

Hypertension Clinical Practice Guideline

This guideline is informational only. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient's needs on an individual basis.

Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.

**Approved by the
National Guideline Directors
May 2009**

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Introduction

Kaiser Permanente's National Guideline Program

The National Guideline Program (NGP) supports the development of a core set of explicit, scientifically-based clinical practice guidelines, practice resources, and evidence synopses to assist Kaiser Permanente (KP) physicians, administrators, and other health care professionals in determining the most effective medical practices.

This core set of evidence-based resources will:

- ♦ Create Programwide economies of scale,
- ♦ Support ongoing performance improvement activities,
- ♦ Consistently provide high quality resources for use in care delivery tools and systems, and
- ♦ Increase KP regions' abilities to leverage clinical guidelines to improve clinical outcomes.

Clinical practice guidance, based on scientific evidence, is essential for providing high quality care and continuously improving on it. Such guidance needs to be integrated into the electronic medical record and other decision support tools to be accessible to clinicians at the point of care. In addition, engaging our members in collaborative, shared decision-making conversations regarding their personal preferences is an essential component of patient-centered quality care. Furthermore, cost-effectiveness of various evidence-based interventions and resource limitations are important considerations. This involves addressing health problems in ways that maximize the health of the population given the available resources.

Who are the National Guideline Directors'?

The National Guideline Directors (NGD) are a group of experts and advocates of evidence-based medicine who provide direction and oversight to the National Guideline Program (NGP). In this role, the NGD selects and approves topics for evidence-based knowledge products, owns Kaiser Permanente's Common Methodology, and is responsible for quality assurance review. This group is composed of representatives from the Care Management Institute (CMI) and all eight regions.

What Is the Guideline Quality Committee?

The Guideline Quality (GQ) Committee is a subcommittee of the NGD consisting of a group of evidence experts from various KP regions and CMI who review and approve all the National Guidelines. This review ensures that the processes used to develop guideline content have adhered to KP evidence-based methods and that the labels applied to clinical recommendations therein are accurate (e.g., "evidence-based" or "consensus-based").

How Are Guidelines Developed?

Guidelines are developed with the use of an “evidence-based methodology” and involve a systematic literature search, critical appraisal of the research design and statistical results of relevant studies, and grading of the sufficiency (quantity, quality, consistency, and relevancy) of the evidence for drawing conclusions. An evidence search includes literature published in peer-reviewed scientific journals, existing evidence-based guidelines, consensus-based statements from external professional societies and government health organizations, and clinical expert opinion of KP regional specialty groups. For additional information on evidence grading, see Table 1 in Appendix A.

To develop a or revise a guideline, CMI consultants work with a multidisciplinary Guideline Development Team (GDT). Each GDT consists of a core group of physicians, representing primary care and the specialties most affected by the guideline topic, and, as appropriate, other content experts from disciplines such as pharmacy, nursing, and health education. The members of a GDT are nominated by the respective National Guideline Directors to represent their regions. The GDT reviews the appraisal of the evidence and develops or revises clinical recommendations based on the current evidence. Each regional representative then presents the draft guideline recommendations to key experts and champions in their regions for critical review and support to improve the likelihood of implementation once the guideline is published.

How Often Are Guidelines Reviewed and Revised?

To keep current with changing medical practices, all guidelines are reviewed, and, if appropriate, revised at least every two years. To develop the Hypertension Clinical Practice Guideline, released in May 2009, a multidisciplinary, interregional GDT first met in March 2009 to define the scope of the guideline. The Project Management Team then performed systematic reviews of the medical literature on each of the clinical questions identified by the GDT, assembled the evidence, and developed draft recommendations for review by the GDT. All of the recommendations and supporting evidence were reviewed in depth by the GDT in a series of conference calls from March through April 2009. The National Guideline Directors’ Guideline Quality Committee reviewed and approved the guidelines in May 2009.

Additionally, a update to recommendation 9 (Discrete Populations – Women of Childbearing Potential) was approved in October 2009.

What Does It Mean for a Guideline to Be Evidence-Based?

Each clinical recommendation within a guideline is labeled as “evidence-based” or “consensus-based.” A recommendation is considered “evidence-based” if there has been a systematic review of the evidence, the evidence is sufficient, and the recommendation is consistent with the evidence. A recommendation can also be considered “evidence-based” if there is insufficient evidence but either no particular intervention is recommended or options are recommended without favoring one of the options over others. A recommendation is considered “consensus-based” if there has been a systematic review of the evidence, the evidence is insufficient to support an evidence-based recommendation, and the GDT decides to make a consensus recommendation.

What Does It Mean for a Guideline to Be Approved and National?

A recommendation that is consistent with the above policies is labeled as "National Guideline Directors Approved." A recommendation that fails to satisfy those criteria is not approved and will be noted as such. A National Guideline Directors Approved guideline for which at least 90% of the recommendations are approved by at least six of the eight KP regions is a "National Guideline." On the topics for which they exist, National Guidelines are the preferred evidence source for KP HealthConnect content.

Contact information:

Hypertension Clinical Lead
KP Southern California
E-mail: Joel.Handler@kp.org

Mary Choi, MPH
Hypertension Project Manager
Care Management Institute
E-mail: mary.choi@kp.org

Acknowledgments

The Kaiser Permanente (KP) Hypertension Clinical Practice Guideline is the result of the extensive clinical expertise, collaborative efforts, and outstanding personal contributions of the following participants:

KP Hypertension Guideline Project Management Team

Joel Handler, MD	Clinical Lead	Care Management Institute
Mary Choi, MPH	Project Manager	Care Management Institute
Joel Whittaker, MPH*	Lead Analyst	KP-Southern California
Qiana Butler, MPH	Analyst	KP-Southern California
Jill Haynes, MPH*	PM and Analyst	Care Management Institute
Wiley Chan, MD	EBM Methodologist	Care Management Institute
Tabitha Pousson	Staff Assistant	Care Management Institute

The following GDT members declared a Conflict of Interest:

Joel Handler, MD – KP Southern California

Served on JNC8 expert panel.

Wiley Chan, MD – KP Northwest

Served on JNC8 expert panel.

Steven Hong, MD – KP Hawaii Served on the State of Hawaii Medicaid Formulary Committee.

* Participated only in the October 2009 update to recommendation 9
(Discrete Populations – Women of Childbearing Potential).

KP Hypertension Guideline Development Team

[Everyone participated in both the 2009 review and the October 2009 update to recommendation 9 (Discrete Populations – Women of Childbearing Potential) unless otherwise noted.]

Colorado	Jonathan A Albert, MD	Physician Lead for Hypertension Task Force
	Erin M Herrera, PharmD	Clinical Pharmacy Specialist in Primary Care
	Jane Kerzee, PharmD	Clinical Pharmacy Supervisor
	Stephanie Schneider, RN	Prevention Specialist II
Georgia	Jeff Goforth, PharmD	Ambulatory Care Clinical Pharmacy Specialist
	James Hipkens, MD	Associate Chief Ambulatory Medicine Region
	John Kaschko, MD	Clinical Informatics
Group Health Cooperative	Dave McCulloch, MD	Medical Director of Clinical Improvement
Hawaii	Steven Hong, MD	Staff Internist
	Ross T Takara, PharmD	Pharmacy
Mid-Atlantic States	John Golden, MD	Clinical Lead for Coronary Artery Disease
	Sherry Weinstein Mayer, MD	Chief, Internal Medicine & Medical Specialties
Northern California	Thomas Downs, MD	Perinatologist
	David Gee, MD	Cardiology
	Marc Jaffe, MD	Endocrinology
	William Muldowney, MD	Nephrology
	Svasti Patel, MD	Internal Medicine
	Linda K Simmons, RD, MS	TPMG Guidelines Project Manager
	Anthony Steimle, MD	Clinical Lead for Heart Failure
	Joseph D Young, MD	TPMG Clinical Lead for Hypertension
Northwest	Donna R Erbs, MPH	Project Manager/Implementation
	Christine Legler, PA-C, DHSc	Family Practice
Ohio	Kathleen Byrne, RN	Implementation and Outreach Coordinator
	Mark Roth, MD	Internist
	William S Schwab, MD	Chief of Geriatrics
Southern California	Gary Besinque, PharmD	Pharmacist
	Jim Dudl, MD	Clinical Lead for Diabetes
Care Management Institute	Andrew Bertagnoli, PhD*	Senior Consultant - Behavioral Medicine & Pain Management
	Craig Robbins, MD, MPH*	Physician Lead, National Guideline Program
	Ruth Shaber, MD*	OB/GYN
	Gladys Tom, MS*	Senior Manager, Knowledge Services

* Participated only in the October 2009 update to recommendation 9 (Discrete Populations – Women of Childbearing Potential).

Guideline Summary

This guideline is informational only. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient's needs on an individual basis.

Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.

Assessment of the Importance of Hypertension Control in KP*

Controlling hypertension is a very effective way of decreasing the incidence of strokes (CVAs) and myocardial infarctions (MIs) in Kaiser Permanente (KP). This is reflected in the numbers needed to treat (NNTs) of **63 for CVAs and 86 for MIs**, for all adults. The **NNT is 36** for the combined end-point of CVA plus MI for all adults.

A 2% improvement in identification, and a 5% improvement in initiation of treatment and maintenance of long term control of the Northern California (NCal) and Southern California (SCal) KP adult members with high blood pressure (hypertension) **can prevent 1324 strokes (CVAs) and 970 myocardial infarctions (MIs)** over the next 5 years. Improving control by 5% in the **other KP Regions prevents another 437 CVAs and 320 MIs**.

Definition of Hypertension

The Hypertension Guidelines Project Management Team used the definition of hypertension to be a blood pressure at or above 140 / 90 mm Hg. The guidelines pertain to uncomplicated hypertension, which is defined as hypertension in nonpregnant adults who do not have diabetes, heart failure, renal insufficiency, or known coronary heart disease.

The JNC7 Report defines blood pressure as:	Systolic Blood Pressure (SBP) mm Hg	Diastolic Blood Pressure (DBP) mm Hg
Normal	< 120	< 80
Prehypertension	120 – 139	80 – 89
Stage 1 hypertension	140 – 159	90 – 99
Stage 2 hypertension	≥ 160	≥ 100

* See Appendix C for the full analysis.

1. Screening for Hypertension

Who to Screen for Hypertension

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians screen adults aged 18 and older for hypertension. *Evidence-based: A*

How Often to Screen for Hypertension

Blood pressure screening every two years is recommended. *Consensus-based*

2. Treatment of Hypertension

When to Begin Pharmacotherapy for Hypertension

In addition to lifestyle interventions, the following are recommended:

- 2A If an individual has blood pressure of 140 to 159 mm Hg systolic, OR 90 to 99 mm Hg diastolic (Stage 1), and does not have target organ damage or diabetes mellitus, then:
 - 2A1 If there is documentation of elevated blood pressure (≥ 140 mm Hg systolic, OR ≥ 90 mm Hg diastolic) for ≥ 2 to 3 months prior to the current measurement, then initiate pharmacotherapy. *Consensus-based*
 - 2A2 If this is the first elevated measurement, wait approximately ≥ 2 to 3 months. After ≥ 2 to 3 months, if blood pressure is ≥ 140 mm Hg systolic, OR ≥ 90 mm Hg diastolic, then initiate pharmacotherapy. *Consensus-based*
- 2B If an individual has blood pressure of 160 to 179 mm Hg systolic, OR 100 to 109 mm Hg diastolic (Stage 2), and does not have target organ damage or diabetes mellitus, then:
 - 2B1 If there is documentation of elevated blood pressure (≥ 140 mm Hg systolic, OR ≥ 90 mm Hg diastolic) for one or more months prior to the current measurement, then initiate pharmacotherapy. *Consensus-based*
 - 2B2 If this is the first elevated measurement, wait approximately one month. After one month, if blood pressure is ≥ 140 mm Hg systolic, OR ≥ 90 mm Hg diastolic, then initiate pharmacotherapy. *Consensus-based*
- 2C If an individual has blood pressure ≥ 180 mm Hg systolic, OR ≥ 110 mm Hg diastolic then initiate pharmacotherapy. *Consensus-based*

3. Appropriate Office-Based Target Blood Pressure*

- 3A When treating an individual with hypertension, the target office blood pressure is $\leq 139 / \leq 89$ mm Hg. *Consensus-based*
- 3B When treating an individual with a prior diagnosis of stroke (excluding subarachnoid hemorrhage, subdural hematoma, and post-traumatic stroke), the target office blood pressure is $\leq 129 / \leq 79$ mm Hg for hypertension and $\leq 119 / \leq 79$ mm Hg for prehypertension. *Consensus-based*

4. Home Blood Pressure Monitoring for Diagnosis and Management

- 4A It is recommended that the diagnosis of hypertension be established in the medical office. *Consensus-based*
- 4B Home self-measurement of blood pressure is recommended to:
 - 4B1 Identify a low-risk subpopulation of individuals with “white coat hypertension,” “without target organ disease or diabetes, for whom medication may not be necessary. These individuals have home blood pressure levels $\leq 134 / 84$ mm Hg but have office blood pressure levels $\geq 140 / \geq 90$ mm Hg. *Consensus-based*
 - 4B2 Attain control in patients with uncontrolled hypertension ($>135/85$ mm Hg by home monitoring) according to drug treatment algorithms, and by using telephone/e-mail/fax or other electronic patient communications in conjunction with standard provider-based clinic visits. *Consensus-based*
 - 4B3 Monitor controlled hypertension over time. *Consensus-based*
- 4C The following quality standards are recommended for home self-measurement of blood pressure:
 - 4C1 Only devices with documented yearly validation within 5 mm Hg systolic and 5 mm Hg diastolic of a blood pressure measure by a nurse, physician, or trained observer are acceptable, preferably those devices approved by Association for the Advancement of Medical Instrumentation, British Hypertension Society, or European Hypertension Society. *Consensus-based*
 - 4C2 Devices with visual or printout memory or using telemonitoring are preferred. *Consensus-based*
 - 4C3 Eligible patients should have observation of blood pressure competency, with particular attention to miscuffing and common pitfalls of technique during yearly validation. Only brachial pressures are acceptable. *Consensus-based*
 - 4C4 A minimum of six home blood pressures should be used, half of which were obtained in the morning. *Consensus-based*

* In nonpregnant adults who do not have diabetes, heart failure, chronic kidney disease, or known coronary heart disease.

- 4C5 Control by home blood pressure monitoring is defined as a mean of $\leq 134 / 84$ mm Hg. *Consensus-based*
- 4C6 Since no home blood pressure equivalency for an office blood pressure of $< 129 / 79$ mm Hg has been demonstrated in the literature, home blood pressure should not be used exclusively as a surrogate in the care of patients with diabetes or chronic kidney disease with a targeted office blood pressure $\leq 129 / 79$ mm Hg. *Consensus-based*

5. First-Line Treatment of Hypertension

Thiazide diuretics (either as a single agent or in combination) are strongly recommended as first-line agents for initial therapy in people with hypertension.
Evidence-based: A

6. Initial Combination Treatment of Hypertension*

- 6A Combination therapy consisting of a thiazide diuretic plus an ACEI is an option for initial therapy for Stage 1 hypertension (systolic blood pressure 140 to 159 mm Hg, OR diastolic blood pressure 90 to 99 mm Hg). *Consensus-based*
- 6B Combination therapy of a thiazide diuretic plus an ACEI is recommended for Stage 2 hypertension (systolic blood pressure > 160 mm Hg, OR diastolic blood pressure > 100 mm Hg). *Consensus-based*

7. Step-Care Therapy for Hypertension

Because most people with hypertension will need more than one drug to control their hypertension effectively:

- 7A **For two drugs:**
If blood pressure is not controlled on a thiazide-type diuretic alone, then a thiazide-type diuretic + ACEI is recommended. *Consensus-based*
- 7B **For three drugs:**
If blood pressure is not controlled on a thiazide-type diuretic + ACEI, then a thiazide-type diuretic + ACEI + dihydropyridine calcium channel blocker is recommended. *Consensus-based*
- 7C **For four drugs:**
If blood pressure is not controlled on a thiazide-type diuretic + ACEI + dihydropyridine calcium channel blocker alone, then a thiazide-type diuretic + ACEI + dihydropyridine calcium channel blocker + a beta-blocker or spironolactone is recommended. *Consensus-based*

* In nonpregnant adults who do not have diabetes, heart failure, chronic kidney disease, or known coronary heart disease.

8. Discrete Populations – Hypertension Treatment for Women of Childbearing Potential

- 8A ACEIs are not recommended for women of childbearing potential. *Consensus-based*
- 8B To treat chronic hypertension in women of child bearing potential:
- ◆ Thiazide diuretics are the first choice.
 - ◆ CCBs are the second choice.
 - ◆ BBs are the third choice.

Consensus-based

- 8C When pregnancy occurs, women receiving antihypertensive therapy should be referred to OB/GYN for hypertension management. *Consensus-based*

9. Discrete Populations – Post-Stroke Treatment of Hypertension

Combination therapy with a thiazide diuretic plus an ACE inhibitor is recommended as initial treatment for patients who are post-stroke, or post-TIA* with hypertension or prehypertension. *Evidence-based: B*

10. Behavioral Change – Supplementary Treatment of Uncomplicated Hypertension with Lifestyle Modifications

- 10A A moderately low-sodium, low-fat diet with a high intake of fruits and vegetables (DASH diet) is recommended to supplement pharmacotherapy for patients with hypertension. *Consensus-based*
- 10B Weight reduction is recommended for patients with a BMI $\geq 25 \text{ kg/m}^2$ on antihypertensive medications. *Consensus-based*
- 10C It is recommended that hypertension patients who consume alcohol have no more than one alcoholic drink (for women) or two alcoholic drinks (for men) daily.
Consensus-based
- 10D Physical activity (at least 30 minutes of walking or equivalent at least three times per week) is recommended for patients with hypertension who are on medications.
Consensus-based

* Transient ischemic attack (TIA) is defined as evidence of an acute disturbance of focal neurological or monocular function with symptoms lasting less than 24 hours thought to be due to arterioembolic or thrombotic vascular disease.

11. Behavioral Change – Adherence to Medications and Lifestyle Modifications

The following are recommended:

- 11A Assist patients to achieve medication and lifestyle adherence by means of a vigorous step-care approach to therapy and an organized system of regular medical follow-up and review. *Evidence-based: B*
- 11B Once-daily medication and combination therapy whenever possible. *Evidence-based: B*
- 11C Address issues of depression and anxiety issues in order to maximize patient adherence. See Depression Guidelines at:
<http://cl.kp.org/pkc/national/cmi/programs/depression/guideline/index.html>
Consensus-based
- 11D Use patient education in conjunction with other strategies, particularly in the context of team care utilizing nurses and pharmacists. *Evidence-based: B*
- 11E Educate patients about their goal pressure because patients who are knowledgeable about their goal blood pressure are more likely to achieve it. *Consensus-based*

12. Use of Aspirin in Hypertensive Patients Receiving Antihypertensive Medications

For primary CVD prophylaxis and in the absence of known CAD, stroke or diabetes mellitus:

- 12A When the CHD risk is high,^{*} low-dose aspirin (81 mg daily) is recommended. A shared decision-making approach, with a review of the benefits and harms, is recommended. *Evidence-based: B*
- 12B For individuals with an intermediate risk^{*} of CHD, low-dose aspirin (81 mg daily) is an option. Use of aspirin should be based on a shared decision-making approach and on each individual's benefit/risk[†] status. *Evidence-based: C*
- 12C When the CHD risk is low,^{*} aspirin is not recommended. For low-risk patients who are already taking aspirin, or who express a desire to begin taking it, a shared decision-making approach, with a review of the benefits and harms, is recommended. *Evidence-based: D*
- 12D Aspirin is not recommended for patients with uncontrolled hypertension. *Evidence-based: D*

* A validated risk calculator such as Framingham should be applied. Using the ATP III Framingham 10-year Hard CHD risk calculator (1, 2): low risk is < 10%, intermediate risk is 10 to 20%, and high risk is > 20%. Using the SCAL/NW Dyslipidemia Guideline CAD Risk Tables (based on Framingham 1991) 10-year Total CHD risk calculator: low risk is < 12.5%, intermediate risk is 12.5 to 25%, and high risk is > 25%.

¹ National Heart Lung and Blood Institute's ATP III Framingham CHD risk calculator-
<http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof>

² 1991 Framingham Risk Calculator based on Anderson KM, et al. An Updated Coronary Risk Profile: A Statement for Health Professionals. Circulation 1991; 83(1): 356-362. KP Northwest link :
<http://internal.or.kp.org/cpg/support/cholest.html>

[†] The benefit for men is primarily reduction in nonfatal MI and the benefit for women is stroke reduction. Low-dose aspirin increases the risk of GI bleeding and hemorrhagic stroke, and the risk of hemorrhagic stroke may increase with uncontrolled hypertension, particularly Stage 2 hypertension. NNTs to prevent one adverse CV outcome vs. NNHs (usually a GI bleed requiring transfusion) for men and women on low-dose aspirin for primary CV prophylaxis for 6.4 years are: women NNT = 333 and NNH = 400; men: NNT = 270 and NNH = 303.

13. Use of Antilipemic Therapy in Hypertensive Patients Taking Antihypertensive Medications

- 13A No recommendation for or against the use of antilipemic therapy in hypertensive patients in the absence of other significant risk factors. *Evidence-based: I*
- 13B Patients with hypertension should be treated for hyperlipidemia according to their total cardiovascular risk profile. (Refer to the KP Dyslipidemia Management in Adults guideline on the KP Clinical Library Web site at <http://cl.kp.org/pkc/scal/cpg/cpg/html/Dyslipid.html>) *Consensus-based*

Rationale Statements

Screening for Hypertension

Who to Screen for Hypertension

- 1 The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians screen adults aged 18 and older for hypertension. *Evidence-based: A*

How Often to Screen for Hypertension

- 2 Blood pressure screening every two years is recommended. *Consensus-based*

Rationale:

Evidence Grade*

Evidence for Recommendation 1: Good.

Evidence for Recommendation 2: Insufficient.

2009 Update:

No new evidence has been identified. Recommendations remain unchanged.

Search Strategy

For Evidence Search and Evidence Summary see USPSTF as of July, 2003.

For most recent search see(<http://www.ahrq.gov/clinic/uspstf/uspshype.htm>). See Appendix B for more information.

2007 Guideline:

Neither the USPSTF nor the KP Hypertension Guideline Development Team (GDT) have found that the interval publications would lead to a change in the recommendations.

The USPSTF⁽¹⁾ found good evidence that blood pressure measurement can identify adults who are at an increased risk for cardiovascular disease due to hypertension, and good evidence that treatment of hypertension substantially decreases the incidence of cardiovascular disease and causes few major harms. The USPSTF concludes the benefits of screening for, and treating, hypertension in adults substantially outweigh the harms and costs.

There is insufficient evidence regarding the interval for screening for hypertension.

The screening interval was chosen by consensus from the various KP Regional Hypertension Guidelines and the USPSTF guideline as of July, 2003.

Source: <http://www.ahrq.gov/clinic/uspstf/uspshype.htm>

* The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

14. Treatment of Hypertension

When to Begin Pharmacotherapy for Hypertension

In addition to lifestyle interventions, the following are recommended:

- 3A If an individual has blood pressure of 140 to 159 mm Hg systolic, OR 90 to 99 mm Hg diastolic (Stage 1), and does not have target organ damage or diabetes mellitus, then:
 - 3A1 If there is documentation of elevated blood pressure (≥ 140 mm Hg systolic, OR ≥ 90 mm Hg diastolic) for ≥ 2 to 3 months prior to the current measurement, then initiate pharmacotherapy. *Consensus-based*
 - 3A2 If this is the first elevated measurement, wait approximately ≥ 2 to 3 months. After ≥ 2 to 3 months, if blood pressure is ≥ 140 mm Hg systolic, OR ≥ 90 mm Hg diastolic, then initiate pharmacotherapy. *Consensus-based*
- 3B If an individual has blood pressure of 160 to 179 mm Hg systolic, OR 100 to 109 mm Hg diastolic (Stage 2), and does not have target organ damage or diabetes mellitus, then:
 - 3B1 If there is documentation of elevated blood pressure (≥ 140 mm Hg systolic, OR ≥ 90 mm Hg diastolic) for one or more months prior to the current measurement, then initiate pharmacotherapy. *Consensus-based*
 - 3B2 If this is the first elevated measurement, wait approximately one month. After one month, if blood pressure is ≥ 140 mm Hg systolic, OR ≥ 90 mm Hg diastolic, then initiate pharmacotherapy. *Consensus-based*
- 3C If an individual has blood pressure ≥ 180 mm Hg systolic, OR ≥ 110 mm Hg diastolic then initiate pharmacotherapy. *Consensus-based*

Rationale:

Evidence Grade*

Evidence for Recommendation 3: Insufficient

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension were included. Selection was limited to studies that randomized participants to head-to-head trials using a step-care approach consisting of various antihypertensive agents. See Appendix B for more information.

2009 Update:

No new evidence has been identified. Recommendations remain unchanged.

* The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

2007 Guideline

When To Begin Therapy for Hypertension

The search of the peer-reviewed medical literature identified no new evidence that evaluated when to begin pharmacotherapy for hypertension. The GDT clarified the existing recommendations for a two- to three-month waiting interval after an initial measurement of hypertension in a consensus-based process.

One RCT analyzed the relation between time of medication initiation and cardiovascular outcomes. In an extension to the Syst-Eur study,⁽²⁾ which ended early due to the success of active treatment, trial medications were given both to participants who had received placebo and to those who had received active treatment in the first, double-blind segment of the trial. All 4,695 participants had systolic hypertension. Immediate versus delayed (median of two years) active treatment resulted in a 28% reduction in stroke ($p = 0.01$) and in a 15% decrease in cardiovascular complications ($p = 0.03$).

The GDT has used the evidence- and consensus-based document, JNC7,⁽³⁾ for guidance in developing this guideline.

