a β-blocker (carvedilol) for 16 weeks, and, after a placebo washout period, were crossed over to the alternative regimen for another 16 weeks; 40 men were randomly assigned to receive placebo. Results indicated that carvedilol caused a decline in sexual function (the rate of sexual intercourse decreased by 50%, and 13.5% of patients experienced sexual dysfunction). Valsartan produced a temporary and non–statistically significant decline in sexual function, and function improved with ongoing treatment: By 16 weeks, the rate of sexual intercourse had increased by 19%. The 2 drugs did not differ in control of blood pressure.

The other study with quality-of-life outcomes evaluated symptom distress associated with a calcium-channel blocker (amlodipine) and an aldosterone receptor antagonist (eplerenone) (9). A total of 269 men and women 50 years of age or older with untreated seated systolic blood pressure of 140 to 190 mm Hg were randomly assigned to receive one of the study drugs after a placebo run-in period. On average, participants were approximately 68 years of age, and 89% were white. Participants were followed for 24 weeks; quality-of-life measures were collected at randomization, 14 weeks, and 24 weeks. At 24 weeks, the groups did not statistically significantly differ in blood pressure control or scores on the Short Form-36 Health Survey. However, there was a statistically significant difference among treatment groups on a summary measure of symptom distress in favor of eplerenone ($P = 0.03$). The amlodipine group experienced symptoms commonly associated with the drug, including ankle swelling, headache, facial flushing, and constipation. Twenty-five percent of amlodipine recipients and 5% of eplerenone recipients experienced edema. Other adverse events were hyperkalemia in 2 eplerenone recipients and 1 amlodipine recipient, and hypokalemia in 2 amlodipine recipients. Erectile dysfunction was reported by 2 of 61 eplerenone recipients and no amlodipine recipients.

Conclusion

In summary, there is no new evidence on the benefits of screening for high blood pressure. New evidence on the harms of treatment of early hypertension shows that pharmacologic therapy is associated with common side effects; serious adverse events are uncommon.

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Table: Studies included on harms of early treatment of high blood pressure.*

Author, Year	Study Objective	Sample Characteristics	Inclusion Criteria	Design	Study Groups	Comparison of Groups and Withdrawals	Main Results	Adverse Events	Summary
Fogari et al, 2001 (8)	To evaluate the effects of valsartan and carvedilol on sexual function in men	N = 160 Age = 40-49 y All married	Newly diagnosed hypertension Men never treated for hypertension DBP ≥ 95 < 110 mm Hg No sexual dysfunction	RCT	120 patients received carvedilol or valsartan for 16 wk, followed by 4 wk of placebo; they then "crossed over" to alternative regimen for another 16 wk 40 patients received only placebo	6 patients were lost to follow-up: 2 had hypotension, and 4 in placebo group had hypertension ≥ 110 mm HG	Mean number of intercourse episodes: At 4 wk: reduced by 43% with carvedilol and by 20% with valsartan ($p < 0.05$) At 16 wk: reduced by 50% with carvedilol but increased by 19% with valsartan	Erectile dysfunction: 15 patients (13.5%) receiving carvedilol 1 patient receiving valsartan and 1 receiving placebo ($P < 0.001$)	Carvedilol produced a decline in sexual function (decreased frequency of sexual activity and increased number of patients who had sexual dysfunction). Valsartan produced a temporary, non-significant decline in sexual function and improved function with ongoing treatment. The drugs did not differ in terms of blood pressure control.
Hollenberg et al, 2003 (9)	To evaluate symptom distress associated with eplerenone compared with amlodipine	N = 269 Mean age: 67 y - eplerenone group 69 y - amlodipine group White: 89%	Age > 50 y Men & women Untreated SBP 140-190 mm Hg	Randomized Trial	134 patients received eplerenone 135 patients received amlodipine Patients were followed for 24 wk QOL measures at 14 and 24 weeks were: SF-36 Health Survey (8 aspects of health-related QOL†); Symptom Distress Index (73 items); Cantril's Ladder (0-10 ladder grade of QOL)	Groups did not differ in age, sex, ethnicity, employment, initial QOL, or baseline BP. Dropout rates did not differ by group but were higher for amlodipine (30 patients [25%]) than eplerenone (19 patients [16%]).	Average decrease in Symptoms Distress Index score with amlodipine and increase in score for eplerenone ($P = 0.03$); 36 of 73 symptoms favored eplerenone, and 1 favored amlodipine. No significant differences in SF-36 Health Survey results Amlodipine was	No eplerenone side effects related to an action on steroid receptors No cases of gynecomastia, tender breasts, or menstrual irregularities Edema: 25% with amlodipine versus 5% with eplerenone	Amlodipine was associated with annoying but not life threatening side effects.