All hypertensive individuals should initiate lifestyle modifications upon receiving their diagnosis (unless no change is needed). Although they may begin pharmacotherapy at the same time, the benefits they will experience from losing weight, increasing physical activity, quitting smoking, and improving diet may reduce the need for medication.

By recommending a pause of one or two months before initiating pharmacotherapy, the benefits from lifestyle alterations may, in some cases, reduce blood pressure in that short period of time. However, there is scant evidence in the literature regarding unmedicated hypertensive individuals who receive short-term interventions. Most studies are too small to be used, and meta-analyses usually cannot be used as they combine a mix of populations. The following studies met our criteria of being at least moderately sized and having a one- to three-month intervention in individuals who were not on medication.

Weight Loss: No studies were found that met the criteria.

Reduced Sodium and/or other Dietary Changes: He⁽⁴⁾ conducted a meta-analysis on the effect of mild salt reduction on blood pressure ($n = 734$). Fifteen of the 18 hypertension studies included were of four to eight weeks' duration. (The other three were from 12 weeks to 12 months long.) Reduction in blood pressure was -4.96 ± 0.40 mm Hg ($p < 0.001$, 95% CI: -5.75 to -4.17 mm Hg) for systolic and -2.73 ± 0.24 mm Hg ($p < 0.001$, 95% CI: -3.21 to -2.25 mm Hg) for diastolic blood pressure.

Increase in Physical Activity: In Whelton's⁽⁵⁾ meta-analysis, only five of 54 trials were known to include unmedicated hypertensive patients, and these trials included a total of 134 participants. Only two trials ($n = 26$) showed significant reduction in systolic blood pressure (~ -10 mm Hg and ~ -16 mm Hg), two showed a nonsignificant reduction, and one showed a nonsignificant increase. Three trials ($n = 53$) showed significant reduction in diastolic blood pressure (~ -9 mm Hg, ~ -10.5 mm Hg, and ~ -10 mm Hg), one showed a nonsignificant reduction, and one did not measure diastolic blood pressure. Study duration ranged from four to 16 weeks.

Seals⁽⁶⁾ studied 35 postmenopausal women with systolic blood pressure of 130 to 159 mm Hg. The exercise intervention took place for 13 weeks. Participants were asked to maintain their baseline weight. At rest measurements showed significant decreases in systolic blood pressure, $p < 0.05$, with a change from baseline of -6 mm Hg (random zero) or -4 mm Hg (Dinamap). Diastolic blood pressure decreased 2 mm Hg (random zero) or -4 mm Hg (Dinamap), $p < 0.05$.

Tsai⁽⁷⁾ studied 102 Taiwanese hypertensive participants aged 20 to 60 (mean age 47), who were greater than 120% of normal weight, in a ten-week exercise program. The reduction in blood pressure at the close of the intervention was -13.1/-6.3 mm Hg, $p < 0.001$, compared with baseline and with controls.

Reduction In Alcohol Intake: Ueshima⁽⁸⁾ studied 54 male drinkers with mild hypertension in an intervention of reduced drinking for three weeks. Subjects went from their usual mean intake of 56 ml/day to 26 ml/day, using a crossover design. There was a significant reduction in blood pressure in the alcohol reduction group compared with controls, i.e., a decrease of -2.6 to -4.8 mm Hg in systolic blood pressure, which was not significant during the first three-week period, $p < 0.05$ during period two; and a decrease of -2.2 to -3.0 mm Hg in diastolic blood pressure, $p < 0.05$ during period one, but not significant during the second period.

There is evidence that beginning a program of salt or alcohol restriction, changes in dietary components, and increased activity may reduce blood pressure. Significant reduction in blood pressure has been demonstrated to occur within three to 16 weeks in the trials cited above. However, it is unclear whether these short-term lifestyle changes can reduce the need for medications.

Determination of when to begin drug therapy and appropriate follow-up is also dependent on the presence or absence of diabetes, other CV risk factors listed in the table below, or target organ damage (TOD). TOD is defined as chronic kidney disease, stroke, transient ischemic attack, coronary artery disease, heart failure, peripheral vascular disease, or retinopathy.

For patients in the lowest risk category and with mild hypertension, a two- to three-month observation period, while lifestyle modifications are tried, is acceptable therapy.

Table 1. Cardiovascular Risk Factors (JNC7⁽³⁾)

Major Risk Factors:	Target Organ Damage:
Age > 65 F, > 55 M	Heart
Diabetes mellitus	Left ventricular hypertrophy
Elevated LDL (or total) cholesterol, or low HDL cholesterol	Angina/prior myocardial infarction
Estimated GFR < 60 ml/min	Prior coronary revascularization
Family history of premature CVD (< 65 F, < 55 M)	Heart failure
Microalbuminuria	Brain
Obesity (BMI ≥ 30 kg/m ²)	Stroke or transient ischemic attack
Physical inactivity	Dementia
Tobacco usage, particularly cigarettes	Chronic kidney disease
	Peripheral arterial disease
	Retinopathy

Guidelines for when to initiate pharmacotherapy for hypertension are summarized in table format below (from JNC7⁽³⁾).

Table 2. Recommendations for Follow-Up Based on Initial Blood Pressure Measurements for Adults Without Acute End Organ Damage⁽³⁾

Initial Blood Pressure, mm Hg*	Follow-up Recommended†
Normal	Recheck in two years
Prehypertension	Recheck in one year‡
Stage 1 hypertension	Confirm within two months‡
Stage 2 hypertension	Evaluate or refer to source of care within one month. For those with higher pressures (i.e., > 180 / 110 mm Hg), evaluate and treat immediately or within one week depending on the clinical situation and any complications.

* If systolic and diastolic categories are different, follow recommendations for shorter time follow-up (e.g., 160 / 86 mm Hg should be evaluated or referred to source of care within one month).

† Modify the scheduling of follow-up according to reliable information about past blood pressure measurements, other cardiovascular risk factors, or target organ disease.

‡ Provide advice about lifestyle modifications.

15. Appropriate Office-Based Target Blood Pressure*

- 4A When treating an individual with hypertension, the target office blood pressure is $\leq 139 / \leq 89$ mm Hg. *Consensus-based*
- 4B When treating an individual with a prior diagnosis of stroke (excluding subarachnoid hemorrhage, subdural hematoma, and post-traumatic stroke), the target office blood pressure is $\leq 129 / \leq 79$ mm Hg for hypertension and $\leq 119 / \leq 79$ mm Hg for prehypertension. *Consensus-based*

Rationale:

Evidence Grade[†]

Evidence for Recommendation 4: Insufficient

2009 Update:

No new evidence has been identified. Recommendations remain unchanged.

Search Strategy

The search of the peer-reviewed medical literature identified no new evidence that evaluated target blood pressure. Only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension were included. Selection was limited to studies that randomized participants to head-to-head trials using a step-care approach of various antihypertensive agents. See Appendix B for more information.

2007 Guideline:

Target Blood Pressure:

One study was found which compared the relationships between target blood pressure and cardiovascular endpoints. The Hypertension Optimal Treatment (HOT) trial⁽⁹⁾ was conducted to answer the question of which target blood pressure level led to the fewest adverse cardiovascular events. Eighteen thousand, seven hundred and ninety (18,790) individuals from 26 countries were enrolled and randomized to three groups: target diastolic blood pressure ≤ 90 mm Hg, target diastolic blood pressure ≤ 85 mm Hg, or target diastolic blood pressure ≤ 80 mm Hg. None of the relationships between the prevalence of outcomes (major CV events, major CV events including silent MI, all MI, all MI including silent cases, all stroke, CV mortality, or total mortality) and the target diastolic blood pressure levels attained were significant.

* In nonpregnant adults who do not have diabetes, heart failure, chronic kidney disease, or known coronary heart disease.

† The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

The authors note that there were far fewer events than had been predicted based on prevalence data and they attribute the lack of significance in the impact of lower blood pressure on event rates to this lack of power. They estimate from their data that five to ten major CV events can be prevented per 1,000 patients treated for one year, if systolic blood pressure is lowered to 140 mm Hg, and diastolic blood pressure is lowered to about 90 mm. They found that little could be gained by treating to lower levels.

The 2002 meta-analysis from the Prospective Studies Collaboration⁽¹⁰⁾ (more than one million individuals) has shown that blood pressure which rises above 115/75 mm Hg results in an increase in CVD deaths. The JNC7 Report⁽³⁾ includes the Collaboration's finding that "for every 20 mm Hg systolic, OR 10 mm diastolic increase in blood pressure, there is a doubling of mortality from both ischemic heart disease and stroke."

With this evidence, and data from the Framingham Study of the high lifetime residual risk of the development of hypertension,⁽¹¹⁾ the JNC7 has strengthened its definitions of blood pressure categories to foster improved control. Blood pressure that is < 119 / < 79 mm Hg is now called "normal" instead of "optimal," as it was in JNC6. Blood pressure ranging from 120 to 139/80 to 89 mm Hg is called "prehypertension" instead of "normal/borderline," to add urgency to the importance of prevention using lifestyle modification. Hypertension remains defined as beginning at 140/90 mm Hg, in the absence of diabetes, heart failure, renal insufficiency, or known coronary disease.

Although epidemiological evidence suggests that a blood pressure of 115/75 mm Hg is associated with fewer cardiovascular outcomes, there are no treatment trials demonstrating that this is a desirable target blood pressure. Therefore, the GDT has chosen the generally accepted, national consensus-derived blood pressure goal of $\leq 139 / \leq 89$ as the appropriate target (JNC7).⁽³⁾

Target Blood Pressure For Patients With Prior Diagnosis of Stroke Rationale:

The search of the peer-reviewed medical literature identified three studies with implications for the setting of target blood pressure in patients with a prior diagnosis of stroke.

- ♦ The PROGRESS trial (Progress Collaborative, 2001)⁽¹²⁾ studied a group of 6,105 patients who had had a stroke or TIA in the previous five years and were randomized to receive an ACEI plus a diuretic if needed, or placebo. Patients were evaluated five times during the first year and at six-month intervals thereafter for five years. The primary outcome of this study was fatal or nonfatal stroke. A total of 727 study participants had a stroke during follow-up: 307 (10%) in the treatment group and 420 (14%) in the placebo group (relative risk reduction, 28% [95% CI: 17% to 38%]; p < 0.0001). Combination drug therapy reduced blood pressure by 12 / 5 mm Hg and stroke risk by 43% (95% CI: 30% to 54%). Single-drug therapy reduced blood pressure by 5/3 mm Hg and produced no discernible reduction in the risk of stroke.

- ♦ In a retrospective review of randomized trials of lowering blood pressure in patients with prior cerebrovascular events, lowering of blood pressure varied among studies, but most reported reductions of 10/5 mm Hg (Rashid, et al., 2003).⁽¹³⁾ This heterogeneity of effect was considered to be due to the use of different medication regimens. Seven studies using eight comparator groups were included, and the authors' analysis concluded that lowering blood pressure reduced stroke (OR = 0.76; 95% CI: 0.63 to 0.92), nonfatal stroke (OR = 0.79; 95% CI: 0.65 to 0.95), myocardial infarction (OR = 0.79; 95% CI: 0.63 to 0.98), and total vascular events (OR = 0.79; 95% CI: 0.66 to 0.95).
- ♦ Arima and Chalmers (2006)⁽¹⁴⁾ reviewed recent randomized trials that studied the role of pharmacotherapy in lowering blood pressure in patients with a prior diagnosis of stroke. Significant secondary prevention of stroke was seen in all studies, with systolic blood pressure reduction of at least 10 mm Hg. These authors recommend that for patients with previous stroke, goal blood pressures of $\leq 130 / 80$ mm Hg in hypertensive subjects and $\leq 120 / 80$ mm Hg in normotensive subjects should be achieved.

Conclusion: Reducing blood pressure by 10 to 12/5 mm Hg has been shown to significantly reduce the rate of recurrence of cardiovascular events, including fatal/nonfatal stroke, fatal/nonfatal MI, and CHF-related events. Although much of the evidence among patients with prior stroke focuses on specific mm Hg blood pressure reductions, the GDT agreed that specific blood pressure targets are needed to foster successful implementation of hypertension guidelines and greater hypertension control among patients. Thus, for secondary prevention in people with a prior diagnosis of stroke, the GDT recommends a target office blood pressure of $\leq 129 / \leq 79$ mm Hg for hypertension and $\leq 119 / \leq 79$ mm Hg for prehypertension.

16. Home Blood Pressure Monitoring for Diagnosis and Management

- 5A It is recommended that the diagnosis of hypertension be established in the medical office. *Consensus-based*
- 5B Home self-measurement of blood pressure is recommended to:
 - 5B1 Identify a low-risk subpopulation of individuals with “white coat hypertension, “ without target organ disease or diabetes, for whom medication may not be necessary. These individuals have home blood pressure levels \leq 134 / 84 mm Hg but have office blood pressure levels \geq 140 / \geq 90 mm Hg. *Consensus-based*
 - 5B2 Attain control in patients with uncontrolled hypertension ($>135/85$ mm Hg by home monitoring) according to drug treatment algorithms, and by using telephone/e-mail/fax or other electronic patient communications in conjunction with standard provider-based clinic visits. *Consensus-based*
 - 5B3 Monitor controlled hypertension over time. *Consensus-based*

Rationale:

Evidence Grade*

Evidence for Recommendation 5: Insufficient.

2009 Update:

No new evidence has been identified. Recommendations remain unchanged.

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes were included. When possible, studies were included if they were primarily concerned with participants without significant comorbid conditions. See Appendix B for more information.

2007 Guideline:

Diagnosis of Hypertension

The updated search of the peer-reviewed medical literature identified no new evidence that evaluated the use of home blood pressure monitoring in determining a diagnosis of hypertension.

* The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

Management of Hypertension

The updated search of the peer-reviewed medical literature identified one meta-analysis of the use of home blood pressure monitoring in the management of hypertension (Verberk, et al., 2005).⁽¹⁵⁾ The studies reviewed used a large number of outcomes to evaluate the value of home blood pressure measurements, and the authors addressed several aspects of home blood pressure monitoring in separate subanalyses of the data. Pooling the data in four studies of the accuracy and reproducibility of home monitoring, the authors concluded that duplicate measurements should be made twice each day, with the average of each set reported. An analysis of 18 trials that compared home blood pressure measurements with office blood pressure measurements found that the reported home measurements were lower than the office measurements. The mean overall difference was 6.9 mm Hg (95% CI: 6.6 to 7.2, p = 0.001) for systolic blood pressure and 4.9 mm Hg (95% CI: 4.7 to 5.1, p = 0.001) for diastolic blood pressure.

Home blood pressure monitoring has its prime utility in managing patients with known hypertension. Its role in diagnosing hypertension is less secure, and the diagnosis of hypertension remains predominantly office-based.

The Ohasama population study and the Self-Measurement of Blood Pressure at Home in the Elderly (SHEAF) trial⁽¹⁶⁾ have shown that the predictive value of home blood pressures may be superior to that of clinic measurements. Home blood pressures are more closely comparable to ambulatory blood pressure data than office pressures. Additionally, home blood pressure devices are widely available and offer the potential for greater patient participation in managing a chronic disease for which the Northern and Southern California KP hypertension registries have enrolled more than 1.2 million members.

A recent national survey (Moser, et al., 2007)⁽¹⁷⁾ showed that 60% of individuals who were aware of a diagnosis of hypertension owned home blood pressure devices. Nurses and pharmacists have successfully implemented home blood pressure algorithms to improve control of hypertension. Home blood pressure protocols have demonstrated success managing diabetic patients with hypertension, and home blood pressures have greater sensitivity and specificity for making a diagnosis of hypertension in patients with end-stage renal failure than measurements of blood pressure obtained at hemodialysis centers. There is also a role for patients with Stage 1 - 4 chronic kidney disease (CKD). Furthermore, <http://members.kp.org> will offer an electronic interface with patients to promote home management of hypertension.

Home blood pressure management also has limitations that need to be recognized, and not everyone is a candidate. Most devices offer only two cuff sizes which will probably not fit the arm of morbidly obese individuals. Studies have shown that 40% of patients do not read the instructions, 50% of patients lack any training in taking a blood pressure and patients frequently fabricate some numbers and omit others. Patients with anxiety syndromes may overuse home blood pressures and suffer panic attacks with secondary blood pressure elevations. Unvalidated devices which have not received a “pass” grade from a professional hypertension society are commonplace. Providers are using random blood pressure protocols and do not know how to evaluate records of blood pressures brought in by patients.

A quality home blood pressure management program has several prerequisites:

1. Selection of patient candidates who:

- ◆ Are reliable,
- ◆ Fit a cuff size option,
- ◆ Are not prone to panic attacks,
- ◆ Are motivated, and
- ◆ Have the mental and physical capability for training and participation.

On kp.org, the physician determines home blood pressure program candidacy, then initiates the process by sending the patient a message to look for the new “My Flowsheet” when they next log onto kp.org.

2. A national KP home blood pressure machine benchmark has been identified with the requirements being: 1) approval by a national hypertension society, 2) memory chip to avoid patient data selection, and 3) bench testing by national KP Biomedical Engineering.

Lifesource UA-767 Plus is available with a large cuff option. This device has an “A” grade from the British Hypertension Society (BHS), a memory chip, and performed better than competitors in a bench-testing procedure by KP National Biomedical Engineering. These machines are not uniformly in stock. Alternative suitable devices with an AAMI (Association for the Advancement of Medical Instrumentation) or an EHS (European Hypertension Society) “pass,” or a BHS “A” or “B” grade, preferably with a memory chip, may be accessed at <http://www.dableducational.com>. Only brachial measurements are acceptable. The patient’s arm should be measured at the point-of-sale to ensure appropriate cuff size.

3. The home blood pressure device needs to be validated approximately every 12 months by a protocol that was recently approved by the National Hypertension Implementation Committee (NHIC) and is available via regional hypertension leaders. These validation procedures can be carried out by medical assistants, nurses, and pharmacists who simultaneously should observe patient technique: use of proper cuff size, arm supported on furniture with cuff at heart level; back supported; legs uncrossed; feet on floor; no talking; bladder emptied if necessary; five minutes of rest prior to first blood pressure, wait at least one minute between subsequent blood pressures. CMI will soon make available standardized patient information material for paper and electronic venues. Patients should be encouraged to attend a Health Education training class.

4. The home blood pressure protocol recommended consists of:

- ◆ Taking 2 to 3 blood pressures BID x 3 consecutive days, although 2 to 3 sequential blood pressures obtained for any three mornings and any three evenings over a seven day span are acceptable.
- ◆ Obtaining morning blood pressures between 6 and 10 am within an hour of awakening prior to morning medications and breakfast, and evening blood pressures between 6 and 10 PM.
- ◆ Averaging all of the blood pressures in a three-day (or six half days over 7 days) sequence, totaling 12 to 18 blood pressures.

Some patients will experience “cuff inflation hypertension” in which case the first blood pressure in a series of two or three will be disproportionately elevated and should be excluded. An average blood pressure $\leq 134 / 84$ mm Hg is considered controlled when the patient does not have diabetes, CKD, or coronary artery disease and is not post-stroke. For those conditions, where the office blood pressure goal is $\leq 129 / 79$ mm Hg, a comparative average home blood pressure threshold has not been established, but less than 125 to 130 / 75 to 80 mm Hg is a reasonable surrogate, with office follow-up.

These management home blood pressure protocols calling for an average blood pressure $\leq 134 / 84$ mm Hg can be used in two contexts:

- ◆ For the patient with uncontrolled hypertension whose medication is being uptitrated and managed at home, the three-day home blood pressure protocol should be performed during the third week following two full weeks of the new medication regimen. After home blood pressure control is achieved, the patient should be brought in for a routine office blood pressure, preferably by a medical assistant, in order to confirm control.
- ◆ For patients with controlled hypertension, the three day protocol is best performed at three month intervals. Patients with controlled uncomplicated hypertension based on home blood pressure reporting every three months need only be seen in the office once yearly, but should be cycled into the first six calendar months of each year (January 1 through June 30) for HEDIS inclusion.

Conclusion: Based on the available evidence and consensus of the GDT, home blood pressure monitoring is an effective method of obtaining accurate and reproducible blood pressure measurements, provided that appropriate measurement technique is applied. Approved and validated measurement devices are needed to assure this accuracy.

2005 Guideline:

Diagnosis of Hypertension

Office blood pressure by mercury sphygmomanometry is widely considered to be the “gold standard” for the diagnosis of hypertension. The increasing popularity of ambulatory and home blood pressure devices has not diminished its importance. There is also concern about the accuracy of alternative measurement devices.⁽³⁾ The mercury sphygmomanometer has been used in all large scale studies whose conclusions have provided data for the relationship of hypertension, target organ damage, and diabetes, as well as for the benefits of treatment. There is, however, concern about accuracy of measurement, observer bias, “white coat hypertension” (“isolated clinic hypertension”), and environmental safety issues (although the elemental form of mercury in the sphygmomanometer is not linked with health/environment problems).

Use of Home Blood Pressure Monitoring

Measuring blood pressure at home, in addition to the office, has the advantage of accessibility, which makes the requirement of frequent monitoring achievable.

Titration of antihypertensive medications using an algorithmic approach may be done according to home blood pressure measurement schedules of varying frequency. One meta-analysis of 18 studies showed schedules ranging from two times per day to two times per week.⁽¹⁸⁾

Generally, management decisions are based upon the mean of these multiple readings. Critical characteristics of home blood pressure monitoring are a validated instrument, a demonstrated competency in patient technique, and a demonstrated reliability in patient blood pressure reporting.

In 2002, the Agency for Health Research and Quality (AHRQ) published a report of their review of the “Utility of Blood Pressure Monitoring Outside the Clinic Setting.”⁽¹⁹⁾ A key question was the distribution of the differences between clinic blood pressure measures and self-measured blood pressure (SMBP) outside of the clinic. Six studies examined this question and met the reviewers’ criteria (minimum size of 100, at least two clinic visits for blood pressure measurement). In all six, the clinic blood pressure was higher than the SMBP. The mean differences ranged from 5.4 to 17.7 mm Hg for systolic blood pressure and from 1.5 to 6.3 mm Hg for diastolic blood pressure. Except for one of the trials, the differences were significant ($p < 0.01$).

Prevalence of White Coat Hypertension based on SMBP

The JNC7 report suggests that self-monitoring of blood pressure can assist in identifying low-risk populations, that is, individuals with elevated office blood pressures and home readings $< 130 / 80$ mm Hg, who do not have target organ damage or diabetes, i.e., “white coat hypertension” (WCH). These patients may not warrant pharmacotherapy.⁽³⁾

The AHRQ review also looked at the prevalence of white coat hypertension and found four studies using SMBP. The prevalence was from 13 to 33 percent, although definitions for office hypertension and SMBP were not precisely the same for all trials. In two of the studies, the WCH prevalence by SMBP was checked against ambulatory blood pressure monitoring and was found to be comparable. The AHRQ report found the literature to be insufficient to determine the prevalence of WCH.⁽¹⁹⁾

White Coat Hypertension and CV Outcomes

Three studies were found that compared cardiovascular outcomes between hypertensives and those with WCH, though all used monitoring by ambulatory blood pressure measurement. The Syst-Eur trial⁽²⁾ showed a reduced cardiovascular benefit in a subgroup of older participants with isolated systolic hypertension and “white-coat hypertension” when treated based on clinic blood pressure monitoring compared with ambulatory blood pressure monitoring.⁽²⁰⁾ This was also found to be true in the general population of patients with hypertension.^(21, 22)

Therefore, the GDT recommends that self-measurement of blood pressure be used to identify a low-risk subpopulation of individuals with “white coat hypertension,” without target organ disease or diabetes, for whom medication may not necessary. These individuals have home blood pressure levels $< 130 / 80$ mm Hg but office blood pressures $\geq 140 / \geq 90$.

Determination of “white coat hypertension” should be made on the basis of multiple daily home blood pressure readings over a period of weeks, usually taken BID between 6 and 9 am and between 6 and 9 pm.^(16, 23)

Assessment of Control

Patients who measure their blood pressure at home can complement traditional office blood pressure measurement to assess the need for additional medications or different dosing. Home measurement also helps to monitor controlled hypertension over time. Cappuccio⁽¹⁸⁾ found that individuals who monitored their blood pressures at home had lower pressures (2.2 / 1.9 mm Hg, when adjusted for publication bias, $p < 0.001$) than those whose hypertension was measured only in the clinic. In addition, 10% more individuals in the intervention group met the target blood pressure.

Relationship of Home Blood Pressure Monitoring to Cardiovascular Outcomes

Two prospective studies were found that compared home vs. office blood pressure determination and prognosis of cardiovascular outcomes.

Ohkubo⁽²⁴⁾ led a study in Ohasama, Japan, which compared home self-measurement with “screening” (office) blood pressure measurements for predicting the risk of cardiovascular and noncardiovascular mortality.

Relative hazard ratios were presented as the increase in risk of mortality for each 1 mm Hg increase in blood pressure. When comparing initial home blood pressure measurement, multiple home measurements and screening blood pressure for systolic blood pressure, both home measurements were significantly correlated with overall mortality, whereas screening measures were not (RH initial home = 1.011 [95% CI: 1.002 to 1.021], RH multiple home = 1.014 [95% CI: 1.003 to 1.025], RH screening = 1.001 [95% CI: 0.992 to 1.009]). Multiple home diastolic blood pressure was found to be a significant predictor for cardiovascular mortality while initial home and screening measures were not (RH = 1.021 [95% CI: 1.001 to 1.041]). Similar patterns were seen when comparing initial and multiple home measurements together vs. screening blood pressure.

This study showed that multiple (mean = 20.8) home systolic blood pressure measurements were the best predictors of cardiovascular and overall mortality, presumably because the large number of measurements in the absence of observer bias and incidence of “white coat hypertension.”

In the SHEAF study⁽¹⁶⁾ (Self-Measurement of Blood Pressure at Home in the Elderly: Assessment and Follow-up), a French prospective cohort study of older hypertensives, participants’ blood pressures were taken in the doctor’s office. A mercury sphygmomanometer was used. Self-measured home blood pressure was also recorded using the Omron-705 CP oscillometric device. (Both devices were also used in the Ohasama research.) The cohort was then observed for three years to assess cardiovascular endpoints (CV mortality [primary endpoint], total mortality, the combination of CV mortality, nonfatal MI, NF stroke, TIA, hospitalization for angina or heart failure, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft surgery).

For home blood pressures, there was a significant association with cardiovascular outcomes for both systolic and diastolic blood pressure, except for home diastolic blood pressure for women. For office blood pressure, there were no significant associations.

In the case of home blood pressure self-measurement, for each increase in systolic blood pressure of 10 mm Hg, the risk of a cardiovascular event increased by 17% (95% CI: 11.0% to 23.8%). For each increase in diastolic blood pressure of 5 mm Hg, the risk of an event increased by 11.7% (95% CI: 5.7% to 18.1%). For office measurement, there was no significant rise in cardiovascular event risk.

When results were expressed per 1 mm Hg rise in blood pressure, findings were similar to those found in the Ohkubo study above.

Neither method correlated with CV mortality or total mortality, which was probably due to insufficient numbers.

The research also identified individuals (9% of the sample) with what was labeled “masked hypertension.” Their blood pressure appeared to be controlled when taken by office measurement but was out of control at home. Their CV event profile was similar to that of participants with uncontrolled hypertension.

These two trials showed that elevated home blood pressure measurement correlates with an increased risk of cardiac morbidity and mortality.

The Effect of Treatment Guided by SMBP

The AHRQ report⁽¹⁹⁾ identified 12 trials which studied this question, but the results varied: Only half the studies showed reduced blood pressure as measured by SMBP. However, the report did not note that there was a comparison to traditional office measurement with regard to blood pressure control and outcomes.

The report found that “available evidence from several trials suggested that use of SMBP can improve blood pressure control; however, further trials that evaluate contemporary SMBP devices are needed.”

The GDT recommends that SMBP be used to attain control in patients with uncontrolled hypertension (> 135 / > 85 mm Hg by home monitoring) and to monitor controlled hypertension over time, according to drug treatment algorithms, and by using telephone/e-mail/fax or other electronic patient communications, in conjunction with standard provider-based clinic visits. The lower blood pressure threshold for outpatient measurement is adapted from the AHRQ observation that the mean differences ranged from 5.4 to 17.7 mm Hg for systolic blood pressure and from 1.5 to 6.3 mm Hg for diastolic blood pressure.

17. First-Line Treatment of Hypertension

Thiazide diuretics (either as a single agent or in combination) are strongly recommended as first-line agents for initial therapy in people with hypertension.

Evidence-based: A

Rationale:

Evidence Grade*

Evidence for Recommendation 6: Good.

2009 Update:

New evidence has been identified. Recommendations remain unchanged.

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension who were randomized to head-to-head trials of first-line antihypertensive agents were included. When possible, studies were included if they were primarily concerned with participants without significant comorbid conditions. See Appendix B for more information.

2007 Guideline:

Good evidence regarding the effectiveness of thiazides compared with placebo and with other antihypertensives was found.

Good evidence regarding the lack of effectiveness of beta-blockers compared with other antihypertensives was found.

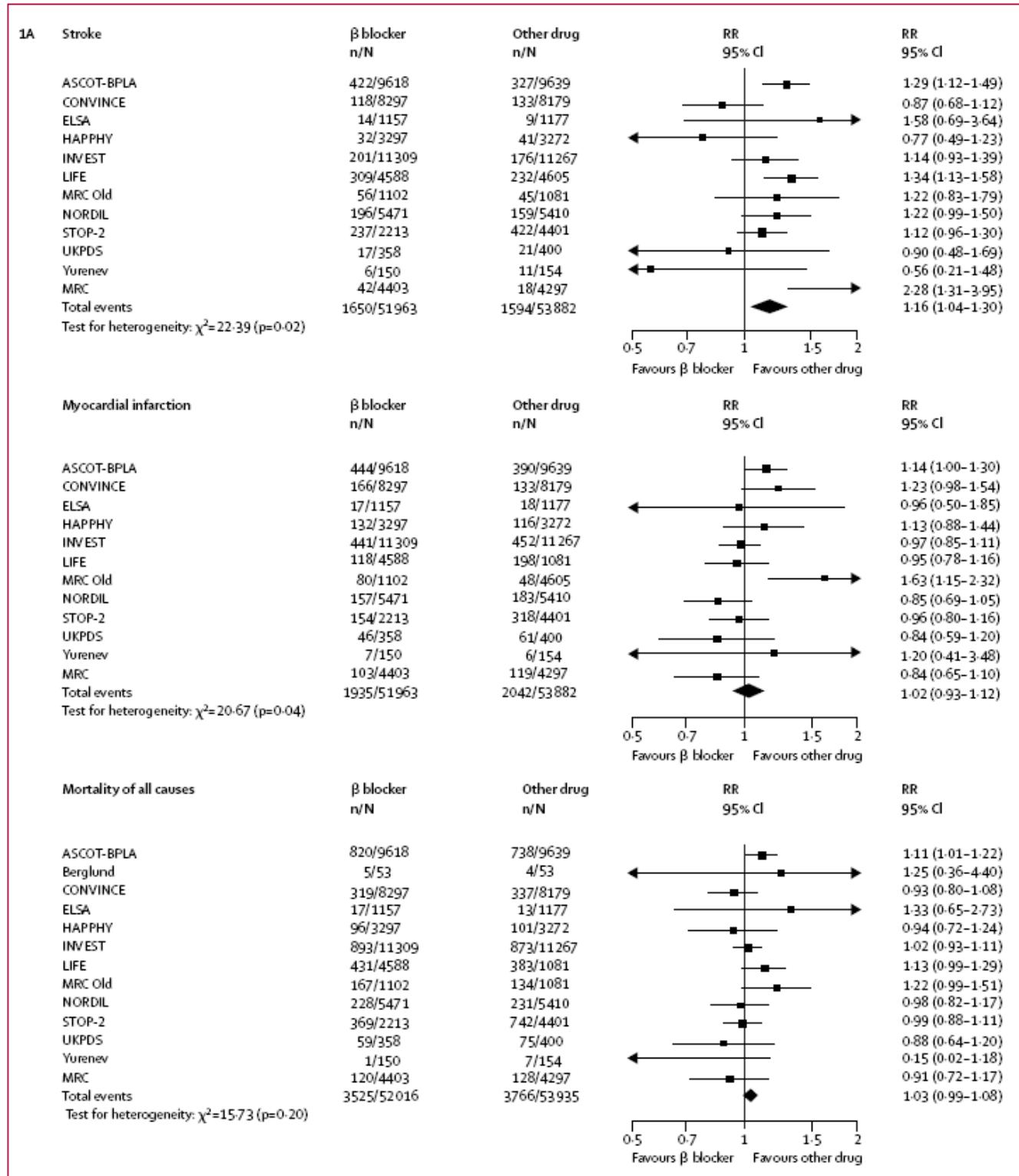
An updated review of the evidence does not support the recommendation of beta-blockers as first-line agents for initial therapy for people with hypertension.

A meta-analysis by Lindholm, et al. (2005)⁽²⁵⁾ comparing beta-blockers with other drugs ($n = 105,951$, see Figure 1) found that the relative risk of stroke was 16% higher with beta-blockers (95% CI: 4% to 30%, $p = 0.009$) than with other drugs. All-cause mortality showed a tendency in the same direction, the relative risk being increased by 3% for beta-blockers (95% CI: -1% to 8%, $p = 0.14$). There was, however, no difference for myocardial infarction. The GDT agreed that based on the reduced benefit for stroke reduction, beta-blocker therapy should not be supported as the first-line agent for initial hypertension therapy.

(Note: There is less certainty about the effectiveness of first-line beta-blocker therapy with regard to a) persons less than 60 years old, and b) use of newer vasodilating beta-blockers or combined alpha- and beta-blocking agents.)

* The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

Figure 1: Outcome Data For All Beta-Blockers Versus Other Antihypertensive Treatment⁽²⁵⁾



Supporting Evidence for Thiazide Diuretics, Beta-Blockers (BBs), Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Blockers (ARBs), or Calcium Channel Blockers (CCBs) Versus Placebo

2007 Guideline:

No new evidence was identified that analyzed thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), or calcium channel blockers (CCBs) versus placebo.

The updated literature search identified four new meta-analyses (summarized below) that included studies of beta-blockers (BBs) versus placebo. Although the meta-analyses report that beta-blocker therapy is favorable compared with placebo or no treatment, these studies did not find evidence that beta-blocker therapy is superior to other antihypertensive drug treatments (for example, thiazides) as first-line therapy. As stated previously, the GDT's decision not to support beta-blocker therapy as first-line therapy was further influenced by the Lindholm, et al. (2005) analysis⁽²⁵⁾ (see summary above), which reported that beta-blocker therapy was not as effective as other hypertensive therapies for stroke reduction.

- ◆ Bradley, et al. (2006)⁽²⁶⁾ pooled the results of four trials of beta-blockers versus placebo or no treatment, involving 23,615 adult participants with mild-to-moderate hypertension. Beta-blockers significantly reduced the risk of stroke (RR = 0.80, 95% CI: 0.66 to 0.96) and total cardiovascular events (RR = 0.88, 95% CI: 0.79 to 0.97). The corresponding number-needed-to-treat with a beta-blocker over five years to prevent one event was 211 for stroke and 140 for any cardiovascular event. There was no evidence that beta-blockade lowered the risk of all-cause mortality.
- ◆ In a meta-analysis that examined the results of 21 RCTs involving 145,811 adult participants with mild-to-moderate hypertension, Khan, et al. (2006)⁽²⁷⁾ analyzed data from a group of placebo-controlled trials of beta-blocker therapy. They reported that beta-blockers reduced the rate of a composite endpoint of death, stroke, or MI compared with placebo (RR = 0.86, 95% CI: 0.74 to 0.99) based on 794 events in 19,414 patients in trials enrolling younger patients. In trials involving older patients, beta-blockers were associated with statistically significant reductions in stroke (RR = 0.78, 95% CI: 0.63 to 0.98).
- ◆ Lindholm, et al. (2005)⁽²⁵⁾ in a meta-analysis of the relative efficacy of beta-blockers, analyzed the results of seven studies comparing beta-blockers with placebo or with no antihypertensive treatment, pooling the results seen in studying adult subjects with mild-to-moderate hypertension. These studies involved 27,433 patients and reported that the relative risk of stroke was reduced by 19% with beta-blockers compared with no treatment or placebo (95% CI: 7 to 29%).

- In a Cochrane database review of the use of beta-blockers for hypertension in nonpregnant adult patients, Wiysonge, et al. (2006)⁽²⁶⁾ pooled the results of 13 RCTs, four of which compared beta-blockers with placebo or no treatment, involving 26,313 participants. These studies used death from any cause as a primary outcome, and the authors reported that no statistically significant effect of beta-blocker therapy could be detected. However, the meta-analysis suggested that significant reduction in the risk of stroke (RR = 0.80, 95% CI: 0.66 to 0.96) was achieved with beta-blocker therapy compared with placebo in hypertensive patients.

2005 Guideline:

The literature search identified one large-scale RCT and two meta-analyses that were suitable for this update. One meta-analysis, the revised Trialists' study,⁽²⁸⁾ added 12 RCTs published from 2001 to those completed by June, 2003, to the original 2000 analysis.⁽²⁹⁾ Many of the constituent studies included populations with comorbid conditions and risk factors in addition to hypertension.

The second meta-analysis, by Psaty,⁽³⁰⁾ was also an update of previous work,⁽³¹⁾ but its aim was to compare low-dose diuretics with the other five major antihypertensive medications. The following studies were included in the meta-analysis:

Study, y	N / Mean Follow-up, y	Full Name	Study, y	N / Mean Follow-up, y	Full Name
VA I, 1967	143 / 1.5	Veteran's Administration	MIDAS, 1996	883 / 3.0	Multicenter Isradipine Diuretic Atherosclerosis Study
VA II, 1970	380 / 3.3	Veteran's Administration	SYST-EUR, 1997 and 1999	4,695 / 2.5	The European Trial on Systolic Hypertension in the Elderly
Carter, 1970	99 / 4.0		VHAS, 1997	1,414 / 2.0	Verapamil in Hypertension and Atherosclerosis Study
Barraclough, et al. 1973	116 / 2.0		ABCD, 1998 and 2000	470 / 5.0	Appropriate Blood Pressure Control in Diabetes

Study, y	N / Mean Follow-up, y	Full Name	Study, y	N / Mean Follow-up, y	Full Name
HSCSG, 1974	452 / 3.0	Hypertension Stroke Cooperative Study Group	FACET, 1998	380 / 2.5	Fosinipril vs. Amlodipine Cardiovascular Events Trial
USPHS, 1977		US Public Health Service Hospitals Cooperative Study	*UKPDS, 1998	758 / 8.4	UK Prospective Diabetes Study
VA-NHLBI, 1978	1,012 / 1.5	VA Nat'l. Heart, Lung, and Blood Institute Feasibility Study	CAPP, 1999	10,985 / 6.1	Captopril Prevention Project
HDFP, 1982	10,940 / 5.0	Hypertension Detection and Follow-up Program Cooperative Group	*NICS-EH, 1999	414 / 4.2	National Intervention Cooperative Study in Hypertensives
Hegeland, 1980	785 / 5.5		*STOP-2, 1999	4,409 / 5.0	Swedish Trial in Old Patients with Hypertension-2
ANBPS, 1980	3,427 / 4.0	Australian National Blood Pressure Study	*INSIGHT, 2000	6,321	Intervention as a Goal in Hypertension Treatment
Kuramoto, et al., 1981	91 / 4.0		*NORDIL, 2000	10,881 / 4.5	Nordic Diltiazem Study
EWPHE, 1985	840 / 4.7	European Working Party on High Blood Pressure in the Elderly	ALLHAT, 2000	14,538 / 3.3	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
MRC, 1985	13,057 / 4.9	Medical Research Council Working Party	*AASK, 2001 and 2002	653 / 3.0	African-American Study of Kidney Disease and Hypertension
Coope and Warrender, 1986	884 / 4.4		*PROGRESS, 2001	6,105 / 3.9	Perindopril Protection Against Recurrent Stroke Study

* Also part of the updated Trialists' meta-analysis.

Study, y	N / Mean Follow-up, y	Full Name	Study, y	N / Mean Follow-up, y	Full Name
HAPPHY, 1987	6,569	Heart Attack Primary Prevention in Hypertension Trial Research Group	IDM, 2001	590 / 2.0	Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study
SHEP pilot, 1989	551 / 2.8	Systolic Hypertension in the Elderly Program	*Lewis, et al. 2001	1,715 / 2.6	
SHEP, 1991 and 1997	4,736 / 4.5	Systolic Hypertension in the Elderly Program	*LIFE, 2002	9,193 / 4.7	Losartan Intervention for Endpoint Reduction in Hypertension Study
STOP, 1991	1,627 / 2.1	Swedish Trial in Old Patients with Hypertension	*CONVINCE, 2002	16,476 / 3.0	Controlled Onset Verapamil Investigation of Cardiovascular Endpoints
MRC, 1992	2,183 / 5.8	Medical Research Council Working Party	*ELSA, 2002	2,334 / 3.8	European Lacidipine Study on Atherosclerosis
Dutch TIA, 1993	1,473	Dutch Transient Ischemic Attack Trial Study Group	*ALLHAT, 2002	33,357 / 4.9	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
PATS, 1995	5,665 / 2.0	Post-Stroke Antihypertensive Treatment Study	*ANBP2, 2002 and 2003	6,083 / 4.1	Australian National Blood Pressure Study2
TEST, 1995	720 / 2.6	Tenormin after Stroke and Transient Ischemic Attack			

* Also part of the updated Trialists' meta-analysis.

Both meta-analyses examined the efficacy of current antihypertensive medications vs. placebo. No new information from either study was sufficient to change our original conclusions that antihypertension agents are superior to placebo.

Multiple trials have demonstrated the effectiveness of these medications as treatments to prevent the cardiovascular complications of hypertension [STOP,⁽³²⁾ MRC-Mild Hypertension,⁽³³⁾ and Blood Pressure Trialists,⁽²⁹⁾ which consisted of (HOPE,⁽³⁴⁾ PART-2,⁽³⁵⁾ QUIET,⁽³⁶⁾ and SCAT⁽³⁷⁾)].

Supporting Evidence for BBs or Thiazide Diuretics Versus CCBs

2007 Guideline:

The updated literature search identified two new meta-analyses that included studies of thiazide diuretics versus CCBs.

- ◆ In their systematic review of RCTs, Bradley, et al. (2006)⁽²⁶⁾ identified four trials studying 44,825 patients that compared the effectiveness of beta-blockers with that of calcium channel blockers, assessing the primary outcomes of stroke and all-cause mortality. These authors performed a meta-analysis of these trials and concluded that compared with calcium channel blockers, beta-blockers were less effective in reducing the risk of all-cause mortality ($RR = 1.06$, 95% CI: 1.00 to 1.14) or stroke ($RR = 1.24$, 95% CI: 1.11 to 1.40).
- ◆ Wiysonge, et al. (2007)⁽³⁸⁾ studied the pooled results of these same trials in their Cochrane database meta-analysis and confirmed these results. Significant heterogeneity is present in these analyses, since all drugs of a class were treated as a single category.

2005 Guideline:

Psaty's 2003 meta-analysis⁽³⁰⁾ compared low-dose diuretics with CCBs and produced one significant finding: diuretics were superior to CCBs in preventing heart failure ($RR = 0.74$ [95% CI: 0.67 to 0.81]). The relative risks for the remaining major outcomes (CHD, stroke, CVD events, CVD mortality, and total mortality) showed no significant differences.

The updated Trialists' meta-analysis⁽²⁸⁾ also compared CCBs with BB or thiazide diuretics. The following studies were added since the 2000 study: AASK⁽³⁹⁾ (participants also had nephropathy), ALLHAT⁽⁴⁰⁾ (population with one or more additional CV risk factor), CONVINCE⁽⁴¹⁾ (additional risk factor), ELSA,⁽⁴²⁾ and SHELL.⁽⁴³⁾ There were no significant differences for major outcomes (stroke, CHD, major CV events, CV death, total mortality), except for heart failure, which favored BB or diuretics ($RR = 1.33$ [95% CI: 1.21 to 1.47]).

Thus, there is no new evidence to show that CCBs are superior to BB or thiazide diuretics for the prevention of important cardiovascular outcomes in hypertension.

2003 Guideline:

Three meta-analyses were found that compared BBs and/or thiazide diuretics against CCBs in people with hypertension. Results for the beta-blocker/diuretic arm in all three studies were not separated by the individual medication.

- ◆ The Opie⁽⁴⁴⁾ study included six RCTs. Four studies compared thiazide diuretics alone; two compared thiazide diuretics and/or BBs (BB/Ds). CCBs, compared with BB/Ds, were significantly more effective at decreasing the rate of stroke ($RR = 0.869$ [95% CI: 0.769 to 0.982], $p = 0.024$), and significantly less effective at decreasing the rate of myocardial infarction (MI) ($RR = 1.182$ [95% CI: 1.036 to 1.349], $p = 0.013$). Differences in the rates of cardiac or all-cause mortality were not significant.

- ◆ The Trialists' study⁽²⁹⁾ was a collaborative meta-analysis in which the constituent studies were determined prospectively. It included five RCTs in the analysis of BBs and/or diuretic vs. CCBs. All five studies were also cited in the Opie paper.⁽⁴⁴⁾ Three compared thiazide diuretics alone (INSIGHT,⁽⁴⁵⁾ NICS-EH,⁽⁴⁶⁾ VHAS⁽⁴⁷⁾), and two compared thiazide diuretics and/or BBs (STOP-2,⁽⁴⁸⁾ NORDIL⁽⁴⁹⁾). The Trialists' study concluded that CCBs significantly decreased the rate of stroke (RR = 0.87 [95% CI: 0.77 to 0.98]). The differences in the rates of cardiac or all-cause mortality were not significant.
- ◆ The meta-analysis by Pahor⁽⁵⁰⁾ included seven RCTs in this comparison. Five of these studies also appeared in the Opie and Trialists' meta-analyses; one in Opie only, one in the Trialists' study only, and two in Pahor only. Four studies compared thiazide diuretics alone; three compared thiazide diuretics and/or BBs. CCBs, compared with BB/D, were found to be significantly more effective at decreasing the rate of stroke (RR = 0.86 [95% CI: 0.76 to 0.98], p < 0.05), while BBs and/or thiazide diuretics were significantly more effective in decreasing both MI (RR = 1.20 [95% CI: 1.04 to 1.37], p < 0.01) and HF (RR = 1.22 [95% CI: 1.03 to 1.46], p < 0.05). The differences in the rates of cardiac or all-cause mortality were not significant.

One subsequent RCT was found that compared CCBs with diuretics.

- ◆ The ALLHAT⁽⁴⁰⁾ trial studied participants with hypertension who were ≥ 55 and who had one or more additional cardiovascular risk factor. Though the population was selected for having risk factors in addition to hypertension, it has been included here because of the significance of its size (n = 33,357 with the doxazosin arm removed). Study drugs were a thiazide diuretic, an ACEI, and a dihydropyridine CCB. The main results showed that when compared with CCBs, thiazide diuretics reduced the risk of all heart failure outcomes (RR = 1.38 [95% CI: 1.25 to 1.52], p < 0.001) and of hospitalized/fatal heart failure (RR = 1.35 [95% CI: 1.21 to 1.50], p < 0.001). There was no significant difference in the incidence of stroke, fatal and nonfatal CHD, nonfatal MI, or all-cause mortality.

Conclusion: Therapy with CCBs was found to be protective against stroke in all three meta-analyses cited, but there was no difference in the ALLHAT trial. BBs and/or thiazide diuretics reduced the rate of MI more than CCBs in two of the three meta-analyses, but no significant difference was seen in ALLHAT. When compared with CCBs, the risk of heart failure was reduced by thiazide diuretics in ALLHAT and by BBs and/or thiazide diuretics in the Pahor study. The use of varying combinations of BBs and/or thiazide diuretics in the constituent trials cited in the meta-analyses hampers the effort to achieve a clear recommendation. However, because of the population, and the large numbers of participants in ALLHAT, the GDT concluded that thiazide diuretics should be recommended over CCBs, even in the absence of a significant difference in mortality rates. In addition, previous trials have shown that CCBs are similar in effectiveness to thiazide diuretics, but have not shown them to be superior (INSIGHT,⁽⁴⁵⁾ NICS-EH,⁽⁴⁶⁾ and NORDIL⁽⁴⁹⁾).

Supporting Evidence for ACEIs versus BBs or Thiazide Diuretics

2007 Guideline:

The updated literature search identified no new evidence identified that analyzed ACEIs versus BBs or thiazide diuretics.

2005 Guideline:

The Psaty meta-analysis compared ACEI with low-dose diuretics and found a significant difference for the prevention of heart failure and stroke (CAPP,⁽⁵¹⁾ ANBP2,⁽⁵²⁾ ALLHAT,⁽⁴⁰⁾ ABCD,⁽⁵³⁾ STOP-2⁽⁵⁴⁾). Diuretics were favored for reduction of the risks of both HF (RR = 0.88 [95% CI: 0.80 to 0.96]) and stroke (RR = 0.86 [95% CI: 0.77 to 0.97]).

The Trialists' update⁽²⁸⁾ added three studies which compared ACEI with BB or thiazide diuretics (ALLHAT, AASK, and ANBP2). The data from the total of six trials revealed no statistical differences in serious outcomes based on the medication used.

The current evidence continues to support the 2003 conclusion that thiazide diuretics are the preferred initial agents for the treatment of hypertension.

2003 Guideline:

One meta-analysis was found that compared ACEIs with BBs and/or diuretics. Of the meta-analyses cited, only the Trialists'⁽²⁹⁾ study examined this comparison, and two RCTs were included. (We did not consider the UKPDS,⁽⁵⁵⁾ since 100% of its population was diabetic.) The data reported are from the STOP-2⁽⁴⁸⁾ and the CAPP⁽⁵¹⁾ trials. Both used thiazide diuretics and/or BBs vs. ACEIs. BBs and/or thiazide diuretics significantly decreased the rate of stroke when compared with ACEIs in CAPP (RR = 1.28 [95% CI: 1.03 to 1.58]), but not in the STOP-2 study.

The differences in the rates of cardiac or all-cause mortality were not significant. However, since both trials used a mixture of BBs and thiazide diuretics, we cannot be certain which effects resulted from which medication.

Two subsequent RCTs were found that compared ACEIs with diuretics. ALLHAT⁽⁴⁰⁾ demonstrated that ACEIs, compared with thiazide diuretics, were less effective at reducing the risk of stroke (RR = 1.15 [95% CI: 1.02 to 1.30], p = 0.02) and combined CVD events (CHD death, nonfatal MI, stroke, coronary revascularization, treated or hospitalized angina, treated or hospitalized heart failure, and peripheral arterial disease) (RR = 1.10 [95% CI: 1.05 to 1.16], p < 0.01). They also increased the risk of all heart failure outcomes (RR = 1.19 [95% CI: 1.07 to 1.13], p < 0.01). There was no significant difference in the incidence of the primary outcomes, fatal or nonfatal MI, or all-cause mortality.

Wing,⁽⁵²⁾ of the Second Australian National Blood Pressure study (ANBP2), showed that ACEIs significantly improved the risk of all CV events or death from any cause (HR = 0.89 [95% CI: 0.79 to 1.00], p = 0.05) compared with thiazide diuretics. ACEIs were also superior in preventing MI (HR = 0.68 [95% CI: 0.47 to 0.98], p = 0.04) and combined nonfatal CV events (HR = 0.86 [95% CI: 0.74 to 0.99], p = 0.03). However, thiazide diuretics were more effective in reducing the risk of fatal stroke (HR = 1.91 [95% CI: 1.04 to 3.5], p = 0.04) compared with ACEIs.