Author, Year	Study Objective	Sample Characteristics	Inclusion Criteria	Design	Study Groups	Comparison of Groups and Withdrawals	Main Results	Adverse Events	Summary
							significantly associated with ankle swelling, headache, facial flushing, constipation, and pronounced heartbeat. Both drugs decreased systolic BP; amlodipine significantly decreased diastolic BP.		
White et al, 2004 (5)	To determine whether extended-release diltiazem at bedtime is superior to ramipril at bedtime for the control of early morning BP	N=261 Men: 61% Mean age: 54 y White: 93%	DBP 90-110 mm Hg during run-in placebo period Patients with history of CAD, stroke, CHF, secondary hypertension, cardiac conduction abnormalities, poorly controlled DM, malabsorption, or CRF were excluded.	Multicenter randomized trial in the US and Canada	Extended-release diltiazem, 240, 360, or 540 mg at bedtime Ramipril, 5, 10, or 20 mg at bedtime 2 week pre-study washout of hypertension medications, 3- to 4-week placebo run-in, then 10 wk of treatment	90% of diltiazem recipients and 92% of ramipril recipients completed the study. AEs were the most common reason for dropping out.	Extended-release diltiazem reduced early morning BP to a greater extent than ramipril (-18/-15 mm Hg vs. -13/-8 mm Hg) ($p < 0.001$).	≥1 AE occurred in 50% of diltiazem recipients and 40% of ramipril recipients. No deaths <u>Withdrawals:</u> 3 patients with serious AE: 1 during placebo run-in, 1 in diltiazem group (facial/peripheral edema), 1 in ramipril group (severe UTI) Most common reason for withdrawal: leg edema with diltiazem (3%) cough with ramipril (2%) <u>Other AEs:</u> <u>Ramipril:</u> cough (8%), HA (12%), Lower-extremity edema (2%) <u>Diltiazem:</u> Cough (0.8%), HA	AEs were very common (40-50% of patients) with both drugs. Serious AEs were uncommon (2%-3%) and 2 of the 3 reported were probably not related to the drug.

Author, Year	Study Objective	Sample Characteristics	Inclusion Criteria	Design	Study Groups	Comparison of Groups and Withdrawals	Main Results	Adverse Events	Summary
								(5%), lower extremity edema (13%)	
Julius et al, 2006 (6)	To examine whether treatment of prehypertension with candesartan prevents or postpones stage 1 hypertension	N = 809 Mean age: 48 y Men: 59-60% White: 80%-84% Mean BMI: 30 kg/m^2	Age 30-65 y Not receiving treatment for hypertension Average BP: SBP = 130-139 mm Hg DBP = ≤ 89 mm HG	Multicenter double-blind RCT in the United States	1) Placebo for 4 y 2) Candesartan, 16 mg, for 2 y, then placebo for 2 y 3-wk run-in period If hypertension developed, patients were given metoprolol or hydrochlorothiazide		Candesartan significantly decreased risk for hypertension at the end of 4 y (relative risk, 0.84)	<u>Serious AEs:</u> 3.5% of candesartan recipients, 5.9% of placebo recipients <u>Other AEs:</u> 89% of candesartan recipients, 88.5% of placebo recipients <u>AEs with higher rate in candesartan vs. placebo:</u> Headache: 21.5% URI: 14.4% Nasopharyngitis: 10% Dizziness: 10% Fatigue: 8.1% Pain in extremity: 7.6% Insomnia: 5.6% Anxiety: 5.6% Hypotension: 1% Syncope: 0.5%	AEs were very common: about 89% of participants. Serious advents are uncommon: 3.5% of candesartan recipients.
Ebbs, 2001 (7)	To determine whether ambulatory BP monitoring can assess the effectiveness of selected antihypertensives in maintaining 24-hour BP control	N = 204 Men: 43-48% Mean age: 54-58 y White: 99% Mean BP: Mean SBP, 152-161 mm Hg Mean DBP, 97-100 mm Hg	DBP 95-110 mm Hg Patients with treatment for hypertension, symptomatic CVD, end-organ damage, secondary or malignant hypertension, intolerance of study medications, hypercholesterolemia, Type I DM, renal impairment, or pregnancy were excluded	Multicenter randomized trial in the United Kingdom	1) Doxazosin, 1, 2, or 4 mg 2) Amlodipine, 5 or 10 mg 3) Enalapril, 5, 10, or 20 mg 4) Bendrofluazide, 2.5 or 5 mg 8 wk placebo run-in period Treatment for up to 14 wk and titrated to achieve BP control and then treatment for another 8 wk		24-h ambulatory SBP and DBP decreased in all groups; no significant differences among groups.	74% of participants reported an AE. Withdrawals: 11% overall due to an AE Most common AE: headache (20%)	AEs were very common (74%); the most common AE was headache. Serious AEs were uncommon (11%).

*Abbreviations: AE = adverse effects; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CRF = chronic renal failure; CVD = cardiovascular disease; DBP = diastolic blood pressure; DM = diabetes mellitus; HA = headache; QOL = quality of life; RCT = randomized controlled trial; SBP = systolic blood pressure; SF-36 = Short Form-36; URI = Upper respiratory infection; UTI = urinary tract infection.

†The 8 aspects of health-related QOL are: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.