There is conflicting evidence regarding ACEIs and diuretics. Based upon the Trialists' study meta-analysis, as well as ALLHAT and ANBP2, both thiazide diuretics and ACEIs can be regarded as effective first-line antihypertensive therapies.

Supporting Evidence for ARBs versus BBs

2007 Guideline:

The updated literature search identified no new evidence identified that analyzed ARBs versus BBs.

2005 Guideline:

There was no new evidence identified that analyzed ARBs vs. BBs.

2003 Guideline:

One RCT was found that compared an angiotensin II receptor blocker (ARB) with a BB. The Losartan Intervention For Endpoint reduction (LIFE)⁽⁵⁶⁾ trial compared treatment with an ARB with therapy with BBs in patients with verified LVH. Sixty-two percent of the subjects on the ARB medication and 58% of those on beta-blockade were also on thiazide diuretics. The ARB arm was found to be superior for reducing the risk of the primary composite endpoint (CV mortality, stroke, or myocardial infarction) (RR = 0.87 [95% CI: 0.77 to 0.98], p = 0.021) and the risk of stroke (RR = 0.75 [95% CI: 0.63 to 0.89], p = 0.001) compared with the beta-blocker.

ARBs have been shown to be more effective than BBs when used with or without diuretics. However, there are no studies comparing ARBs with ACEIs or with diuretics as first-line therapy.

Supporting Evidence for Thiazide Diuretics versus BBs

2007 Guideline:

The updated literature search identified one new meta-analyses that included studies of diuretics versus BBs. A meta-analysis of trials involving beta-blockers included a subanalysis of recent trials comparing the effects of beta-blockers versus diuretics in adult hypertensive patients, using the primary outcomes of all-cause mortality and stroke.

- ◆ Analyzing the results of five RCTs including 18,241 participants, Bradley, et al.⁽²⁶⁾ found no difference between groups taking beta-blockers and diuretics in either outcome. Significant heterogeneity was present in this study, as all drugs of one class were viewed as a single entity.

2005 Guideline:

The meta-analysis by Psaty,⁽³⁰⁾ evaluated thiazide diuretics vs. BBs (MRC 1985,⁽³³⁾ HAPPHY,⁽⁵⁷⁾ MRC 1992⁽⁵⁸⁾), and there was one significant finding favoring diuretics for the prevention of CVD events (RR = 0.89 [95% CI: 0.80 to 0.98]). Therefore, the updated meta-analysis continues to support the 2003 conclusion that thiazide diuretics are the preferred initial agents for the treatment of hypertension.

Supporting Evidence for ARBs versus CCBs or ACEIs**2007 Guideline:**

There was no new evidence identified that analyzed ARBs versus CCBs or ACEIs.

2005 Guideline:**ARBs vs. CCBs**

The VALUE trial⁽⁵⁹⁾ (n = 15,245) studied valsartan (n = 7,649) vs. amlodipine (n = 7,596) in participants 50 years and older with hypertension and at least one additional CHD risk factor. They were followed for a mean of 4.2 years. Fatal and nonfatal MI, which favored the CCB (HR = 1.19, p = 0.02, NNT = 143), showed a significant difference, as did new-onset diabetes, which favored the ARB (HR = 0.77, p = 0.0001). No statistically significant differences were found for the other primary outcomes (composite of cardiac mortality and morbidity [the latter two were also studied separately] fatal and nonfatal stroke, and all-cause death).

This study suggests that CCBs are more efficacious than ARBs for the prevention of fatal/nonfatal MI.

ARBs vs. ACEIs

No studies were found that compared ARBs vs. ACEIs.

Supporting Evidence for CCBs versus Placebo or BBs**2007 Guideline:**

The updated literature search identified no new evidence identified that analyzed CCBs versus placebo or BBs.

Supporting Evidence for CCBs versus ACEIs**2007 Guideline:**

The updated literature search identified one new RCT that analyzed CCBs versus ACEIs.

- ♦ Leenen, et al. (2006)⁽⁶⁰⁾ published the results of the ALLHAT trial, an RCT evaluating the use of CCBs versus ACEIs in preventing events including fatal and nonfatal heart disease, all-cause mortality, and stroke. All participants were at least 55 years old and had mild-to-moderate hypertension. Both previously treated and untreated patients were included in this study, which involved 18,102 persons. Treatment was randomized, with one group receiving lisinopril and the other group receiving amlodipine. The mean follow-up was 4.9 years, at which point the status of 2.9% of the patients was unknown. There were no significant differences seen between the two groups with respect to the outcomes listed above.

2005 Guideline:

The revised Trialists' meta-analysis added four new trials for the analysis of CCBs vs. ACEIs: ALLHAT⁽⁴⁰⁾ (population with hypertension and at least one additional risk factor), AASK⁽³⁹⁾ (hypertension and nephropathy), the most recent ABCD study⁽⁵³⁾ (hypertension plus diabetes), and JMIC-B⁽⁶¹⁾ (hypertension and CHD). Though the smaller studies were all conducted in populations with comorbidities, the amount of data from ALLHAT was sufficiently large (CCB vs. ACEI analysis, n = 18,113) that it overpowered that from the other trials (AASK, n = 653; ABCD, n = 480; JMIC-B, n = 1,650).

There were two significant findings. CCBs were more effective for reducing the risk of stroke (RR = 1.12 [95% CI: 1.01 to 1.25]). ACEIs were found to reduce heart failure significantly more than CCBs (RR = 0.82 [95% CI: 0.73 to 0.92]).

Although CCBs prevented more strokes and ACEIs were better at preventing heart failure, the overall effect is that neither is clinically different in the prevention of serious CV outcomes.

2003 Guideline:

The ALLHAT study compared each of these medications with a thiazide diuretic but did not present data that compared them with each other.

Overall Conclusion:**2007 Guideline:**

Ongoing review of the evidence continues to confirm the 2005 evidence-based recommendation that "thiazide diuretics are recommended as first-line agents for initial therapy" for hypertension. There is sufficient evidence that for patients > 60 years of age, BBs are less effective as first-line therapy for uncomplicated hypertension.

2005 Guideline:

Ongoing review of the evidence continues to confirm the 2003 evidence-based recommendation that "thiazide diuretics are recommended as first-line agents for initial therapy" for hypertension. For example, while CCBs perform better than ACEIs at preventing stroke, they were not superior to thiazide diuretics or BBs in reducing other outcomes. CCBs were also significantly better than ARBs at preventing fatal and nonfatal MI. ACEIs were not found to be superior to thiazide diuretics or BBs for any outcome.

2003 Guideline:

To summarize, both thiazide diuretics and ACEIs outperform BBs, CCBs, and alpha-blockers as first-line therapy for hypertensive patients without significant comorbidities. (There is insufficient evidence to consider ARBs as the first choice treatment.) Though the ANBP2⁽⁵²⁾ study found ACEIs to be more effective than thiazide diuretics; the ALLHAT⁽⁴⁰⁾ study, favoring diuretics, included more participants than any other head-to-head study and took place in a population that is closer to that of KP. Although thiazide diuretics, ACEIs, BBs, ARBs, and CCBs are effective for initial treatment of hypertension, the GDT recommends thiazide diuretics as initial therapy because: 1) they are at least equal in efficacy to other classes, 2) no other drug class has been found to be consistently superior to them, and 3) they have an excellent cost profile.

Other Considerations:

Though our intention is to formulate recommendations for the hypertension population without comorbid conditions, most large studies contain subpopulations with other cardiovascular diseases and risk factors.

It is often difficult to draw clear conclusions about single first-line drugs, because most study subjects need multiple medications by the end of trials to control their blood pressure. Data are rarely presented separately by drug combination.

18. Initial Combination Treatment of Hypertension*

- 7A Combination therapy consisting of a thiazide diuretic plus an ACEI is an option for initial therapy for Stage 1 hypertension (systolic blood pressure 140 to 159 mm Hg, OR diastolic blood pressure 90 to 99 mm Hg). *Consensus-based*
- 7B Combination therapy of a thiazide diuretic plus an ACEI is recommended for Stage 2 hypertension (systolic blood pressure > 160 mm Hg, OR diastolic blood pressure > 100 mm Hg). *Consensus-based*

Rationale:***2009 Update:***

New evidence has been identified. Recommendations remain unchanged.

Evidence Grade[†]

Evidence for Recommendation 7: Insufficient

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension who were randomized to head-to-head trials of first-line antihypertensive agents were included. When possible, studies were included that were primarily concerned with participants without significant comorbid conditions. See Appendix B for more information.

* In nonpregnant adults who do not have diabetes, heart failure, chronic kidney disease, or known coronary heart disease.

† The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

A comprehensive literature search for the 2009 update resulted in one multi-center RCT which examined the effects of initial combination therapy on important outcomes relevant to this problem formulation (Jamerson, et al. 2008).⁽⁶²⁾ This trial (ACCOMPLISH)⁽⁶²⁾ randomized 11,462 patients with stage 2 hypertension (age > 55 years) to treatment with either amlodipine/benazapril (5/20 mg; titrated to 10/40 mg) or benazapril/HCTZ (20/12.5 mg; titrated to 40/25 mg) in a one-to-one ratio. The trial was terminated early at 36 months (mean) when interim results showed a 20% risk reduction (95% CI: 0.72 - 0.90, p < 0.001) favoring ACEI/CCB for the primary endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, coronary revascularization procedure [PCI or CABG] and/or resuscitated sudden death (Absolute Risk Reduction = 2.2%, Number Needed to Treat = 48). All primary endpoint components except coronary revascularization were individually non-significant, but analysis removing coronary revascularization remained significant; and, analysis of the hard endpoints alone (fatal and nonfatal MI plus fatal and nonfatal stroke) also showed a highly significant risk reduction difference of 20% favoring CCB/ACEI (95% CI: 0.67 - 0.92). Blood pressure reduction was similar in both arms of the study, with a 0.9 mm Hg SBP difference favoring ACEI/CCB.

Although the results of ACCOMPLISH⁽⁶²⁾ may show that the combination of ACEI/CCB has an advantage over ACEI/thiazide-diuretics, there are important limitations that should be considered. Study investigators used approximately one half the dose of thiazide that was used in the lowest dosed thiazide placebo-controlled outcome trials (SHEP,⁽⁶³⁾ MRC trials,⁽⁵⁸⁾ and EWPHBPE⁽⁶⁴⁾). The 25 mg of HCTZ used in ACCOMPLISH⁽⁶²⁾ is a lesser comparative dosage than the 25 mg of chlorthalidone (which is about twice as potent) used in ALLHAT,⁽⁶⁵⁾ the major comparative trial upon which the recommendation of thiazides as first-line therapy is based (see Table 1).

Table 1: Thiazide used in thiazide placebo-controlled trials with accompanying dosages

Trial Name	Thiazide and Doses Used
SHEP	Chlorthalidone (12.5 mg/d or 25 mg/d)
MRC	Hydrochlorothiazide (25 mg/d or 50 mg/d) + Amiloride (2.5 mg/d or 5 mg/d)
EWPHBPE	Hydrochlorothiazide (25 mg/d) + Triamterene (50 mg/d)
ALLHAT	Chlorthalidone (12.5mg/d - 5 mg/d) vs. Amlodipine (2.5mg/d - 10 mg/d) vs. Lisinopril (10 mg/d-40 mg/d)

Additionally, HCTZ has a shorter elimination half life (5.6 to 14.8 h) than does chlorthalidone (40 h to 60 h). The longer elimination half-life of chlorthalidone may have more effectively lowered overnight blood pressures with better blood pressure control overall in that arm of ALLHAT,⁽⁶⁵⁾ resulting in better outcomes. Many studies and meta-analyses demonstrate the paramount importance of blood pressure control rather than drug type. In ACCOMPLISH,⁽⁶²⁾ only 37.3% of patients had a baseline BP ≤ 139/79 mmHg.

Conclusion: The recommendation of lisinopril-HCTZ as a first-line combination therapy is based on the known efficacy of the individual components, as well as cost considerations. At this time, lisinopril/HCTZ combination therapy (generic Prinzide®) remains the preferred initial combination therapy for both stage 1 and stage 2 hypertension.

In 2009, the GDT also agreed on a consensus basis not to promote other HCTZ fixed-dose combination drugs (e.g., Ziac [bisoprolol/HCTZ] or Tenoretic [atenolol/chlorthalidone]) as options for initial combination therapy because the HCTZ dose in Ziac is suboptimal and furthermore, beta-blockers are now regarded as less favorable compared to calcium channel blockers according to the recommended step-care therapy algorithm for hypertension (see rationale for Step-care Therapy).

2007 Guideline:

No RCTs or meta-analyses were found that measured the effects on important health outcomes of initial combination therapy for hypertension. Ongoing review of the evidence continues to confirm the 2005 evidence-based recommendations.

2005 Guideline:

No RCTs or meta-analyses were found that measured the effects on important health outcomes of initial combination therapy for hypertension.

One large observational study was found (Women's Health Initiative Observational Study)⁽⁶⁶⁾ which generated the hypothesis that combinations of diuretics plus ACEI or beta-blockers were superior to those of diuretics plus CCBs for the prevention of CVD mortality. However, due to the limitations of its design, it did not adequately test the theory and could not be used as evidence for this guideline.

The expanded JNC7⁽³⁾ report mentions recommendations and considerations for the use of combination therapy. The algorithm for treatment of hypertension suggests that Stage 1 hypertension (systolic blood pressure 140 to 159 mm Hg, OR diastolic blood pressure 90 to 99 mm Hg) be treated with thiazide-type diuretics for most individuals, and that clinicians "may consider ACEI, ARB, BB, CCB or combination."

Because most patients will need two or more drugs to lower their blood pressure rates to goal, JNC7 suggests that the "addition of a second drug from a different class should be initiated when use of a single agent in adequate doses fails to achieve the goal." Since using drugs from more than one class enables use of smaller doses, side effects are often diminished with this approach.

Combination medications have been found to increase medication refill adherence.⁽⁶⁷⁾

There is a clear recommendation from the JNC7 for the use of dual medication therapy when first treating Stage 2 hypertension (systolic blood pressure > 160 mm Hg, OR diastolic blood pressure > 100 mm Hg). This usually consists of a thiazide-type diuretic and ACEI or ARB, a BB, or a CCB. However, the report states that "caution is advised in initiating therapy with multiple agents, particularly in some older persons and in those at risk for orthostatic hypotension, such as diabetics with autonomic dysfunction."

Additional supporting evidence for the choice of thiazide diuretics and ACEI can be found in the First-Line Therapy section.

19. Step-Care Therapy for Hypertension

Because most people with hypertension will need more than one drug to control their hypertension effectively:

8A **For two drugs:**

If blood pressure is not controlled on a thiazide-type diuretic alone, then a thiazide-type diuretic + ACEI is recommended. *Consensus-based*

8B **For three drugs:**

If blood pressure is not controlled on a thiazide-type diuretic + ACEI, then a thiazide-type diuretic + ACEI + dihydropyridine calcium channel blocker is recommended.
Consensus-based

8C **For four drugs:**

If blood pressure is not controlled on a thiazide-type diuretic + ACEI + dihydropyridine calcium channel blocker alone, then a thiazide-type diuretic + ACEI + dihydropyridine calcium channel blocker + a beta-blocker or spironolactone is recommended.

Consensus-based

Rationale:

Evidence Grade*

Evidence for Recommendation 8: Insufficient

2009 Update:

New evidence has been identified. Recommendations have been changed based on new evidence and expert/consensus opinion.

Search Strategy

See Appendix B for more information.

Direct Evidence from Step-Care Therapy Trials

A comprehensive literature search was conducted to identify RCTs, systematic reviews, and meta-analyses which explicitly evaluate pharmacologic “step-care” protocols for uncomplicated hypertension. No studies were found that compared any particular step-care therapy approach to another with regard to hard health outcomes.

In the absence of direct evidence, all of the pharmacologic step-care recommendations listed above are based on expert/consensus opinions of the GDT, evidence from first-line drug treatment trials, and cost considerations.

* The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

In 2009, the GDT revised the step-care algorithm by moving dihydropyridine CCB to third position, and beta-blocker/spironolactone to fourth position. The rationale for this change was based mainly on the expert consensus of the GDT, which took into consideration two main factors: 1) indirect evidence from meta-analyses demonstrating the relative lack of effectiveness of beta-blockers vs. comparator drugs, particularly for stroke prevention, and 2) the significant reduction in the cost of the calcium channel blockers (amlodipine) in 2008. An expanded summary and rationale for the recommended hypertension step-care algorithm is provided below.

Evidence from First-Line Treatment Studies (2009 Update Search)

The GDT agreed that drugs that have been found to be beneficial as first-line treatments should be added in a stepwise fashion as additional classes of medications are needed. The 2009 update literature search identified two meta-analyses (Bangalore 2008a, Bangalore 2008b)^(68, 69) and one multi-center RCT (ACCOMPLISH; Jamerson, et al. 2008)⁽⁶²⁾ which directly compared the performances of various first-line therapies in preventing the relevant outcomes. An overview of these studies is presented below.

- ♦ In a meta-analysis conducted by Bangalore, et al. (2008a),⁽⁶⁸⁾ beta-blockers were compared to placebo and other antihypertensive agents (comparison group) to assess the role of heart rate reduction on cardiovascular event risk among patients with hypertension. Nine RCTs evaluating 68,220 patients were included. Mean age was 58 years and mean follow-up time was 3.5 years. Mean SBP from baseline to study end significantly decreased within the beta-blocker and comparison groups ($p < 0.0001$ for both groups). However, the between group comparison was not significant. There was a significant decrease in heart rate in the beta-blocker group compared to the comparison group (12% vs. 1%; $p < 0.0001$). Risk reductions between the two groups were similar with regard to cardiovascular outcomes, nonfatal MI, heart failure, and all-cause mortality. However, meta-regression analyses in the beta-blocker group demonstrated that lower heart rate was significantly associated with a greater risk for all-cause mortality, cardiovascular mortality, MI, stroke, or heart failure ($p < 0.0001$ for each outcome).
 - ♦ In this meta-analysis, dose of medication was not adjusted for in the analyses. Furthermore, the beta-blocker atenolol was mainly used in most of the studies which limits the generalizability of these results to other types of beta-blockers.
- ♦ In a meta-analysis conducted by Bangalore, et al. (2008b),⁽⁶⁹⁾ beta-blockers were compared to placebo and other antihypertensive medications for prevention of new-onset heart failure in hypertensive patients. A total of 12 RCTs enrolling 112,177 patients were included. Mean age ranged from 52 to 76 years and mean follow-up time ranged from 2.1 to 9 years. A random effects model was used for meta-analyses. Beta-blockers were more effective in reducing systolic blood pressure compared to placebo (12.6 ± 7.8 mm Hg). However, when compared to other antihypertensive medications, beta-blockers were similar. With regard to the primary outcome (new-onset heart failure), there was a 23% reduction in the beta-blocker group compared to placebo (95% CI: 0.60 - 1.01, $p = 0.055$) although not significant. When compared to other antihypertensive medications, heart failure incidence was similar for the beta-blocker and comparison groups (2.1% vs. 2.1%, $p = 0.91$). This trend was also seen in comparisons between beta-blockers and individual antihypertensive medications classes (e.g., ACEI/ARBs and CCBs).

- ◆ A subgroup meta-analysis of new-onset heart failure in the young and the elderly (mean age < 60 vs. mean age \geq 60) demonstrated a similarity between beta-blockers and other antihypertensive medications in both cohorts (elderly incidence: 2.3% vs. 2.3%, p = 0.96; young incidence: 1.2% vs. 1.2%, p = 0.88). Additionally, beta-blocker use resulted in a 19% increased risk of stroke in the elderly compared to a 22% decreased risk of stroke in the young compared to other antihypertensive medications.
- ◆ Of note, one of the placebo-controlled trials was a mixed beta-blocker diuretic study. When this study was excluded from the analysis, the mean reduction in systolic blood pressure increased to 10.2 mm Hg and the risk of HF was no longer significant compared to placebo (RR: 0.88, 95% CI: 0.57 - 1.34, p = 0.544).
- ◆ In this meta-analysis, dose of medication was not adjusted for in the analyses and mean age was used as the cut-off for age stratification which could potentially lead to misclassification. Additionally, the studies included in the meta-analysis were those that assessed heart failure as a secondary endpoint. As such, these RCTs were not powered to evaluate heart failure. Furthermore, the beta-blocker atenolol was used in 66% of patients which limits the generalizability of these results to other types of beta-blockers.

Three additional meta-analyses (Bradley,⁽²⁶⁾ Lindholm,⁽²⁵⁾ and Wiysonge⁽³⁸⁾) published prior to the 2009 update search were added to the evidence review because they were not included in 2007 step-care rationale. These 3 meta-analyses, along with the Bangalore et al. meta-analyses, suggest that beta-blockers may not be as effective as comparator drugs for first-line management of hypertension. A brief overview of these studies is presented below.

- ◆ In their systematic review of RCTs, Bradley, et al. (2006)⁽²⁶⁾ identified four trials studying 44,825 patients that compared the effectiveness of beta-blockers with that of calcium channel blockers, assessing the primary outcomes of stroke and all-cause mortality. These authors performed a meta-analysis of these trials and concluded that compared with calcium channel blockers, beta-blockers were less effective in reducing the risk of all-cause mortality (RR = 1.06, 95% CI: 1.00 to 1.14) or stroke (RR = 1.24, 95% CI: 1.11 to 1.40).
- ◆ Wiysonge, et al. (2007)⁽³⁸⁾ studied the pooled results of these same trials in their Cochrane database meta-analysis and confirmed these results. Significant heterogeneity is present in these analyses, since all drugs of a class were treated as a single category.
- ◆ A meta-analysis by Lindholm, et al. (2005)⁽²⁵⁾ comparing beta-blockers with other drugs (n = 105,951, see Figure 1) found that the relative risk of stroke was 16% higher with beta-blockers (95% CI: 4% to 30%, p = 0.009) than with other drugs. All-cause mortality showed a tendency in the same direction, the relative risk being increased by 3% for beta-blockers (95% CI: -1% to 8%, p = 0.14). There was, however, no difference for myocardial infarction. The GDT agreed that based on the reduced benefit for stroke reduction, beta-blocker therapy should not be supported as the first-line agent for initial hypertension therapy.

- ◆ One trial (ACCOMPLISH)⁽⁶²⁾ randomized 11,462 patients with stage 2 hypertension (age > 55 years) to treatment with either amlodipine/benazapril (5/20 mg; titrated to 10/40 mg) or benazapril/HCTZ (20/12.5 mg; titrated to 40/25 mg) in a one-to-one ratio. The trial was terminated early at 36 months (mean) when interim results showed a 20% risk reduction (95% CI: 0.72 - 0.90, p < 0.001) favoring ACEI/CCB for the primary endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, coronary revascularization procedure [PCI or CABG] and/or resuscitated sudden death (Absolute Risk Reduction = 2.2%, Number Needed to Treat = 48). All primary endpoint components except coronary revascularization were individually non-significant, but analysis removing coronary revascularization remained significant; and, analysis of the hard endpoints alone (fatal and nonfatal MI plus fatal and nonfatal stroke) also showed a highly significant risk reduction difference of 20% favoring ACEI/CCB (95% CI: 0.67 - 0.92). Blood pressure reduction was similar in both arms of the study, with a 0.9 mm Hg SBP difference favoring ACEI/CCB.
 - ◆ Although the results of ACCOMPLISH⁽⁶²⁾ may show that the combination of ACEI/CCB has an advantage over ACEI/thiazide-diuretics, there are important limitations that should be considered. Study investigators used approximately one half the dose of thiazide that was used in the lowest dosed thiazide placebo-controlled outcome trials (SHEP,⁽⁶³⁾ MRC trials,⁽⁵⁸⁾ and EWPHE⁽⁶⁴⁾) as well as a major comparator trial, ALLHAT.⁽⁶⁵⁾

Supplemental Evidence:

CAFÉ⁽⁷⁰⁾ (An ASCOT⁽⁷¹⁾ Substudy)

In addition to RCTs from first-line treatment studies, the GDT also considered supplemental results from one RCT. CAFÉ (Williams, et al. 2006)⁽⁷⁰⁾ evaluated the effect of BB+thiazide vs. CCB+ACEI on central aortic pressures. Because this study focused on the intermediate outcome of blood pressure, it did not meet the inclusion criteria for our literature search. Nevertheless, the GDT considered the CAFÉ results to be clinically relevant for decisions made at the expert consensus level.

- ◆ The CAFE (2006)⁽⁷⁰⁾ prospective substudy (n = 2,199) of ASCOT⁽⁷¹⁾ showed that central aortic pressure was not lowered as much with atenolol compared to amlodipine (central aortic systolic BP change: 4.3 mmg Hg; 95% CI: 3.3 – 5.4, p < 0.0001) though brachial pressures were the same. Central aortic pressure was not reduced as much by atenolol due to bradycardia related prolongation of the systolic ejection time, which in turn increased the likelihood that pressure wave reflection from the periphery would augment the outgoing pressure wave. Central aortic pressure reduction is a better predictor of stroke reduction than brachial pressure.

European Society of Hypertension (2007)⁽⁷²⁾ and NICE/British Society of Hypertension (2006)⁽⁷³⁾ Guidelines

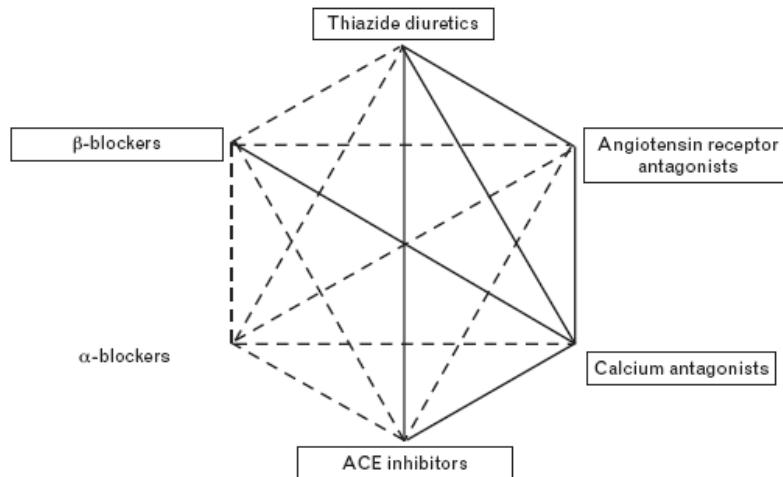
In addition to the evidence presented above, the NICE/British Society of Hypertension (2006)⁽⁷³⁾ and European Society of Hypertension (2007)⁽⁷²⁾ published clinical practice guidelines addressing step-care and combination therapy. Relevant excerpts from each guideline are presented below.

- ◆ According to the European Society of Hypertension Guideline for the management of Arterial Hypertension (2007):⁽⁷²⁾

“Antihypertensive drugs of different classes can be combined if 1) they have different and complementary mechanisms of action, 2) there is evidence that the antihypertensive effect of the combination is greater than that of either combination component, 3) the combination may have a favourable tolerance profile, the complementary mechanisms of action of the components minimizing their individual side effects.

“The following two-drug combinations have been found to be effective and well tolerated, and have been favourably used in randomized efficacy trials. They are indicated with a continuous thick line in the diagram of Figure 2.

- ◆ Thiazide diuretic and ACE inhibitor
- ◆ Thiazide diuretic and angiotensin receptor antagonist
- ◆ Calcium antagonist and ACE inhibitor
- ◆ Calcium antagonist and angiotensin receptor antagonist
- ◆ Calcium antagonist and thiazide diuretic
- ◆ Beta-blocker and calcium antagonist (dihydropyridine)
 - ◆ “The combination of a thiazide diuretic and a beta-blocker is also a time honoured combination which has been used successfully in many placebo and actively controlled trials, but evidence is now available that these drugs have dysmetabolic effects which may be even more pronounced when they are administered together. Thus, this combination, although still valid as a therapeutic alternative, should be avoided in patients with metabolic syndrome and when there is a high risk of incident diabetes.”



Possible combinations between some classes of antihypertensive drugs. The preferred combinations in the general hypertensive population are represented as thick lines. The frames indicate classes of agents proven to be beneficial in controlled intervention trials.

Figure 2: Source: ESH Guideline 2007⁽⁸⁹⁾

- ◆ The NICE/British Hypertension Society Guidelines (2006)⁽⁷³⁾ make the following step-care therapy recommendations:

1.4.6 **New** If initial therapy was with a calcium-channel blocker or a thiazide-type diuretic and a second drug is required, add an ACE inhibitor (or an angiotensin-II receptor antagonist if an ACE inhibitor is not tolerated). If therapy was initiated with an ACE inhibitor (or angiotensin-II receptor antagonist), add a calcium-channel blocker or a thiazide-type diuretic. **B***

1.4.7 **New** If treatment with three drugs is required, the combination of ACE inhibitor (or angiotensin-II receptor antagonist), calcium-channel blocker and thiazide-type diuretic should be used. **B**

1.4.8 **New** If blood pressure remains uncontrolled on adequate doses of three drugs, consider adding a fourth and/or seeking expert advice. **C**

1.4.9 **New** If a fourth drug is required, one of the following should be considered: **C**

- a higher dose of a thiazide-type diuretic or the addition of another diuretic (careful monitoring is recommended) or
- beta-blockers or
- selective alpha-blockers.

* From NICE/British Hypertension Society Guidelines:

"Recommendations provide guidance about appropriate care. Ideally, these should be based on clear evidence: a robust understanding of the benefits, tolerability, harms and costs of alternative patterns of care. They also need to be feasible in the healthcare setting addressed. There are three categories, and each recommendation may be positive or negative, conditional or unconditional, reflecting current evidence and the understanding of the Guideline Development Group."

A* Recommendation: There is robust evidence to recommend a pattern of care.

B* Provisional recommendation: On balance of evidence, a pattern of care is recommended with caution.

C* Consensus opinion: Evidence being inadequate, a pattern of care is recommended by consensus."

Addition of Spironolactone

According to Moser and Setaro (2006),⁽⁷⁴⁾ resistant hypertension is generally defined as uncontrolled hypertension despite three antihypertensive medications from three different classes including a diuretic. Since there are no randomized controlled trials comparing different agents in the fourth position, recommendations are generally based upon open label studies, expert opinion, and other reports that have shown significant spironolactone benefit (Epstein and Calhoun, 2007; Ouzan et al, 2002; Nishizaka et al, 2003; Goodfriend and Calhoun, 2004; Vogt et al, 2007; Handler, 2008).⁽⁷⁵⁻⁷⁹⁾ Additionally, there are reasons to prefer spironolactone even for resistant patients who do not have hyperaldosteronism (Epstein and Calhoun, 2007).⁽⁷⁵⁾

One particular open label study of the ASCOT⁽⁷¹⁾ trial (Dahlof et al, 2005) distinguishes spironolactone from other agents. In ASCOT, the study protocol included three drugs, and after that, participating physicians could select any fourth drug they preferred. In a separate analysis of the ASCOT⁽⁷¹⁾ study performed by Chapman, et al. (2007),⁽⁸⁰⁾ spironolactone performed best of any fourth position drug, and when used in 1411 patients, blood pressure reductions (e.g., at 22/10 mm Hg) were observed. Though Chapman, et al. (2007) included, by far, the largest number of patients involved in a drug treatment study of resistant hypertension, physician familiarity and patient selection bias may have played a role. Most of the patients receiving spironolactone were in the atenolol + thiazide + doxazosin arm of the trial, as opposed to the amlodipine + ACEI + doxazosin arm, because the atenolol-based study arm had reduced blood pressure control compared to the amlodipine-based arm. This difference amounted to 6/2 mm Hg in the first 3 months, and 3/2 mm Hg at the end of the 5.5 year trial. Inferring that atenolol may have inferior blood pressure reducing efficacy compared to amlodipine is possible, but was not directly studied. On the basis of greater familiarity and the lack of need for follow-up laboratory, atenolol may be slightly preferred as a fourth drug, but the evidence suggests that spironolactone should be an alternative selection.

Conclusion: The rationale for moving dihydropyridine CCB to third position, and beta-blocker/spironolactone to fourth position is based mainly on consensus opinion and centers around the following issues:

- ◆ Several meta-analyses demonstrate the inferiority of beta-blocker effectiveness to that of comparator drugs, particularly for the stroke endpoint. The 2008 Bangalore meta-analysis (2008b)⁽⁶⁹⁾ showed that beta-blocker induced bradycardia appears to lead to increased cardiovascular events.
- ◆ The ACCOMPLISH⁽⁶²⁾ trial demonstrates equivalent or possibly superior performance of the calcium channel blocker, amlodipine, to hydrochlorothiazide, which is currently the first-line choice for anti-hypertensive therapy.
- ◆ The ASCOT⁽⁷¹⁾ trial showed that there was an additional 3/2 mmHg blood pressure reduction with amlodipine compared to atenolol. Therefore, moving CCB to third position may reduce the number of members requiring four drugs compared to three drugs. Reducing pill burden also promotes patient adherence.
- ◆ The BHS/NICE 2006⁽⁷³⁾ and EHS 2007⁽⁷²⁾ hypertension treatment guidelines prefer CCB over BB for the third drug, particularly in older patients.
- ◆ The cost of generic amlodipine was dramatically reduced in 2008. Cost/year for amlodipine 5 mg is \$20, compared to atenolol 50 mg at \$6, chlorthalidone 25 mg at \$38, and Prinzide 20/25 mg at \$20.

- Additionally, the GDT agreed by consensus that while beta-blockers might be the preferred fourth line drug, spironolactone should be considered an alternative option as a fourth drug for treatment of resistant hypertension based on evidence from a sub-group analysis of the ASCOT⁽⁷¹⁾ trial.

2007 Guideline:

No new meta-analyses were found that prospectively examined combination or step-care therapy and also measured cardiovascular health outcomes.

Supporting Evidence for CCBs plus ACEIs versus BBs plus Diuretics or BBs

The updated literature search identified one new RCT that included studies of CCBs plus ACEIs versus BBs plus diuretics or BBs.

- In a multicenter RCT involving 19,257 participants, Dahlof, et al. (ASCOT, 2005)⁽⁷¹⁾ compared the effect of two antihypertensive treatments. One group received amlodipine, with perindopril added as needed for blood pressure control, and the other received atenolol, with bendroflume-thiazide added as needed. The primary outcomes in this study included nonfatal myocardial infarction and fatal coronary heart disease. This trial was ended prematurely after the atenolol group demonstrated an increased, but not significant, number of primary endpoint events (474 versus 429). Compared with the atenolol group, all-cause mortality was reduced 11% in the amlodipine group; however, this result did not reach a predetermined level of statistical significance. Stroke incidence was reduced 23%. A limitation of this publication is that both study groups received treatment with combinations of two drugs, and thus the effects of individual agents are difficult to ascertain.

Conclusion: This study does not change the weight of evidence reviewed in prior updates of this guideline. Therefore, the recommendations regarding step-care therapy are unchanged.

2005 Guideline:

No new meta-analyses or RCTs were found that prospectively examined combination or step-care therapy and also measured cardiovascular health outcomes.

The JNC7 report⁽³⁾ recommends that two medications be used for Stage 2 hypertension (systolic blood pressure > 160 mm Hg, OR diastolic blood pressure > 100 mm Hg) or when blood pressure is > 20 mm Hg systolic, OR > 10 mm Hg diastolic above goal. If a patient has not attained goal blood pressure, JNC7 recommends that clinicians “optimize dosages or add additional drugs until goal blood pressure is achieved.”

One new clinical trial was located in which step therapy was used, but the outcomes were hard to characterize due to a complicated study design. The Study on Cognition and Prognosis in the Elderly (SCOPE)⁽⁸¹⁾ treated participants with a diuretic and 8 mg or 16 mg of an ARB, or with a placebo plus diuretic, for the first four months. At that time, due to a change in study protocol, both those in the placebo group and those in the ARB arm whose blood pressure was not yet at goal, were treated with additional antihypertensive medications. It then became an ARB vs. a non-ARB, non-ACEI trial. Because of the long period of placebo use in the control group before initiation of other medications, it is impossible to compare the ARB group with the control group.

The GDT recommended that the step-care therapy guidelines be amended slightly from 2003.

Thiazide-type diuretics remain the initial drug of choice. If blood pressure is not controlled on a thiazide-type diuretic alone, then a thiazide-type diuretic + ACEI is recommended.

There has been increasing evidence of ACEIs' effectiveness in preventing adverse cardiovascular outcomes in low-risk populations (ANBP2).⁽⁵²⁾ ACEIs are very effective at preventing adverse outcomes in those with heart failure and coronary artery disease (EUROPA,⁽⁸²⁾ HOPE,⁽³⁴⁾ Collaborative Group on ACE Inhibitor Trials (CATS)⁽⁸³⁾).

ACEIs are recommended for chronic kidney disease, as they have been demonstrated to preserve renal function (K/DOQI Guidelines, 2004;⁽⁸⁴⁾ AASK⁽³⁹⁾).

ACEIs and diuretics, when used together, reduce hypokalemia (which can accompany diuretic use) and hyperkalemia (which can result from ACEI use alone).

If blood pressure is not controlled on a thiazide-type diuretic + ACEI, then a thiazide-type diuretic + ACEI + beta-blocker is recommended.

Beta-blockers are the next choice since they are cardioprotective in high-risk people (ISIS I,⁽⁸⁵⁾ TIMI IIB,⁽⁸⁶⁾ MIAMI,⁽⁸⁷⁾ BHAT,⁽⁸⁸⁾ and Norwegian Multicenter Study for CAD;⁽⁸⁹⁾ COPERNICUS,⁽⁹⁰⁾ CIBIS-II,⁽⁹¹⁾ and MERIT-HF⁽⁹²⁾ for heart failure; UKPDS for diabetes mellitus⁽⁹³⁾) and have been successfully used in large hypertension trials as part of combined therapy (ALLHAT,⁽⁴⁰⁾ SHEP⁽⁹⁴⁾).

If blood pressure is not controlled on a thiazide-type diuretic + ACEI + beta-blocker, then a thiazide-type diuretic + ACEI + beta-blocker + dihydropyridine calcium channel blocker (e.g., extended-release nifedipine) is recommended.

Both dihydropyridine CCBs (STOP-2,⁽⁴⁸⁾ INSIGHT,⁽⁴⁵⁾ ALLHAT,⁽⁴⁰⁾ Syst-Eur,⁽²⁾ Syst-China,⁽⁹⁵⁾ and HOT⁽⁹⁾) and non-dihydropyridine CCBs (e.g., verapamil, diltiazem) (NORDIL,⁽⁴⁹⁾ INVEST,⁽⁹⁶⁾ CONVINCE,⁽⁴¹⁾ VHAS⁽⁴⁷⁾) have been proven to reduce adverse cardiovascular endpoints when given to individuals with hypertension. However, non-dihydropyridine CCBs are not recommended when individuals are taking beta-blockers, because of the increased risk of symptomatic bradycardia and heart block.

2003 Guideline:

Thiazide diuretics are the preferred choice for first-line treatment for hypertension, but 40 to 60% of the population will need a second drug to achieve blood pressure control, regardless of first choice of drug. No RCTs were found that tested whether any particular subsequent drug combination is superior to another with regard to outcomes. Most drug trials are not confined to monotherapy, but few, if any, randomize and report outcomes in terms of specific combinations of drugs.

Many trials have demonstrated the effectiveness of thiazide diuretics, ACEIs, BBs, and CCBs when used alone and in combination, to reduce the risk of adverse cardiovascular outcomes. Efficacy in reducing outcomes (and/or blood pressure levels) was first demonstrated in placebo-controlled trials (e.g., EWPHBPE,⁽⁶⁴⁾ HOPE,⁽³⁴⁾ PART2,⁽³⁵⁾ QUIET,⁽³⁶⁾ SCAT,⁽³⁷⁾ STOP,⁽³²⁾ SYST-EUR,⁽⁹⁷⁾ SYST-CHINA,⁽⁹⁵⁾) and later, in head-to-head trials (e.g., ALLHAT,⁽⁴⁰⁾ CALM,⁽⁹⁸⁾ CAPPP,⁽⁵¹⁾ CONVINCE,⁽⁴¹⁾ INSIGHT,⁽⁴⁵⁾ MIDAS,⁽⁹⁹⁾ MRC-Elderly,⁽⁵⁸⁾ NICS-EH,⁽⁴⁶⁾ NORDIL,⁽⁴⁹⁾ STOP-2,⁽¹⁰⁰⁾ VHAS,⁽⁴⁷⁾ etc.).

Many drug trials have used thiazide-type diuretics in combination with ACEIs or BBs as two-drug combination therapy, and have demonstrated effectiveness (ALLHAT,⁽⁴⁰⁾ CAPPP,⁽⁵¹⁾ INSIGHT,⁽⁴⁵⁾ LIFE,⁽⁵⁶⁾ NORDIL,⁽⁴⁹⁾ STOP,⁽³²⁾ STOP-2,⁽¹⁰⁰⁾ SHEP,⁽⁶³⁾ and VHAS⁽⁴⁷⁾).

There is very limited evidence of the effectiveness of the combination of calcium channel blockers and thiazide-type diuretics as two-drug combination therapy (optional second choice in SYST-EUR⁽⁹⁷⁾ and SYST-CHINA⁽⁹⁵⁾).

There is very limited clinical evidence demonstrating the effectiveness of ARBs compared with first-line medications. One trial (LIFE⁽⁵⁶⁾) compared an ARB with a beta-blocker but did not compare it with diuretics or with CCBs. The LIFE trial enrolled only a subset of all hypertensive patients, those with LVH, and demonstrated slightly improved outcomes with ARBs as compared with BBs.

When clinical outcomes are similar among medications, other factors (such as side effects, tolerability, and drug costs) can be used to select an appropriate stepwise approach (JNC6⁽¹⁰¹⁾).

20. Discrete Populations – Hypertension Treatment for Women of Childbearing Potential

- 9A ACEIs are not recommended for women of childbearing potential. *Consensus-based*
- 9B To treat chronic hypertension in women of child bearing potential:
 - ◆ Thiazide diuretics are the first choice.
 - ◆ CCBs are the second choice.
 - ◆ BBs are the third choice.

Consensus-based
- 9C When pregnancy occurs, women receiving antihypertensive therapy should be referred to OB/GYN for hypertension management. *Consensus-based*

Rationale:

Evidence Grade*

Evidence for Recommendation 9: Insufficient.

2009 Update:

In May 2009, there was a mid cycle update of this problem formulation. New evidence has been identified. Recommendations have changed.

Search Strategy

A comprehensive literature search of Cochrane, BMJ/Clinical Evidence, PubMed, and OVID websites was conducted to identify systematic reviews, meta-analyses, evidence-based clinical practice guidelines, and randomized controlled trials (RCTs) on which antihypertensive medications should be used in women of child-bearing potential. No studies were found that addressed the specific benefits of ACEI use in women of child bearing potential. However, the primary concern is adverse fetal effects. Given the high rate of unintended pregnancies and the lack of systematic approaches for discontinuing ACEI use in women of child bearing potential who become pregnant, studies which assessed first trimester exposure to antihypertensives were identified.

* The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

Specifically, three case-control studies, one cohort study, one Cochrane systematic evidence review (which included one cohort study that was applicable), one guideline by the National Institute for Health and Clinical Excellence (NICE) and the British Hypertension Society (BHS), one guideline by the BHS, and one FDA medication advisory were identified in the literature search. A cohort study by Cooper et al. (2006) was found during a previous guideline update. Supplemental information on adverse effects of ACEI's in 2nd and 3rd trimester of pregnancy is presented, which underpins the overwhelming expert consensus to avoid ACEI's in pregnancy.

Treatment and Management of Hypertension

Thiazide diuretics either alone or in combination with ACEI's, are recommended as first-line agents for initial therapy in people with hypertension. If blood pressure is uncontrolled by the above-noted therapy, a CCB should be added to the diuretic and ACEI regimen. Lastly, if blood pressure is still uncontrolled, the addition of BBs is recommended. Because ACEI's are not recommended for women of child bearing potential, thiazide diuretics are recommended as first-line therapy, followed by CCBs as second choice, and BBs as third.

Beginning in 2008, the American Journal of Hypertension published a series of position papers on the management of hypertension during pregnancy. One position paper (published in 2008) notes the following: "if disagreements occur (between the hypertension expert and OB/GYN), it is prudent to note that it is the obstetrician who has been managing the pregnancy for months, who is responsible for both the mothers' and fetus' outcomes, and who may be required to defend bad outcomes to official committees and boards" (Lindheimer, et al., 2008).⁽¹⁰²⁾ Because OB/GYN has the ultimate responsibility for maternal and fetal health, pregnant women receiving antihypertensive therapy should be referred to OB/GYN for hypertension management.

Case Control and Cohort Studies and Cochrane Systematic Evidence Review – 1st Trimester Exposure

Caton, et al., (2009)⁽¹⁰³⁾ was a case-control study that reviewed US birth defect surveillance data. Specifically, mothers of 5,021 case infants with cardiovascular malformations (CVMs) and mothers of 4,796 control infants were evaluated to determine whether antihypertensive medications resulted in fetal CVMs. Fetal CVMs included heterotaxy/situs inversus, single ventricle, conotruncal defects, atrioventricular septal defects, right ventricular outflow tract obstructions (RVOTOs), left ventricular outflow tract obstructions (LVOTOs), septal defects, and anomalous pulmonary venous return. However, the numbers of patients reported to have been treated with ACEIs in this study were small (8 cases and 3 controls). Compared with mothers of control infants, mothers of CVM infants were more likely to be older, heavier, and to have developed gestational diabetes.

To test the hypothesis that ACEIs increased the risk of CVMs, the relationship between first trimester use of ACEIs or other antihypertensive medications and the risk of CVMs was compared. A modest yet non-significant elevation in the risk for CVMs related to first trimester use of ACEIs was observed (adjusted OR 1.9, 95% CI: 0.5 to 7.2). Significant increases in the risk of CVMs (using adjusted odds ratio calculations) were detected in relation to the other medication classes combined, antiadrenergic agents, and specifically beta-blockers (see Table 1). Estimates for CVMs were elevated but not statistically significant in women reporting ACEI use (adjusted OR: 1.9%, 95% CI: 0.5 to 7.2). Increases in the risk of CVMs (ranging in adjusted ORs from 1.7 to 2.6) were detected in relation to the use of other medication classes.

Table 1: Adjusted ORs for the Association between First Trimester Use of ACEIs or Other Antihypertensive Medication Classes and the Risk of Cardiovascular Malformations

First-Trimester Use	Controls (n=4796)	Any Study CVM (n=5021)	OR (95% CI) ^a
ACE inhibitors	3	8	1.9 (0.5 to 7.2)
Other medication classes	27	56	1.7 (1.1 to 2.8)
Antidiuretic agents	24	51	1.8 (1.1 to 2.9)
β-Blockers	10	31	2.6 (1.2 to 5.3)
Calcium channel blockers	6	8	1.0 (0.3 to 3.0)
Diuretics	1	8	5.5 (0.7 to 44.6)

^aReference group indicated no history of hypertension. ORs were adjusted for study center, maternal age at delivery (<35 years or ≥35 years), prepregnancy body mass index (underweight/normal or overweight/obese), and gestational diabetes.

Source – Caton et al. (2009)

An exploratory analysis (to generate new hypotheses) was also completed to assess the risk of CVMs in relation to first trimester exposures (as well as second, third trimester, and untreated hypertension) to antidiuretic agents (including BBs), diuretics, and CCBs. First-trimester antihypertensive treatment was associated with pulmonary valve stenosis (PVS) (OR 2.6, 95% CI: 1.3 to 5.4), Ebstein malformation (crude OR 11.4, 95% CI: 2.8 to 34.1), coarctation of the aorta (CoA) (OR 3.0, 95% CI: 1.3 to 6.6), and secundum atrial septal defects (OR 2.4, 95% CI: 1.3 to 4.4).

Table 2 below presents the adjusted ORs for the association between first trimester exposure and risk of CVM by medication class. While the effect estimates are unstable (due to the relatively small numbers of patients exposed), the elevated risks for CVMs were observed for all the medication classes (excluding CCBs). The overall findings of this study suggest that all hypertensive medications appear to be associated with CVMs.

Table 2: Adjusted ORs for the Association Between First Trimester Use of Antihypertensive Medication and the Risk of Selected Cardiovascular Malformations by Medication Class

First-Trimester Use	Controls (n=4796), N†	RVOTO										Septal Defect, Secundum ASD (n=1137)	
		Any Study CVM (n=5021)		PVS (n=534)		Ebstein Malformation (n=85)		LVOTO, CoA (n=406)					
		N	OR (95% CI)*	N	OR (95% CI)*	N	OR (95% CI)*	N	OR (95% CI)*	N	OR (95% CI)*		
Centrally-acting antidiuretic agent‡													
Any	15	27	1.5 (0.8 to 2.9)	3	1.7 (0.3 to 6.0)	3	16.9 (3.0 to 62.1)	4	3.2 (0.8 to 10.2)	6	1.5 (0.5 to 3.9)		
Methyldopa	13	26	1.7 (0.9 to 3.4)	3	1.9 (0.4 to 7.1)	2	12.7 (1.4 to 58.3)	4	3.7 (0.9 to 12.1)	6	1.8 (0.7 to 5.0)		
β-Blocker§													
Any	10	31	2.6 (1.2 to 5.3)	7	5.0 (1.8 to 13.8)	1	8.1 (0.2 to 58.9)	3	3.6 (0.6 to 14.1)	8	2.8 (1.1 to 7.5)		
Atenolol	5	11	1.9 (0.6 to 5.4)	2	4.2 (0.4 to 29.4)	0		1	2.4 (0.1 to 21.5)	1	0.9 (0.1 to 7.8)		
Labetalol	3	11	3.1 (0.9 to 11.2)	1	2.8 (0.1 to 34.9)	0		2	8.0 (0.7 to 70.3)	4	5.9 (1.0 to 40.1)		
Calcium channel blocker													
Any	6	8	1.0 (0.3 to 3.0)	0		0		0		5	3.4 (0.9 to 12.5)		
Diuretic¶													
Any	1	8	5.5 (0.7 to 44.6)	2	16.8 (0.9 to 994)	1	81.5 (1.0 to 6400)	1	12.0 (0.2 to 944)	3	13.2 (1.1 to 692)		
ACE inhibitor#													
Any	3	8	1.9 (0.5 to 7.2)	0		1	27.1 (0.5 to 343)	0		2	2.9 (0.2 to 25.6)		
Angiotensin II receptor blocker**													
Any	0	5		1		0		0		2			
ACE inhibitor or angiotensin II receptor blocker**													
Any	3	13	3.2 (0.9 to 11.1)	1	2.8 (0.1 to 34.9)	1	26.4 (2.3 to 306)	0		4	5.9 (1.0 to 40.1)		

*Reference group indicates no history of hypertension. For CVMs with ≥ 5 exposed cases, ORs were adjusted for study center, maternal age at delivery (<35 years or $\geq 35 +$ years), prepregnancy body mass index (underweight/normal or overweight/obese), and gestational diabetes. For CVMs with <5 exposed cases, crude ORs with exact 95% CIs were calculated.

†There were 4335 controls in the pulmonary valve stenosis analysis because of differences in case ascertainment by study center. The numbers of exposed controls were the same.

‡Data include clonidine and methyldopa.

§Data include atenolol, betaxolol, bisoprolol, labetalol, metoprolol, pindolol, and propranolol.

||Data include amlodipine, diltiazem, nifedipine, nisoldipine, and verapamil.

¶Data include acetazolamide, hydrochlorothiazide, and triamterene.

#Data include benazepril, enalapril, fosinopril, lisinopril, quinapril, and ramipril.

**Data include losartan, olmesartan, and valsartan.

Source – Caton, et al. (2009)

In a cohort study of 1,418 women identified from the Swedish Birth Register, Lennestål, et al. (2009)⁽¹⁰⁴⁾ evaluated the use of antihypertensives in early pregnancy and delivery outcome, specifically infant congenital heart malformations. Women with concomitant diabetes (pre-existing and gestational) were excluded from the review. Cardiovascular defects occurred with an adjusted OR of 2.59 (95% CI: 1.92 to 3.51). Among singleton infants, the risk for preterm birth (OR 3.33, 95% CI: 2.89 to 3.84), low birth weight (OR 4.72, 95% CI: 4.11 to 5.41), and being small for gestational age (OR 4.23, 95% CI: 3.55 to 5.03) was increased, while the risk for heavy infants or being large for gestational age (OR 0.70, 95% CI: 0.54 to 0.89) was decreased. Cardiovascular defects occurred with an adjusted OR of 2.59 (95% CI: 1.92 to 3.51). The results were similar when women used ACEIs (n = 105) or other antihypertensives, notably BBs. Stillbirth rate was increased (RR 1.87, 95% CI: 1.02 to 3.02) without any clear drug specificity.

Table 3: Risk for Any Cardiovascular Defect According to Antihypertensive Drug(s) Used in Early Pregnancy

Antihypertensive drugs used	Number of infants		OR/RR ^a	95% CI
	Malformed	Total		
More than one drug group	9	218	4.00 ^a	1.83–7.60
Only one drug group	33	1,226	2.37	1.68–3.35
ACE inhibitor	5	150	2.90 ^a	0.94–6.76
Other than ACE inhibitor	37	1,294	2.54	1.84–3.52
Only beta-blocking agent	25	798	2.76	1.79–4.08
Only calcium-channel blocker	3	217	1.15 ^a	0.24–3.35
Only ACE inhibitor	2	91	1.68 ^a	0.20–6.08
Only angiotensin II antagonist	0	45	0.00 ^a	0.00–8.25
Only other	3	67	2.50 ^a	0.52–7.32

Odds ratio (OR) after adjustment for year of birth, maternal age, parity, smoking, and BMI with 95% confidence interval (95% CI)

^a Relative risk (RR) was calculated as the observed number of cases over the expected number and with 95% CI estimated from exact Poisson distributions

Source – Lennestal (2009)

A systematic evidence review by Abalos, et al (2007)⁽¹⁰⁵⁾ examined the performance of antihypertensive medications (compared with placebo/no intervention and other antihypertensives) in 4,282 women (in 46 RCTs) with mild to moderate hypertension during pregnancy. Only one study included in the review recruited women during the first trimester of pregnancy.

- Sibai, et al. (1990)⁽¹⁰⁶⁾ compared no medication to methyldopa or labetalol in women with chronic hypertension during pregnancy. In a population of 263 patients with mild chronic hypertension at 6-13 weeks' gestation, 90 women received no drug, 87 received methyldopa, and 86 received labetalol. No differences among the 3 groups were reported regarding the incidences of pre-eclampsia (15%, 18.4%, and 16.3% respectively), abrupted placenta (2.2%, 1.1% and 2.3% respectively) or preterm delivery (10%, 12.5, and 11.6% respectively). A mid-trimester loss in the methyldopa group was reported along with one stillbirth in each remaining group.

Cooper, et al. (2006)⁽¹⁰⁷⁾ reported on an analysis of a cohort of 29,507 infants born to mothers in the Tennessee Medicaid system between 1995 and 2000. They identified 411 infants born to women who had received antihypertensive medication during the first trimester of pregnancy. These patients were further divided into two groups, those who had taken ACEIs (n = 209) and those who had taken any other antihypertensive medication (n = 202). Among infants exposed to ACEIs in the first trimester, the proportion of major malformations was 7.1%. Compared with infants who had no exposure to antihypertensive medications, the risk ratio for major malformations was 2.71 (95% CI: 1.72 to 4.72). Major congenital malformations included cardiovascular malformations (e.g., atrial septal defect, patent ductus arteriosus, ventricular septal defect, and pulmonic stenosis), musculo-skeletal malformations, gastrointestinal malformations, central nervous system malformations, genital malformations, and urologic malformations. Exposure to other antihypertensive medications was not associated with increased risk of major malformations. Hypertensive women not on antihypertensive drug therapy were not included in this study.

A case-control study by Kallen et al. (2003)⁽¹⁰⁸⁾ evaluated cardiovascular defects in infants born to Swedish mothers exposed to a variety of medications (including but not limited to antihypertensives, insulin, fertility drugs, erythromycin, and naproxen). The population included a total of 577,730 case and control infants. In 1,996 women exposed to antihypertensive medications during early pregnancy, the results indicated an approximate doubling of the risk of cardiovascular defects in women with first trimester exposures to any antihypertensive drug (n = 1,996; OR 2.03, 95% CI: 0.38 to 1.57) and beta blockers (n = 1,548; OR 1.85, 95% CI: 1.24 to 2.75). While the associations between maternal drug use and infant cardiovascular defect were identified for antihypertensive drugs and beta-blocking agents, there was no statistically significant difference between medication classes. Hypertensive women not on antihypertensive medications were not studied in this population.

Sorensen et al. (2001)⁽¹⁰⁹⁾ examined the risk of congenital fetal malformations following exposure to CCBs. Data on drug exposure was obtained on 22,865 congenital abnormality cases and 31,151 controls (infants born without congenital abnormalities) obtained from a Hungarian congenital abnormalities birth surveillance system. Among the cases, 586 mothers (2.6%) had been exposed to CCBs during pregnancy compared with 907 control cases (2.4%). The overall prevalence ratios for 17 congenital abnormalities varied between 1.1 and 1.4, and there was no significant increased risk of limb deficiencies or other congenital abnormalities. These results suggest that fetuses exposed to CCBs in utero were not at an increased risk of developing congenital abnormalities, a similar observation made in the Caton et al. study. Similar to other studies that relied on patient recollection on the medications prescribed, this study is also at risk of potential recall bias.

Supplemental Information

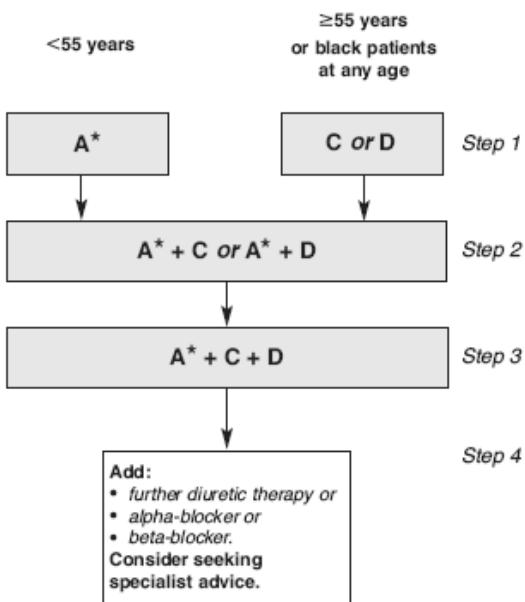
Guidelines

In 2006, NICE teamed with the BHS to update its 2004 hypertension guideline with new pharmacologic management recommendations.⁽¹¹⁰⁾ As the main objective of this update was to generate recommendations regarding the optimal sequencing of drug treatment for hypertension, head-to-head studies comparing any combination of ACEI's, angiotensin-II receptor antagonists (ARBs), BBs, CCBs and thiazide-type diuretics were included in the review. In addition to results in general hypertensive populations, patients with isolated systolic hypertension (ISH), black patients, and younger patients (defined as < 55 years) were considered separately in secondary analyses. A total of 20 studies were identified that satisfied the inclusion criteria for comparisons involving the above-noted drug classes and were used to generate the recommendations included within the algorithm below (Figure 1).

While the guidelines note that BBs are not preferred initial therapy for hypertension, it recommends that they be considered in younger people, particularly those with intolerance or contraindication to ACEIs and ARBs, women of child bearing potential, or patients with evidence of increased sympathetic drive.

In these circumstances, if therapy is initiated with a beta-blocker and a second drug is required, the guideline recommends to add a CCB rather than a thiazide-type diuretic to reduce the patients' risk of developing diabetes.

Figure 1: Treatment of Newly Diagnosed Hypertension



A = ACE inhibitor (*or ARB if ACEI-intolerant); C = calcium-channel blocker; D = thiazide-type diuretic. Beta-blockers are not a preferred initial therapy for hypertension but are an alternative to A in patients < 55 years in whom A is not tolerated or contraindicated (includes women of child-bearing potential). Black patients are only those of African or Caribbean descent. In the absence of evidence, all other patients should be treated according to the algorithm as non-black.

Source – NICE/BHS (2006)

Recommendations developed by the BHS in 2004 note that ACEIs/ARBs should be avoided in women of child bearing potential due to the danger of fetal renal mal-development (Williams 2004).⁽¹¹¹⁾

Table 5 – Compelling and Possible Indications, Contraindications, and Cautions for the Major Classes of Antihypertensive Drugs

Class of drug	Compelling indications	Possible indications	Caution	Compelling contraindications
Alpha-blockers	Benign prostatic hypertrophy		Postural hypotension, heart failure ^a	Urinary incontinence
ACE inhibitors	Heart failure, LV dysfunction, post MI or established CHD, type I diabetic nephropathy, 2 ^o stroke prevention ^a	Chronic renal disease, ^b type II diabetic nephropathy, proteinuric renal disease	Renal impairment ^b PVD ^c	Pregnancy, renovascular disease ^d
ARBs	ACE inhibitor intolerance, type II diabetic nephropathy, hypertension with LVH, heart failure in ACE-intolerant patients, post MI	LV dysfunction post MI, intolerance of other antihypertensive drugs, proteinuric renal disease, chronic renal disease, heart failure ^b	Renal impairment ^b PVD ^c	Pregnancy, renovascular disease ^d
Beta-blockers	MI, angina	Heart failure ^f	Heart failure ^f , PVD, diabetes (except with CHD)	Asthma/COPD, heart block
CCBs (dihydropyridine) CCBs (rate limiting)	Elderly, ISH Angina	Elderly, Angina MI	— Combination with beta-blockade	— Heart block, heart failure
Thiazide/thiazide-like diuretics	Elderly, ISH, heart failure, 2 ^o stroke prevention			Gout ^g

COPD = chronic obstructive pulmonary disease; ISH = isolated systolic hypertension; PVD = peripheral vascular disease; LVH = left ventricular hypertrophy; ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; MI = myocardial infarction.

^aHF when used as monotherapy.

^bACE inhibitors or ARBs may be beneficial in chronic renal failure but should only be used with caution, close supervision and specialist advice when there is established and significant renal impairment.

^cCaution with ACE inhibitors and ARBs in peripheral vascular disease because of association with renovascular disease.

^dACE inhibitors and ARBs are sometimes used in patients with renovascular disease under specialist supervision.

^eIn combination with a thiazide/thiazide-like diuretic.

^fBeta-blockers are increasingly used to treat stable heart failure. However, beta-blockers may worsen heart failure.

^gThiazide/thiazide-like diuretics may sometimes be necessary to control BP in people with a history of gout, ideally used in combination with allopurinol.

Source – Williams 2004

FDA Tool: Advisory for ACEIs

In June 2006, the FDA issued a public health advisory on the use of ACEIs during pregnancy.⁽¹¹²⁾ Based entirely on the 2006 Cooper, et al. study, the FDA labeled ACEIs with a pregnancy category C for the first three months and category D for the last six months (second and third trimesters). Pregnancy category C means that the risk in pregnancy is possible but unknown, because no good studies of pregnant women have been conducted, and animal studies either have shown risk in pregnancy or have not been conducted. Pregnancy category D means that there have been studies in pregnant women showing that the drug was associated with some risk for the unborn baby (fetus), but the benefit of the drug may still outweigh that risk for some patients. Specifically, the FDA issued the following recommendations:

- ◆ Healthcare providers who care for women of reproductive age should counsel those who are treated with an ACEI about the potential risks of these drugs throughout pregnancy, especially during the second and third trimesters.
- ◆ Pregnant women should only be prescribed ACEIs if the expected benefit clearly exceeds the potential risk.
- ◆ Women who become pregnant should have their ACEI changed to a different medication as soon as possible.
- ◆ Women who are taking ACEIs to treat high blood pressure should tell their healthcare professionals if they are planning a pregnancy or think they might be pregnant.

Case Reports and Observational Studies - 2nd and 3rd Trimester Exposure

Plausible renal pathophysiology and numerous case reports suggest that 2nd and 3rd trimester exposure to ACEI's results in adverse outcomes including mortality. When taken during pregnancy, ACEI's are known to cross the placental barrier, enter the fetal circulation and potentially alter fetal development, particularly the development of the kidneys (Boubred et al., 2006).⁽¹¹³⁾ Studies indicate that the fetus and newborn infant may experience renal failure, varying from transient to oligohydramnios to severe neonatal renal insufficiency leading to death. One study reports that calvarial hypoplasia associated with ACE inhibitor exposure has been associated with impaired cranial ossification due to increased uterine pressure on the developing bones of the skull due to prolonged oligohydramnios (Bhatt-Mehta et al., 1993).⁽¹¹⁴⁾ Other studies have reported that human fetuses display a higher vulnerability to ACEI's, exhibiting a malformative syndrome that does not appear in studies of animal counterparts. A reason for this vulnerability is the earlier intrauterine development of the kidney and renin-angiotensin-aldosterone (RAS) system in humans, organ systems that are specific targets of ACEI's pharmacological effect (Tabacova et al., 2005).⁽¹¹⁵⁾ In humans, these systems develop prior to skeletal formation occurring at the end of the first trimester, with continued vulnerability throughout the pregnancy.

Conclusion

Studies examining fetal and maternal effects of antihypertensive drugs in first trimester pregnancy are limited to a few case control and record linkage studies (Lennestal, Cooper) with inconsistent results. Inconsistencies among the studies are noted regarding adverse effects on hypertensive pregnant patients treated with 1) antihypertensive medication in general, and 2) individual classes of antihypertensive agents. Only one study examined adverse effects of untreated hypertension. These observational studies do not have the power to support the view that any particular group of agents, i.e., BBs or CCBs, is preferable in early pregnancy. In addition, the results of these studies do not indicate that any particular group of agents, including ACE's, are not preferable in early pregnancy. As a result, there is insufficient direct evidence to recommend for or against the use of any specific class of antihypertensive drug therapy in first trimester pregnancy.

Nevertheless, plausible renal pathophysiology and numerous case reports suggest that 2nd and 3rd trimester exposure to ACEI's results in adverse outcomes including mortality. This has lead to overwhelming expert consensus that ACEI's are contraindicated during pregnancy. In the absence of a systematic approach for discontinuing ACEI use in women of child bearing potential and a high rate of unplanned pregnancies in the population, early pregnancy ACEI exposure may carry on to later trimester exposure. As a result, such concerns call for the recommendation against use of ACEI's in women of child bearing potential.

2007 Guideline:

One publication was identified in the peer-reviewed medical literature that addressed the risks associated with the use of ACEIs during pregnancy.

- ♦ Cooper, et al. (2006)⁽¹¹⁶⁾ reported on an analysis of a cohort of 29,507 infants born to mothers in the Tennessee Medicaid system between 1995 and 2000. They identified 411 infants born to women who had received antihypertensive medication during the first trimester of pregnancy. These patients were further divided into two groups, those who had taken ACEIs ($n = 209$) and those who had taken any other antihypertensive medication ($n = 202$). Among infants exposed to ACEIs in the first trimester, the proportion of major malformations was 7.1%. Compared with infants who had no exposure to antihypertensive medications, the risk ratio for major malformations was 2.71 (95% CI: 1.72 to 4.27). Exposure to other antihypertensive medications was not associated with increased risk of major malformations.

Conclusion: One large retrospective cohort study found that exposure to ACEIs in early pregnancy prior to a positive pregnancy test was associated with increased risk of major congenital abnormalities. Use of ACEIs in patients who are pregnant is unsafe. Thus, use of ACEIs should be avoided in patients at risk for pregnancy, and appropriate counseling should be provided to those who become pregnant while taking ACEIs.

21. Discrete Populations – Post-Stroke Treatment of Hypertension

Combination therapy with a thiazide diuretic plus an ACE inhibitor is recommended as initial treatment for patients who are post-stroke, or post-TIA* with hypertension or prehypertension. *Evidence-based: B*

Rationale:

Evidence Grade[†]

Evidence for Recommendation 10: Good.

2009 Update:

No new evidence has been identified. Recommendations remain unchanged.

Search Strategy

Only RCTs, clinical trials, systematic reviews, or meta-analyses with clinical outcomes that studied individuals with a prior diagnosis of stroke or TIA who were randomized to head-to-head trials of antihypertensive agents were included. See Appendix B for more information.

2007 Guideline:

Two large RCTs were identified in the peer-reviewed medical literature that addressed the treatment of patients who had been previously diagnosed with stroke or TIA.

- ♦ The PROGRESS trial (Progress Collaborative, 2001)⁽¹²⁾ studied a group of 6,105 patients who had had a stroke or TIA in the previous five years and who were randomized to receive either an ACEI plus a diuretic, if needed, or placebo. Patients were evaluated five times during the first year and at six-month intervals thereafter for five years. The primary outcome of this study was fatal or nonfatal stroke. A total of 727 study participants had a stroke during follow-up: 307 (10%) in the treatment group and 420 (14%) in the placebo group (relative risk reduction 28% [95% CI: 17 to 38%]; p < 0.0001).

* Transient ischemic attack (TIA) is defined as evidence of an acute disturbance of focal neurological or monocular function with symptoms lasting less than 24 hours thought to be due to arterioembolic or thrombotic vascular disease.

† The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

- ◆ The MOSES trial (Schrader, et al., 2005)⁽¹¹⁷⁾ was a multicenter RCT that studied 1,404 patients with hypertension who had been diagnosed with a cerebrovascular event during the preceding 24 months. These patients were randomized to eprosartan or nitrendipine therapy, with the suggested addition of diuretics, then beta-blockers, then alpha-blockers, then centrally acting substances as needed to achieve target blood pressure. The primary endpoint was the composite of all-cause mortality and the number of cardiovascular and cerebro-vascular events, including all recurrent events.
 - ◆ A total of 34.4% received monotherapy with eprosartan and 33.1% with nitrendipine. Mean follow-up was 2.5 years. The primary endpoint was the composite of total mortality and all cardiovascular and cerebrovascular events (including myocardial infarction, new cardiac failure, intracerebral hemorrhage, recurrence of stroke, and TIA or prolonged reversible ischemic neurological deficit, including all recurrent events).
 - ◆ Blood pressure was reduced comparably in both groups. During follow-up, 461 primary events occurred: 206 in the eprosartan group and 255 in the nitrendipine group (incidence density ratio [IDR] = 0.79; 95% CI: 0.66 to 0.96; p < 0.014). There were 77 cardiovascular events in the eprosartan group and 101 in the nitrendipine group (IDR = 0.75; 95% CI: 0.55 to 1.02; p = 0.06).
 - ◆ There were 102 cerebrovascular events in the eprosartan group and 134 in the nitrendipine group (IDR = 0.75; 95% CI: 0.58 to 0.97; p = 0.03). A total of 236 cerebrovascular events occurred: 102 in the eprosartan group and 134 in the nitrendipine group (IDR = 0.75; 95% CI: 0.58 to 0.97; p < 0.026).
 - ◆ There were 31 ischemic strokes in the eprosartan group versus 39 in the nitrendipine group, 66 TIAs in the eprosartan group versus 92 in the nitrendipine group, and 5 intracerebral hemorrhages in the eprosartan group versus 3 in the nitrendipine group.
 - ◆ However, the strength of the evidence from this study is somewhat limited because of the small number of events observed and the nonstandard approach for statistical analysis. In particular, the authors used an endpoint that included a broad range of clinical events, including TIAs (a soft endpoint), and tallied multiple TIAs in the same patient, rather than just the first event.

Conclusion: Based on the evidence from the PROGRESS trial, the GDT finds that, for reducing cardiovascular events in patients with a prior diagnosis of stroke or TIA. The benefits of the combination of a thiazide diuretic plus an ACE-inhibitor exceed the harms and costs. Because of its methodologic flaws, the results of the MOSES trial were given very little weight in the discussion about this clinical question. Treatment with a thiazide diuretic and an ACEI should be given as initial therapy for patients who are post-stroke.

22. Behavioral Change – Supplementary Treatment of Uncomplicated Hypertension with Lifestyle Modifications

- 11A A moderately low-sodium, low-fat diet with a high intake of fruits and vegetables (DASH diet) is recommended to supplement pharmacotherapy for patients with hypertension. *Consensus-based*
- 11B Weight reduction is recommended for patients with a BMI $\geq 25 \text{ kg/m}^2$ on antihypertensive medications. *Consensus-based*
- 11C It is recommended that hypertension patients who consume alcohol have no more than one alcoholic drink (for women) or two alcoholic drinks (for men) daily. *Consensus-based*
- 11D Physical activity (at least 30 minutes of walking or equivalent at least three times per week) is recommended for patients with hypertension who are on medications. *Consensus-based*

Rationale:

Evidence Grade*

Evidence for Recommendation 11: Insufficient.

2009 Update:

No new evidence has been identified. Recommendations remain unchanged.

Search Strategy

Initially, only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension who were treated with antihypertensive medications and were randomized to intervention vs. control groups were searched for. There were no studies with hard outcomes and few with treated populations, so the intermediate outcome of blood pressure was used, as were some studies with untreated populations. See Appendix B for more information.

2007 Guideline:

No new evidence has been identified. Recommendations are unchanged from the 2005 update.

2005 Guideline:

No additional evidence was found since the 2003 guideline that would change the recommendations.

* The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

2003 Guideline:**All Recommendations:**

No studies were found with clinical outcomes. Consequently, the assumption is made that lowering blood pressure can serve as a reasonable intermediate measure, since an association has been found between blood pressure and clinical outcomes in clinical trials of hypertension medications. This partially accounts for the consensus-based nature of the behavior change guidelines.

Few studies took place in hypertensive populations which were treated with antihypertensive medications. These data were used whenever possible, but it was often necessary to extrapolate from an untreated population to draw conclusions. This also contributes to the fact that these are consensus-based guidelines.

Despite the limitations of the evidence, these measures are recommended because there is indirect evidence of effectiveness since they lower blood pressure, they carry no risks other than those of ordinary life, they may offer additional health benefits, and they are low in cost for both members and KP.

Recommendation 11A:***Supporting Evidence for Recommending a Moderately Low-Sodium, Low-Fat Diet with High Intake of Fruits and Vegetables (DASH diet) to Augment Pharmacotherapy***

A literature search of diet therapy and hypertension yielded no meta-analyses which addressed interventions for hypertension patients on medication.

Jurgens⁽¹¹⁸⁾ conducted a meta-analysis of sodium reduction trials as far back as 1973 (an update of Graudal's 1998 JAMA meta-analysis⁽¹¹⁹⁾). Inclusion criteria were 1) randomization to either a low- or high-sodium diet; 2) use of 24-hr urinary excretion to measure sodium intake; 3) if subjects were taking part in another intervention, the intervention was identical during both low- and high-sodium diets; 4) both systolic blood pressure and diastolic blood pressure were reported; and 5) mean age > 15 years. Ninety-six references (with 137 populations) were included, and the analysis covered appropriate trials that were evaluated in four previous meta-analyses (Grobbee,⁽¹²⁰⁾ Cutler,⁽¹²¹⁾ Law,⁽¹²²⁾ and Midgley⁽¹²³⁾). It includes 11 additional studies and omitted three with diabetic populations. Few studies were longer than four weeks, and most used very restricted salt intakes that may not be feasible in a free-living population.

There were 58 studies in persons with hypertension. They included those on and off anti-hypertensive medications. The effect on systolic blood pressure was -4.18 mm Hg (95% CI: -5.08 to -3.27; p < 0.0001) and -1.98 mm Hg on diastolic blood pressure (95% CI: -2.46 to +1.32; p < 0.0001). Mean sodium reduction was 118 mmol / 24 hours for 28 days.

Appel⁽¹²⁴⁾ reported on the outcomes of the Trial of Nonpharmacologic Interventions in the Elderly (TONE) in which 681 mildly hypertensive subjects, aged 60 to 80 years, were randomly assigned to a low-sodium and weight-reduction, low-sodium alone, or control diet. (This article discusses both obese and nonobese participants but only those assigned to the reduced-sodium or control groups.)

Participants were on a single medication for hypertension, and their mean baseline blood pressure was 128.0/71.3 mm Hg. All subjects were withdrawn from their medications at three months. At that time, those on the low-sodium diet showed a mean reduction of 4.3 mm Hg systolic blood pressure ($p < 0.001$) and 2.0 mm Hg diastolic blood pressure ($p = 0.001$). The participants then continued in the trial until reaching a study endpoint (systolic blood pressure ≥ 150 mm Hg, diastolic blood pressure ≥ 90 mm Hg, resumption of medication, or a CV event during follow-up). Mean follow-up was 27.8 months. Fifty-nine percent (59%) of those on the low-sodium intervention reached an endpoint compared with 73% of controls ($RH = 0.68$; $p < 0.001$).

This trial showed that a free-living population of older hypertensive individuals can achieve and maintain a reduced sodium diet, with the help of significant interaction with “interventionists.” Members of this group showed a significant decrease in blood pressure while on a medication, and significantly more of them, once withdrawn from the drug, were able to maintain their endpoint-free status compared with control group members.

The DASH diet (Dietary Approaches to Stop Hypertension – Vollmer⁽¹²⁵⁾) was a successful trial of a diet high in fruits, vegetables, and whole grains, and low in fat and refined sugars, for those with hypertension. In this trial, the DASH diet was compared with a control (“typical American”) diet, but participants in each arm ate at a higher sodium (Na+) level (150 mmol/d), an intermediate level (100 mmol/d), and a lower level (50 mmol/d) for 30 days each. Weight remained constant during the study. Blood pressure levels were reduced by the DASH diet, but not significantly. The significant reductions were seen with increasing increments of sodium restriction. Individuals were excluded from the study if they were on medications.

Hypertensive participants in the trial showed a significant decrease in systolic blood pressure when the lower vs. higher sodium control diets were compared (-8.3 mm Hg [95% CI: -10.0 to -6.6], $p \leq 0.05$) as well as with the lower vs. higher sodium DASH Diet (-4.9 mm Hg, [95% CI: -6.6 to -3.3], $p \leq 0.01$). When the lower sodium DASH diet was contrasted with the higher sodium control diet, mean systolic blood pressure decreased by 11.5 mm Hg ([95% CI: -14.1 to -8.9], $p \leq 0.01$). A similar pattern was seen for diastolic blood pressure.

In sum, there is a great deal of evidence about the direct relationship of sodium consumption to blood pressure. Although there are no large-scale, randomized trials which address this question in hypertensive individuals on pharmacotherapy, the dietary modifications of increasing intake of fruits and vegetables, and decreasing sodium and fat can be recommended on a consensus basis because of their success in decreasing blood pressure in varied populations, in addition to the many other health benefits they offer.

Recommendation 11B:

Supporting Evidence for Weight Reduction as an Adjunct to Pharmacotherapy

Mulrow⁽¹²⁶⁾ performed a Cochrane meta-analysis (substantive update, 1998; most recent amendment, 2004) whose aim was to evaluate weight reduction diets vs. regular diets and/or placebo in decreasing blood pressure in obese hypertensive adults, and to assess whether weight reduction diets are better than pharmacotherapy. Eighteen trials were initially included, none of which reported morbidity and mortality outcomes or had adequate power to do so.

The weight reduction interventions were generally successful and participants lost between 3% and 9% of body weight, but net loss could not be compared due to differences in follow-up time. There were reductions of approximately 3.00 mm Hg in both systolic and diastolic pressure. Stepped approaches to pharmacotherapy resulted in greater decreases in blood pressure (about 6.00 / 5.00 mm Hg) than did diet. However, when trials allowed subjects to take antihypertensive medications while on the weight reduction diet, they required less medication than did those on the normal diet. These analyses did not answer questions about long-term effects of weight reduction or weight reduction attempts.

As part of the Hypertension Optimal Treatment (HOT) study,⁽¹²⁷⁾ patients with a BMI ≥ 27 and on medications were randomized to receive a weight reduction intervention (diet counseling, group support) or to the control group. Those in the intervention lost significantly more weight than controls at six months (but not at three, 12, 18, 24, or 30 months). They regained their weight after six months, but used “a significantly smaller number of medication steps” to control their blood pressure at all time intervals, except at three months. For example, medication steps needed at six months: Intervention Group -2.92 ± 1.25 steps; Control Group -3.47 ± 1.29 steps; $p = 0.03$.

To summarize, due to the scant data available which assess the effectiveness of weight reduction in lowering blood pressure for individuals on antihypertensive medications, and the lack of information on the impact weight reduction has on disease outcomes, recommendations to lose weight to improve hypertension must be consensus recommendations. Weight reduction must be seen as an adjunct rather than as sole therapy for hypertension. In addition to small reductions in blood pressure, weight loss may also result in the need for less medication.

Recommendation 11C:

Supporting Evidence for Alcohol Moderation

Many epidemiological studies have established a dose-response relation between excessive drinking (more than two drinks/day) and increased blood pressure. Klatsky and Friedman,⁽¹²⁸⁾ in their 1985 investigation, studied KP multiphasic examination data in 66,510 normo- and hypertensive adults who were not on antihypertension medication. Generally, the authors found a strong relation between alcohol use and an increase in blood pressure, but it was not a uniform relation in the entire population.

There was a slight increase for white and black men who drank one to two drinks daily, and a continuing increase for white men, peaking at six to eight drinks/day. White women, however, showed a significant increase in systolic blood pressure at only three drinks/day. In black males, diastolic pressure showed a continuous increase, but the data for black women had the least consistent correlation. The study distinguished between nondrinkers who were previously heavy drinkers and lifelong abstainers to prevent confounding, but in fact, there was no difference in their blood pressure levels.

Most RCTs examining this question take place in very small populations, for short duration, and either do not study, or do not separate, results for hypertensive participants who are being treated with medications. Most of these studies were excluded from consideration.

In the PATH Study (Cushman,⁽¹²⁹⁾ n = 266 participants with hypertension), Veterans Administration patients in the intervention group took part in a cognitive-behavioral program with six counseling sessions over three months, followed by a minimum of three sessions at monthly intervals for the remainder of the six-month treatment phase. The maintenance period consisted of at least of six visits at one- to three-month intervals. More frequent visits took place, if needed.

This is one of the few trials with a large population, a long follow-up interval (two years), and separate analysis of hypertension patients. Hypertension participants were not on medications. The intervention group of the hypertensive stratum lowered alcohol intake from the baseline of 4.6 drinks/day by 2.6, to 2.0 drinks/day, whereas the control group decreased alcohol by 0.7 drinks/day from 4.3 to 3.6 drinks/day (p of between-group difference < 0.001). The goal was for the intervention group to decrease baseline alcohol ingestion by 50% or to 14 drinks/week. In the hypertension group, 46% of the intervention group had reached that goal at six months, and 33% remained at the goal at two years. (The corresponding results for the control group were 22% and 18%.)

Blood pressure levels in the intervention group were reduced by -5.5/-6.8 mm Hg, which was not significantly different from that of the controls (-4.7/-4.4). The authors attribute this lack of a significant result to the fact that the reduction in alcohol consumption in the intervention arm was not as great as expected, a function of the difficulty of effecting this change in a free-living population. In sum, reduction in drinking was significantly different between groups, but reduction in blood pressure was not.

A successful intervention trial in a French work-site health program (Lang,⁽¹³⁰⁾ n = 129) in heavy drinkers achieved a nonsignificant reduction in the number of drinks taken per day at one year when compared with controls (-2.8 for the intervention group, -1.6 for controls, p between-group difference = ns). The goal of the study was for intervention participants to monitor their gamma glutamyltransferase (GGT) levels and decrease drinking until their GGTs were in the normal range. They were seen by their physicians, who were trained for this intervention, at their yearly work-site physical examination, and were counseled then and at four additional follow-up visits. Eighteen percent (controls) vs. 21% (intervention) of participants were on antihypertension medications. Blood pressure levels also decreased at (one year) and two years:

Systolic: Intervention group [-11.5] +14.0 mm Hg;
Control group [-6.0] -7.4 mm Hg, p [< 0.05] < 0.05 (difference between groups)

Diastolic: Intervention group [-6.0] -9.5 mm Hg;
Control group [-5.3] -5.5 mm Hg, p value not stated.

In this study, the decrease in alcohol ingestion was not significantly different between groups, but the difference in blood pressure reduction was significant.

Further evidence of alcohol's effect on blood pressure was provided by Parker,⁽¹³¹⁾ who studied men who were treated for hypertension ($n = 63$). The trial aimed to distinguish whether cutting sodium consumption in drinkers who reduce their alcohol intake further decreases blood pressure. At the start of the study, the men were divided into four groups:

Group 1: usual alcohol intake, low-sodium diet and placebo sodium pills

Group 2: usual alcohol intake, low-sodium diet and actual sodium pills to equal a normal sodium intake

Group 3: reduced alcohol intake (low-alcohol beer) and, low-sodium diet and placebo sodium pills

Group 4: reduced alcohol intake (low-alcohol beer) and, normal sodium intake (as above).

The change in alcohol intake at the end of the four week trial period was as follows: the “usual intake” groups (one and two) increased alcohol consumption from 7.75 to 7.95 drinks/day. The groups which were assigned to low-alcohol beer (three and four) reduced consumption from 7.67 to 0.81 drinks/day.

Change in systolic blood pressure, mm Hg, at four weeks:

Group 1: -0.5 (95% CI: -3.6 to 2.7) $p = ns$

Group 2: -0.4 (95% CI: -4.4 to 4.0) $p = ns$

Thus, reducing sodium alone did not cause a meaningful reduction in systolic pressure.

Group 3: -4.7 (95% CI: -6.6 to -2.9) $p < 0.01$

Group 4: -6.9 (95% CI: -10.8 to -2.9) $p < 0.001$

Reducing alcohol made a significant difference in systolic blood pressure, but lowering sodium had no additional effect.

Similar results were seen for changes in diastolic blood pressure, mm Hg, at four weeks:

Group 1: -0.1 (95% CI: -2.2 to 1.9) $p = ns$;

Group 2: -0.9 (95% CI: -3.1 to 1.4) $p = ns$;

Group 3: -3.5 (95% CI: -4.4 to -2.6) $p < 0.01$;

Group 4: -4.0 (95% CI: -6.2 to -1.8) $p < 0.001$

The researchers found that blood pressure levels improved significantly with decrease in alcohol ingestion but that there was no additional advantage to following a low-salt diet. This finding argues against the hypothesis that higher blood pressure in drinkers may be a function of consuming high-sodium foods that may accompany the drinking habit. It supports the idea that, in heavy drinkers, it may be more important to focus on changing to a moderate alcohol habit than to counsel toward a low-salt diet. In this study, a significant reduction in drinking alcohol led to a significant decrease in blood pressure.

Puddey⁽¹³²⁾ also studied treated hypertension patients ($n = 44$ men) and used a crossover design with low-alcohol beer to substitute for usual drinking. Participants were randomly assigned to two groups. While the first group decreased their alcohol for six weeks, the other drank normally. They then switched protocols for another six weeks. During low-alcohol periods, participants decreased alcohol intake from 452 to 68 ml/week (from 6.5 to 1.0 drinks/day). Blood pressure decreased from 134/77 to 128/83 mm Hg (± 6.0 mm Hg), $p < 0.001 / < 0.01$. The authors commented that change in blood pressure was smaller than expected, largely because the participants were already well controlled with medications. Nevertheless, a significant reduction in drinking alcohol led to a significant decrease in blood pressure.

From the examples here (the larger, longer studies available and those in participants on medications) the relationship between the change in drinking and blood pressure reduction is not always clear. All were limited by self-report methodology. However, even if particular interventions did not yield significant differences between the results for the intervention and control groups, the interventions did reduce systolic blood pressure from 4.7 to 14.0 mm Hg, which has positive implications for public health.

There is, in addition, a sizable observational literature pointing to the correlation between intake of more than two alcoholic drinks/day and significant increases in blood pressure, as well as examples of significant reductions in blood pressure when drinking is curtailed. The current literature of small RCTs usually has the aim of reducing the alcohol intake of heavy drinkers and observing the effect on blood pressure; thus, the conclusions do not allow for the determination of a specific number of drinks/day at or below which there is no effect on blood pressure. Given the lack of sufficient large-scale RCTs of significant duration in patients with hypertension on pharmacological therapy, these recommendations must be based on expert consensus.

Note: The definition of moderate drinking (one to two drinks/day) is from the US Department of Agriculture/Department of Health and Human Services publication *The Dietary Guidelines* (1995). One drink equals 12 oz. of regular beer, 5 oz. of wine, or 1.5 oz. of 80-proof distilled spirits.

Recommendation 11C:

Supporting Evidence for Physical Activity as an Adjunct to Pharmacotherapy

Only one RCT examined the relation between physical activity and blood pressure in treated hypertensive patients (Arroll⁽¹³³⁾). A second limitation in the literature for evaluating this question is that most studies include subjects with a range of blood pressures, from normotension through a moderate level of hypertension. Few separate the findings by baseline blood pressure level.

Fagard's⁽¹³⁴⁾ 2001 meta-analysis included 44 RCTs (68 training groups/programs) of at least four weeks duration. The issue of treatment with medications was not discussed.

Results for the question of overall physical activity and its relation to blood pressure control were examined by blood pressure status. The training-induced net change of blood pressure (95% CI) averaged -7.4 (-10.5 to -4.3) / -5.8 (-8.0 to -3.5) mm Hg in the 16 hypertensive groups after a median of 16 weeks of training. Fagard also analyzed the influence of training characteristics, although these findings were not stratified by blood pressure level. Neither frequency of activity, duration of the session, kcal/week expended, nor exercise intensity (moderate to hard) were significantly related to change in blood pressure.

Arroll⁽¹³³⁾ studied salt restriction and physical activity in 208 treated hypertensive men and women in the community. Four groups, including a control group, were formed and given advice (simple oral or written information). Both the exercise and the salt-restricted groups showed significant reductions in systolic pressure at three months (-14.3 mm Hg; -13.1 mm Hg), but the group testing both exercise and reduction in salt did not. No groups demonstrated significant blood pressure changes at six months.

To summarize, moderate-intensity exercise programs which take place about three times per week seem to result in reductions in blood pressure levels of about 7.4/5.8 mm Hg. However, there are insufficient analyses available in treated hypertensives to support an evidence-based recommendation.

All Recommendations:

Supporting Evidence for Interventions with Multiple Lifestyle Modalities as Adjuncts to Pharmacotherapy

The PREMIER⁽¹³⁵⁾ study in untreated individuals ($n = 810$; 307 with hypertension) with high-normal (labeled prehypertension in JNC7) or Stage 1 hypertension examined the impact of two intensive behavioral interventions (Groups two and three) when compared with a short session of generic advice (Group one). Group two's intervention was based on the "established" recommendations to decrease weight (by 15 lb if $BMI \geq 25 \text{ kg/m}^2$), do at least 180 min/wk of moderate-intensity exercise, decrease dietary sodium to $\leq 100 \text{ mEq/day}$, have a daily intake of no more than 1 oz of alcohol/day for men and $\frac{1}{2}$ oz for women, and reduce the percentage of calories from total fat to $\leq 30\%$, and the percentage of calories from saturated fat to $\leq 10\%$. Group three followed the same "established" guidelines plus those of the DASH (Dietary Approach to Stop Hypertension) diet (nine to 12 servings of fruits and vegetables daily, two to three servings of low-fat dairy foods/day, reduced consumption of saturated fats to $\leq 7\%$ of calories, and reduced consumption of total fats to $\leq 25\%$).

Participants in the two intervention groups met 18 times in group or individual sessions with the interventionist over six months and kept diaries on food, alcohol, and activity. Trial results showed that both interventions significantly lowered blood pressure after six months, but participants in the "established" + DASH arm did not do significantly better than those in the "established-only" arm.

Reductions in blood pressure at six months, mm/Hg:

“**Advice-only:**” 7.8 / 3.8

“**Established-only:**” 12.5 / 5.8

[p of change in Established minus change in Advice < 0.001 / ns]

“**Established + DASH:**” 14.2 / 7.4

[p of change in Established + DASH minus change in Advice < 0.001 / 0.001]

The DASH diet group performed less well than what would have been expected based on previous research, possibly because this group attained a fruit/vegetable intake of 7.8 servings daily vs. 9.6 in the original DASH study. In addition, the effort of maintaining a large number of dietary and behavioral changes may have resulted in “subadditivity” (decreased adherence with multiple interventions).

The DEW-IT trial⁽¹³⁶⁾ tested multiple lifestyle interventions (dietary change [DASH diet]), sodium reduction, weight reduction, alcohol reduction, and exercise) for nine weeks in 44 overweight or obese hypertensive subjects (average blood pressure 130 to 170 mm Hg/ 80 to 100 mm Hg) on a stable dose of one medication or fixed dose combination pill. Mean ambulatory blood pressure was reduced by -10.5/ -5.9 mm Hg in the intervention group and by -1.1/ -0.6 mm Hg in controls. The net change was -9.4/ -5.3 mm Hg (p < 0.0001 / < 0.002). There was also a significant net weight reduction of 4.9 kg (p < 0.0001), net decrease in total cholesterol (25 mg/dl, p = 0.001), net decrease in LDL-cholesterol (18 dm/dl, p = 0.005), and a net improvement in fitness measures (five-minute heart rate reduction = 8.6, p = 0.011; ratio perceived exertion -2, p = 0.035).

The PREMIER study (in untreated individuals) and the DEW-IT trial (in individuals on one medication) demonstrated a comparable and impressive reduction in blood pressure when multiple interventions were implemented. The results compare favorably with results of the single approaches assessed here.

Conclusion: There is little question that successful reductions in dietary sodium (and changes in other dietary components), weight, and alcohol intake and an increase in exercise can each contribute to reduction in hypertension and medication requirements. However, because of the heterogeneity of the literature, the lack of studies with disease outcomes, and the lack of research in treated hypertensive patients, there is not a sufficient foundation on which to propose evidence-based recommendations.

Nevertheless, because there is a preponderance of successful (although small) blood pressure reduction results in these lifestyle interventions, a lack of adverse effects when compared with medications, and a generally health-promoting nature of the approaches, recommending positive lifestyle changes in addition to pharmacotherapy can be strongly endorsed on a consensus basis.

23. Behavioral Change – Adherence to Medications and Lifestyle Modifications

The following are recommended:

- 12A Assist patients to achieve medication and lifestyle adherence by means of a vigorous step-care approach to therapy and an organized system of regular medical follow-up and review. *Evidence-based: B*
- 12B Once-daily medication and combination therapy whenever possible. *Evidence-based: B*
- 12C Address issues of depression and anxiety issues in order to maximize patient adherence. See Depression Guidelines at:
<http://cl.kp.org/pkc/national/cmi/programs/depression/guideline/index.html>
Consensus-based
- 12D Use patient education in conjunction with other strategies, particularly in the context of team care utilizing nurses and pharmacists. *Evidence-based: B*
- 12E Educate patients about their goal pressure because patients who are knowledgeable about their goal blood pressure are more likely to achieve it. *Consensus-based*

Rationale:

Evidence Grade*

Evidence for Recommendation 12A,B,D: Good.

Evidence for Recommendation 12C, E: Insufficient.

2009 Update:

No new evidence has been identified. Recommendations remain unchanged.

Search Strategy

Initially, only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension who were treated with antihypertensive medications and were randomized to intervention vs. control groups were searched for. There were no studies with hard outcomes and few with treated populations, so the intermediate outcome of blood pressure was used, as were some studies with untreated populations. See Appendix B for more information.

* The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

2007 Guideline:**Once Daily Medication**

Once-daily medication dosage is supported by a meta-analysis and a Cochrane systematic review.

- ◆ The meta-analysis (Iskedjian, et al., 2002)⁽¹³⁷⁾ indicated medication adjustments were effective in improving patient adherence. Pooling the results of eight studies involving a total of 11,485 observations, the authors compared reduction in blood pressure with once-daily, twice-daily, and multiple daily dosing antihypertensive drug regimens and concluded that daily dosing regimens for antihypertensive medications are associated with higher rates of adherence than the other dosing regimens.
- ◆ A Cochrane Database systematic review by Schroeder, et al. (2004)⁽¹³⁸⁾ examined 38 RCTs of adherence and concluded that reducing the number of daily doses appeared to be effective in increasing adherence to antihypertensive medication therapy and that a variety of educational interventions were ineffective.

Educational programs for hypertensive patients are recommended for patient adherence; however, there is no clear consensus as to which program components are the most effective.

- ◆ A meta-analysis conducted by Chodosh, et al. (2005)⁽¹³⁹⁾ evaluated the effectiveness and components of self-management programs for hypertension (n = 13 studies), osteoarthritis (n = 14 studies), and diabetes mellitus (n = 26 studies) in older adults. In the hypertension arm, 17 comparisons from 13 studies reported changes in systolic and diastolic blood pressure resulting from interventions, including an educational handbook, educational session, meditation or meditation with biofeedback, anxiety management training, and a 12-week intervention that included an emphasis on weight loss, dietary changes, and behavior modification. This meta-analysis concluded there is evidence to support chronic disease self-management programs as clinically and statistically significant in older adults, but also notes that evidence regarding the self-management program components is limited.
- ◆ Another meta-analysis, by Boulware, et al. (2001),⁽¹⁴⁰⁾ assessed behavioral interventions in 15 studies (n = 4,072). This study evaluated the effectiveness of patient-centered counseling, patient self-monitoring of blood pressure, and structured training courses. The study found counseling to be more effective than usual care combined with training courses, whereas self-monitoring or training courses offered improvement over usual care. Lastly, this study concluded that combined interventions do not offer improvement over counseling.
- ◆ A systematic review by Fahey, et al. (2005)⁽¹⁴¹⁾ contained a total of 56 RCTs with categorized interventions, including self-monitoring (n = 15), education – patient (n = 16), education – health professional (n = 9), health professional-led care (n = 6), an organized system of regular review allied to vigorous antihypertensive drug therapy (n = 7), and appointment reminders (n = 6). Fahey, et al. note that educational interventions directed to either patients or providers are unlikely to produce clinically important reductions in either systolic OR diastolic blood pressure. These authors did report, however, based on the study (HDFP, 1979),⁽¹⁴²⁾ that a step-care approach to therapy and an organized system of regular medical follow-up and review was effective in enhancing patient adherence.

Motivational interviewing is an educational component currently under evaluation.

It is a style of counseling that focuses on a patient's readiness to change a behavior.

- ◆ Ogedegbe, et al. (2007)⁽¹⁴³⁾ published the RCT design for an ongoing study evaluating motivational interviewing in an African American population comparing standard care versus standard of care with four motivational interviewing sessions.

Depression and anxiety issues should be addressed to maximize patient adherence.

- ◆ Wang, et al. (2002)⁽¹⁴⁴⁾ conducted a comparative study ($n = 496$) on use of antihypertensive medications and responses to a telephone structured survey. This study utilized prescription data to ascertain adherence, with results indicating an association between depressive symptoms and poor compliance with antihypertensive medications. After controlled for potential confounding effects such as demographic variables, the authors found that an increase in the severity of depressive symptoms was significantly associated with lower odds of compliance.
- ◆ Morris, et al. (2006),⁽¹⁴⁵⁾ using data from an ongoing RCT ($n = 492$), found an association with adherence for factors such as age, sex, race, and depression. They found that depression affected diastolic and systolic pressure; however, only the finding for diastolic pressure was statistically significant.
- ◆ Knight, et al. (2001)⁽¹⁴⁶⁾ retrospectively reviewed one year of medical records of 525 patients (mean age, 65 ± 11 years) being treated for hypertension. Lack of knowledge of goal blood pressure was very common in this sample, ranging from 43% to 66% in the three systems from which patients were drawn. Independent predictors of poor control were older age, multidrug regimens, lack of knowledge by patients of their target systolic blood pressure, and a report of antihypertensive drug side effects. Only 39% of the patients studied had a mean blood pressure $< 140/90$ mm Hg, although all were in active treatment for hypertension. One significant limitation of this retrospective analysis is that the treatment of individual patients was managed by individual physicians, so that no common treatment pattern could be evaluated.
- ◆ Walsh, et al. (2006)⁽¹⁴⁷⁾ published a meta-analysis of 44 studies reporting 57 comparisons of quality improvement interventions aimed at increasing patient adherence in the treatment of hypertension. Most of the trials compared more than one intervention strategy. Team change was used in 36 of the comparisons, and patient education was used in 28 of the comparisons. The majority of the studies showed improvement in blood pressure control in the target group. Team change, including the involvement of pharmacists and nurses, and patient education were associated with the greatest reduction in blood pressure. Several different trial designs were pooled in the meta-analysis.

Overall Conclusion: The medical literature includes several studies and meta-analyses of interventions intended to improve adherence to medical treatment and lifestyle advice aimed at reducing blood pressure. Most of these studies did not examine long-term health outcomes, but rather they equated adherence with reduction of blood pressure. Some studies measured adherence to medication regimens directly.

This literature suggests that a number of different interventions are valid and effective:

- (1) There is good evidence to suggest that an organized system of treatment and follow-up that delivers a step-care approach to therapy can be effective in reducing blood pressure in hypertensive patients.
- (2) Once-daily medication is also associated with greater medication compliance.
- (3) There is good evidence that a multidisciplinary approach to treatment, involving other health care team members in addition to physicians, has been shown to improve blood pressure control.
- (4) The literature also suggests that emotional factors, especially depression, can be barriers to adherence, but there is no evidence that addressing these conditions improves adherence. Thus the recommendation regarding this intervention is a consensus recommendation.
- (5) Although there is insufficient evidence from RCTs evaluating the effect of patient knowledge of personal blood pressure goals on health outcomes, there are some observational data to suggest that patients' lack of knowledge of their systolic blood pressure is a significant predictor of poor blood pressure control. Hence, the GDT also supports educating patients regarding their individual goal pressures.

Supplemental Information – Patient Knowledge of Goal Blood Pressure

At the 2007 session of the annual American Society of Hypertension meetings in Chicago, Illinois, an international perspective of national hypertension guidelines included presentations from Bryan Williams MD (United Kingdom), Giuseppe Mancia MD (European Society of Hypertension), Norman Campbell MD (Canadian Society of Hypertension, and William Cushman MD and Suzanne Oparil MD (American Society of Hypertension). Dr. Oparil is president of the American Society of Hypertension (ASH). A point of international consensus, also included in the ASH charter, is the importance given to patient knowledge of their personal blood pressure as well as their blood pressure goal. Dr. Williams described the highly successful "know your numbers" patient outreach program in the United Kingdom as a contributor to their five year reduction in overall cardiovascular mortality by 35%.

Use of Aspirin in Hypertensive Patients Receiving Antihypertensive Medications

For primary CVD prophylaxis and in the absence of known CAD, stroke or diabetes mellitus:

- 13A When the CHD risk is high,^{*} low-dose aspirin (81 mg daily) is recommended. A shared decision-making approach, with a review of the benefits and harms, is recommended.
Evidence-based: B
- 13B For individuals with an intermediate risk^{*} of CHD, low-dose aspirin (81 mg daily) is an option. Use of aspirin should be based on a shared decision-making approach and on each individual's benefit/risk[†] status. *Evidence-based: C*
- 13C When the CHD risk is low,^{*} aspirin is not recommended. For low-risk patients who are already taking aspirin, or who express a desire to begin taking it, a shared decision-making approach, with a review of the benefits and harms, is recommended.
Evidence-based: D
- 13D Aspirin is not recommended for patients with uncontrolled hypertension.
Evidence-based: D

Rationale:

Evidence Grade[‡]

Evidence for Recommendation 13: Good.

* A validated risk calculator such as Framingham should be applied. Using the ATP III Framingham 10-year Hard CHD risk calculator (1, 2): low risk is < 10%, intermediate risk is 10 to 20%, and high risk is > 20%. Using the SCAL/NW Dyslipidemia Guideline CAD Risk Tables (based on Framingham 1991) 10-year Total CHD risk calculator: low risk is < 12.5%, intermediate risk is 12.5 to 25%, and high risk is > 25%.

1 National Heart Lung and Blood Institute's ATP III Framingham CHD risk calculator-
<http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof>

2 1991 Framingham Risk Calculator based on Anderson KM, et al. An Updated Coronary Risk Profile: A Statement for Health Professionals. Circulation 1991; 83(1): 356-362. KP Northwest link :
<http://internal.or.kp.org/cpg/support/cholest.html>

† The benefit for men is primarily reduction in nonfatal MI and the benefit for women is stroke reduction. Low-dose aspirin increases the risk of GI bleeding and hemorrhagic stroke, and the risk of hemorrhagic stroke may increase with uncontrolled hypertension, particularly Stage 2 hypertension. NNTs to prevent one adverse CV outcome vs. NNHs (usually a GI bleed requiring transfusion) for men and women on low-dose aspirin for primary CV prophylaxis for 6.4 years are: women NNT = 333 and NNH = 400; men: NNT = 270 and NNH = 303.

‡ The criteria for grading the strength of the evidence as either "good," "fair," or "insufficient" adheres to the KP National Guideline Program's "Policies and Procedures" documents entitled "Label and Language of Recommendations" and "KP System for Grading the Strength of a Body of Evidence," which are located in Appendix A.

2009 Update:

No new evidence has been identified. Recommendations remain unchanged.

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes were included. When possible, studies were included that were primarily concerned with participants without significant comorbid conditions. See Appendix B for more information.

2007 Guideline:

In the interim from the 2005 update, two meta-analyses were located in the peer-reviewed medical literature that studied trials of the use of aspirin.

- ◆ These meta-analyses used the same trials to extract data; one meta-analysis concentrated on the general population (Bartolucci and Howard, 2005),⁽¹⁴⁸⁾ the other was a sex-specific analysis (Berger, et al., 2006).⁽¹⁴⁹⁾ The trials used by both meta-analyses included the Hypertension Optimal Treatment trial (HOT),⁽¹²⁷⁾ the United States Physicians' Health Study (USPHS),⁽¹⁵⁰⁾ the British Doctors' Trials, the Thrombosis Prevention Trial (TPT), and the Women's Health Study. Findings from Bartolucci and Berger confirm the findings of the previous recommendations.

Based on the Berger, et al. (2006) meta-analysis, the benefit of aspirin therapy for men is primarily reduction in nonfatal MI and the benefit for women is stroke reduction. Low-dose aspirin increases the risk of GI bleeding and hemorrhagic stroke, and the risk of hemorrhagic stroke may increase with uncontrolled hypertension, particularly Stage 2 hypertension.

The number needed to treat (NNT) to prevent one adverse CV outcome versus the number needed to harm (NNH, usually a GI bleed requiring a transfusion) for men and women on low-dose aspirin for primary CV prophylaxis for 6.4 years are as follows: for women, NNT = 333 and NNH = 400; for men, NNT = 270 and NNH = 303.

Table 3. Aspirin for Primary CVD Prophylaxis: Summary of NNT and NNH Data (from Berger, et al., 2006)

	NNT to prevent one CV event* over 6.4 years of aspirin treatment	NNH to cause one GI bleed over 6.4 years of aspirin treatment
Women	3331	400
Men	2701	303

A small RCT (Magen, et al., 2005)⁽¹⁵¹⁾ found that aspirin combined with statins was more effective than aspirin or statins alone in improving endothelial function, thereby reducing systolic and diastolic blood pressure. Because this study had a small patient group (n = 41), more research is necessary to determine the validity of these findings.

* The benefit for men is primarily reduction in nonfatal MI and the benefit for women is stroke reduction.

The systematic review and evidence-based clinical practice guideline by Hayden, et al. (2001),⁽¹⁵²⁾ examined the benefits and harms of using aspirin therapy for the primary prevention of CVD. Pooled results from primary prevention trials (HOT, BMD, PHS, TPT, PPP), showed the following:

- ◆ Subjects taking aspirin were statistically significantly less likely to experience CAD events, defined as nonfatal MI or death due to CAD (OR = 0.72, 95% CI: 0.60 to 0.87).
- ◆ Aspirin therapy had no statistically significant effect on reducing stroke rates (OR = 1.02, 95% CI: 0.85 to 1.23). Hemorrhagic stroke rates (OR = 1.4, 95% CI: 0.9 to 2.0) were slightly elevated among aspirin users; however, the increased risk was not statistically significant.
- ◆ Pooled results indicate that the risk of gastrointestinal bleeding was increased for aspirin users (OR = 1.7, 95% CI: 1.4 to 2.1).
- ◆ According to the USPSTF, if 1,000 patients with a 5% risk of CAD events in five years are treated with aspirin, 6 to 20 MIs would be prevented, while 0 to 2 hemorrhagic strokes and 2 to 4 GI bleeds would be caused. (See Table 4).

Hayden, et al. concluded that “The net effect of aspirin improves with increasing risk for coronary heart disease. Consideration of underlying risk for coronary heart disease, as well as the relative values patients attach to the main outcomes, can help patients and providers decide whether aspirin chemoprevention is warranted.”

The USPSTF ultimately concluded the following:

“The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians discuss aspirin chemoprevention with adults who are at increased risk for coronary heart disease. Discussions with patients should address both the potential benefits and harms of aspirin therapy. The USPSTF found good evidence that aspirin decreases the incidence of coronary heart disease in adults who are at increased risk for heart disease. It also found good evidence that aspirin increases the incidence of gastrointestinal bleeding and fair evidence that aspirin increases the incidence of hemorrhagic strokes. The USPSTF concluded that the balance of benefits and harms is most favorable in patients at high risk for coronary heart disease (those with a 5-year risk $\geq 3\%$) but is also influenced by patient preferences.”⁽¹⁵²⁾

(Note: coronary heart disease events = nonfatal acute MI and fatal CAD.)

Table 4. Estimated Benefits and Harms of Aspirin Therapy for Patients at Different Levels of Risk for Coronary Heart Disease Events* (from Hayden, et al., 2001)⁽¹⁵²⁾

Outcome	Estimated 5-Year Risk for CHD Events at Baseline		
	1%	3%	5%
Effect on all-cause mortality	No change	No change	No change
CHD events avoided, n	3 (1 - 4)	8 (4 - 12)	14 (6 - 20)
Ischemic strokes avoided, n	0	0	0
Hemorrhagic strokes precipitated, n	1 (0 - 2)	1 (0 - 2)	1 (0 - 2)
Major gastrointestinal bleeding events precipitated, n	3 (2 - 4)	3 (2 - 4)	3 (2 - 4)

-
- * Estimated based on 1,000 patients receiving aspirin for 5 years and a relative risk reduction of 28% for coronary heart disease (CHD) events in those who received aspirin (CHD events = nonfatal acute myocardial infarction, fatal CHD). Values in parentheses are 95% confidence intervals. The following caveats apply to these estimates:
- 1) Reduction in CHD risk may be smaller in women, but data are limited.
 - 2) For elderly persons, absolute risk of hemorrhagic stroke and major gastrointestinal bleeding may be two to three times higher in patients receiving aspirin; however, aspirin may provide benefit in elderly persons by reducing ischemic stroke, the incidence of which increases with age. Aspirin does not appear to improve incidence of ischemic stroke in middle-aged patients.
 - 3) Risk of hemorrhagic stroke may be greater with larger doses of aspirin.
 - 4) Aspirin may not prevent myocardial infarction in patients with uncontrolled hypertension (systolic blood pressure > 150 mm Hg).
 - 5) Long-term outcomes (> 5 to 7 years) are unknown.
 - 6) Patients at high risk (> 10% 5-year risk) may derive greater benefit from aspirin, including a 15% to 20% reduction in ischemic stroke and all-cause mortality, because their risk is similar to that of patients with known CHD.

Conclusion: Continuing research has validated the recommendation regarding the use of aspirin as concomitant therapy for patients with controlled hypertension. Based on the information and evidence presented, the GDT concluded that among people with controlled hypertension, the use of aspirin therapy for primary CVD prophylaxis should be based on individual CHD risk levels, such that:

- ◆ When the CHD risk is high, low-dose aspirin (81 mg daily) is recommended. A shared decision-making approach, with a review of the benefits and harms, is recommended.
- ◆ For individuals with an intermediate risk of CHD, low-dose aspirin (81 mg daily) is an option. Use of aspirin should be based on a shared decision-making approach and each individual's benefit/risk status.
- ◆ When the CHD risk is low, aspirin is not recommended. For low-risk patients who are already taking aspirin, or who express a desire to begin taking it, a shared decision-making approach, with a review of the benefits and harms, is recommended.

2005 Rationale:

Since the 2003 guideline was produced, one relevant randomized trial and two meta-analyses were published. Their findings support the previous recommendations.

Ridker's trial⁽¹⁵³⁾ in 39,876 women aged 45 and older contained a hypertensive subset of more than 6,000. Testing low-dose aspirin (100 mg qod) they found a significant reduction in stroke (0.73, p = 0.04 [95% CI: 0.54 to 0.98]), and ischemic stroke (0.70, p = 0.03 [95% CI: 0.51 to 0.96]) in women whose blood pressure was > 140 / > 90 mm Hg.

The meta-analysis by Lip⁽¹⁵⁴⁾ and that of Bredie⁽¹⁵⁵⁾ used data from the Hypertension Optimal Treatment trial (HOT),⁽¹²⁷⁾ the United States Physicians' Health Study (USPHS),⁽¹⁵⁰⁾ and the Thrombosis Prevention Trial (TPT),⁽¹⁵⁶⁾ all of which were discussed in the 2003 guideline.

2003 Rationale:

Supporting Evidence for Aspirin versus Placebo

In the Hypertension Optimal Treatment (HOT) trial,⁽⁹⁾ 18,790 patients aged 50 to 80 years were randomly assigned either to 75 mg/day of aspirin or a placebo. Hansson found that adding low-dose aspirin to active antihypertensive treatment reduced the risk of all myocardial infarction (excluding silent cases) by 36% (ARR = 0.0048; RR = 0.64 [95% CI: 0.49 to 0.85]; p = 0.02; NNT = 208). Major cardiovascular events were reduced by 15% (ARR = 0.0057; RR = 0.85 [95% CI: 0.73 to 0.99]; p = 0.03; NNT = 176) (For both measures, the difference was not significant when silent MIs were included.) This benefit occurred without an additional risk of stroke (as had been seen, although nonsignificantly, in previous primary prevention studies). There were no significant differences found for stroke, CV mortality, or total mortality.

Although rates of fatal bleeding were equal in the two groups, nonfatal bleeding was significantly more frequent among patients receiving aspirin than placebo (ARR = 0.0040; RR = 2.12 [95% CI: 1.41 to 3.81]; NNT = 250; p < 0.001). The addition of aspirin to antihypertensive therapy can therefore be recommended, provided that risks of GI bleeding are carefully assessed.

In the Physicians' Health Study (PHS),⁽¹⁵⁰⁾ 22,071 healthy male physicians were randomly assigned to either 325 mg aspirin every other day or placebo. (The PHS was not specifically a hypertension trial.) Aspirin use was associated with a significant risk reduction for both fatal and nonfatal MI (0.56 [95% CI: 0.45 to 0.70]; p < 0.00001). There was no significant trend in response dependent on either systolic, OR diastolic blood pressure levels.

The Thrombosis Prevention Trial⁽¹⁵⁶⁾ (TPT - also not a hypertension trial) studied 5,499 men aged 45 to 69 who were at increased risk of CHD. Two hundred forty-five men were using antihypertensive medication at the time of recruitment, and 1,421 men did so at some stage during the trial. Meade found that the benefit of aspirin (75 mg/day, controlled release) in primary prevention of cardiovascular events was strongly correlated with systolic blood pressure level.

Systolic blood pressure [mm Hg – relative risk (confidence intervals not given)]

Coronary Heart Disease

< 130 RR = 0.55

130 to 145 RR = 0.75

> 145 RR = 0.94

p value of interaction = 0.0015

Stroke

< 130 RR = 0.41

130 to 145 RR = 0.21

> 145 RR = 1.42

p value of interaction = 0.006

Major Cardiovascular Events (CHD and Stroke)

< 130 RR = 0.59

130 to 145 RR = 0.68

> 145 RR = 1.08

p value of interaction = 0.0001

There is one large systematic review of aspirin for the primary prevention of cardiovascular events by Hayden for the U.S. Preventive Services Task Force (USPSTF).⁽¹⁵²⁾ The influence of hypertension on the effectiveness of aspirin chemoprevention was examined in the trials that compared aspirin use with a placebo. The GDT has reviewed the same trials individually, as described above.

Two additional studies were included which either did not include or did not describe populations with hypertension. On the basis of evidence from the TPT, PHS, and HOT trials, Hayden⁽⁹⁵⁾ concluded that aspirin appears to reduce coronary heart disease risk in patients with treated hypertension, but its effects may be attenuated in patients with poorly controlled blood pressure.

Other Considerations

Clinical Evidence summarized systematic reviews (including the PHS study) evaluating the role of antiplatelet treatment in individuals without symptoms of cardiovascular disease, and found insufficient evidence from RCTs to identify which individuals would have more benefit or harm from regular aspirin treatment. Although the meta-analysis did not specifically address the hypertensive population intended for this guideline, the results provide useful background information on aspirin treatment. A meta-analysis of five trials of antiplatelet treatment (mainly aspirin) in asymptomatic individuals produced the following summary estimates of effect (OR):

Vascular events

(nonfatal MI, nonfatal stroke, or vascular death): 0.86 (95% CI: 0.8 to 0.9)
MI: 0.71 (95% CI: 0.6 to 0.8)
Stroke: 1.05 (95% CI: 0.9 to 1.2)
Major extracranial bleeds (mainly GI): 1.70 (95% CI: 1.4 to 2.1)

Derry⁽¹⁵⁷⁾ performed a systematic review and meta-analysis to evaluate the incidence of GI hemorrhage associated with long-term aspirin therapy and to determine whether changes in dose or formulation had an effect on GI bleeding. A meta-analysis of 24 RCTs comparing aspirin with placebo or no treatment was performed, but only one RCT evaluated aspirin in hypertensive patients. The majority of the studies looked at aspirin therapy for other indications or secondary prevention; thus, their findings cannot necessarily be generalized to individuals without cardiovascular symptoms. Long-term aspirin therapy was associated with a significant increase in the risk of GI hemorrhage [RR = 1.68; (95% CI: 1.51 to 1.88)], and the authors saw no evidence that reducing the dose or using modified release formulations would reduce the risk of that outcome.

24. Use of Antilipemic Therapy in Hypertensive Patients Taking Antihypertensive Medications

- 14A No recommendation for or against the use of antilipemic therapy in hypertensive patients in the absence of other significant risk factors. *Evidence-based: I*
- 14B Patients with hypertension should be treated for hyperlipidemia according to their total cardiovascular risk profile. (Refer to the KP Dyslipidemia Management in Adults guideline on the KP Clinical Library Web site at <http://cl.kp.org/pkc/scal/cpg/cpg/html/Dyslipid.html>) *Consensus-based*

Rationale:

Evidence Grade*

Evidence for Recommendation 13: Insufficient.

* The criteria for grading the strength of the evidence as either “good,” “fair,” or “insufficient” adheres to the KP National Guideline Program’s “Policies and Procedures” documents entitled “Label and Language of Recommendations” and “KP System for Grading the Strength of a Body of Evidence,” which are located in Appendix A.

2009 Update:

New evidence has been identified. Recommendations remain unchanged.

Search Strategy

No appropriate Cochrane or Clinical Evidence Systematic Reviews were found on statin use in hypertensive patients. PubMed was searched from 1965 to 03/07. See Appendix B for more information.

2007 Rationale:

One meta-analysis of 20 RCTs studying the effect of antilipemic therapy on hypertension was identified in the peer-reviewed medical literature (Strazullo, et al., 2007).⁽¹⁵⁸⁾ It showed a small but statistically significant reduction of systolic blood pressure. A limitation of this meta-analysis was that no large studies were included because blood pressure values were not reported and/or concomitant antihypertensive treatment was not consistent during the trial.

Although the results of this meta-analysis are promising, it does not affect the current recommendations.

2005 Rationale:

No additional evidence was found since the 2003 guideline that would change the recommendations.

Since the 2003 guideline was completed, one trial was published in hypertension patients who had total cholesterol concentrations of 250 mg/dl or lower - the ASCOT-LLA.⁽¹⁵⁹⁾ After a mean of 3.3 years of follow-up the trial was stopped, because treatment with a statin resulted in a significant reduction in CHD events compared with placebo. However, it should be noted that this study was conducted in individuals who had at least three of the following risk factors: LVH, other abnormalities on ECG, type 2 diabetes, PAD, previous stroke or TIA, male gender, age 55+, microalbuminuria, proteinuria, smoking, family history of premature CAD, or a ratio of plasma total cholesterol to HDL cholesterol > 6. Thus, the results may not apply to a hypertensive population with fewer or no risk factors.

The JNC7⁽³⁾ has also confirmed that “all (hypertensive) patients with lipid abnormalities for LDL, HDL, or TG should be treated according to the ATP III recommendations.”

In summary, a diagnosis of hypertension alone, in the absence of other significant risk factors, should not be the sole indication for initial statin use, and patients with hypertension and dyslipidemia should be treated according to their total cardiovascular risk profile.

2003 Guideline:**Supporting Evidence for Statins versus Placebo**

A subset of participants ($n = 10,355$) from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial⁽⁶⁵⁾ (ALLHAT) was randomized (in a nonblinded fashion) to determine whether pravastatin (40 mg/day) compared with “usual care” reduced mortality in older, moderately hypercholesterolemic,* hypertensive patients. “Usual care” was described as treatment for lowering LDL-C, according to the discretion of the primary care physician, but vigorous cholesterol-reducing therapy was discouraged in this group. No significant differences in outcome rates were found in the pravastatin group for fatal coronary heart disease (CHD) and nonfatal myocardial infarction (MI), stroke, heart failure, and all-cause mortality.

Assessing the applicability of this research to our clinical question raises doubts due to a number of areas of potential bias; nonblinded study design, which may have contributed to the high cross-over rates (26% of usual care patients who received statins); and the requirement of additional risk factors in the population.

Due to the lack of evidence for the use of statins in the general hypertension population, a recommendation cannot be made regarding their use in those who are actively treated with antihypertensive medications and are not hyperlipidemic.

Other Considerations:

The Heart Protection Study⁽¹⁶⁰⁾ (HPS) randomly allocated 40 mg of simvastatin or a placebo to 20,536 adults aged 40 to 80 years with coronary artery disease, other occlusive arterial disease, or diabetes to determine the benefit of adding statins to existing treatment. All-cause mortality, nonfatal MI, and stroke were significantly reduced, and the authors concluded that five years of treatment would protect 70 to 100 people out of 1,000 from a major vascular event. The results of this study, however, cannot be applied to our population, because participants were identified as having coronary artery disease, other occlusive arterial disease, or diabetes.

All other large studies reviewed were also in populations with comorbid conditions (e.g., cardiovascular disease, and other risk factors). More importantly, specific data on the hypertensive populations were not separated for analysis.

* Fasting LDL-C level of 120 to 189 mg/dl for those with no known CHD or 100 to 129 mg/dl for those with known CHD.

Appendix A: Criteria for Grading the Evidence

Label and Language of Recommendations

Revised: April 2008

RECOMMENDATION LABEL	RECOMMENDATION STATEMENT*	EVIDENCE BASE
Evidence-Based Recommendations		
Evidence-Based, A	The GDT strongly recommends the intervention.	The intervention improves important health outcomes, based on good evidence, and the Guideline Development Team (GDT) concludes that benefits substantially outweigh harms and costs.
Evidence-Based, B	The GDT recommends the intervention.	The GDT concludes that the intervention improves important health outcomes, based on 1) good evidence that benefits outweigh harms and costs; or 2) fair evidence that benefits substantially outweigh harms and costs.
Evidence-Based, C	The GDT makes no recommendation for or against the intervention. [†]	Evidence is sufficient to determine the benefits, harms, and costs of an intervention, and there is at least fair evidence that the intervention improves important health outcomes. But the GDT concludes that the balance of the benefits, harms, and costs is too close to justify a general recommendation.
Evidence-Based, D	The GDT recommends against the intervention.	The GDT finds at least fair evidence that the intervention is ineffective, or that harms or costs outweigh benefits.
Evidence-Based, I	The GDT makes no recommendation for or against the intervention. [†]	The GDT concludes that evidence that the intervention is effective is lacking, of poor quality, or conflicting and the balance of benefits, harms, and costs cannot be determined.
Consensus-Based Recommendations		
Consensus-Based	The GDT recommends the intervention.	The recommendation is based on the consensus of the GDT, typically in the setting of insufficient evidence.
Consensus-Based	The GDT has determined that the intervention is an option.	The recommendation is based on the consensus of the GDT, typically in the setting of insufficient evidence.
Consensus-Based	The GDT recommends against the intervention.	The recommendation is based on the consensus of the GDT, typically in the setting of insufficient evidence.
Note that most consensus-based recommendations will have evidence grade " Insufficient ." For the rare consensus-based recommendations which have " Good " or " Fair " evidence, the evidence must support a different recommendation, because if the evidence were good or fair, the recommendation would usually be evidence-based.. In this kind of consensus-based recommendation the evidence label should point this out, e.g., "Good, supporting a different recommendation."		

* All statements specify the population for which the recommendation is intended.

†At the discretion of the GDT, the recommendation may use the language, "option," but must list all the equivalent options.

KP System for Grading the Strength of a Body of Evidence

Level/Grade	Therapy/Prevention/Screening	Diagnosis	Prognosis/Etiology
Grade GOOD	<p>Type and number of studies</p> <ul style="list-style-type: none"> At least one well-designed and conducted systematic review (SR)/meta-analysis (MA) (consider heterogeneity) of RCTs Two or more well-designed and conducted RCTs with narrow confidence intervals One well-designed and conducted multi-center RCT with narrow confidence intervals <p>Quality</p> <ul style="list-style-type: none"> Low risk of bias Adequate sample size and power No major methodological concerns <p>Consistency</p> <ul style="list-style-type: none"> For SR/MA, no major conflict in results (consider heterogeneity). If significant heterogeneity exists, drop to Poor For individual RCTs, no major conflict in results If major conflicts do exist, drop to "Insufficient" <p>Relevancy</p> <ul style="list-style-type: none"> No compelling reason not to generalize the published work to the target KP population 	<p>Type and number of studies</p> <ul style="list-style-type: none"> At least one well-designed and conducted SR/MA (consider heterogeneity) of cross-sectional studies using independent gold standard Two or more well-designed and conducted cross-sectional studies using an independent gold standard <p>Quality</p> <ul style="list-style-type: none"> Low risk of (verification) bias Independent gold standard No major methodological concerns <p>Consistency</p> <ul style="list-style-type: none"> For SR/MA no major conflict in results (consider heterogeneity) For individual studies, consistent diagnostic accuracy <p>Relevancy</p> <ul style="list-style-type: none"> No compelling reason not to generalize the published work to the target KP population 	<p>Type and number of studies</p> <ul style="list-style-type: none"> At least one well-designed and conducted SR/MA (consider heterogeneity) of prospective cohort studies Two or more well-designed and conducted prospective cohort studies <p>Quality</p> <ul style="list-style-type: none"> Low risk of bias Acceptable loss to follow-up (< 20%) No major methodological concerns <p>Consistency</p> <ul style="list-style-type: none"> For SR/MA no major conflict in results (consider heterogeneity) For individual studies, consistent prognosis in similar populations <p>Relevancy</p> <ul style="list-style-type: none"> No compelling reason not to generalize the published work to the target KP population
Grade FAIR	<p>Type and number of studies</p> <ul style="list-style-type: none"> Single well-designed and conducted RCT with narrow confidence intervals Two or more RCTs of lower quality Well-designed and conducted SR/MA of cohort studies (consider heterogeneity) <p><i>For screening interventions only, the following are also acceptable as Fair evidence:</i></p> <ul style="list-style-type: none"> Two or more well-designed and conducted cohort studies Two or more well-designed and conducted case-control studies Two or more well-designed and conducted time series studies <p>Quality</p> <ul style="list-style-type: none"> Minor methodological concerns <p>Consistency</p> <ul style="list-style-type: none"> For SR/MA, no major conflict in results (consider heterogeneity) For individual studies, no major conflict in results If major conflicts do exist, drop to "Insufficient" <p>Relevancy</p> <ul style="list-style-type: none"> No compelling reason not to generalize the published work to the target KP population 	<p>Type and number of studies</p> <ul style="list-style-type: none"> Single well-designed and conducted cross-sectional study Two or more cross-sectional studies of lower quality Well-designed and conducted SR/MA of lower quality studies <p>Quality:</p> <ul style="list-style-type: none"> Minor methodological concerns Independent gold standard <p>Consistency:</p> <ul style="list-style-type: none"> For SR/MA, no major conflict in results (consider heterogeneity) For individual studies, no major conflict in results <p>Relevancy</p> <ul style="list-style-type: none"> No compelling reason not to generalize the published work to the target KP population 	<p>Type and number of studies</p> <ul style="list-style-type: none"> Single well-designed and conducted prospective cohort study Two or more prospective cohort studies of lower quality Well-designed and conducted SR/MA (consider heterogeneity) of either retrospective cohort studies, case control or untreated control arms in RCTs <p><i>For etiology only, the following is also acceptable as Fair evidence:</i></p> <ul style="list-style-type: none"> Two or more well-designed, well-conducted retrospective cohort studies Two or more well-designed, well-conducted case control studies, preferably confirmed by one or more cohort studies <p>Quality:</p> <ul style="list-style-type: none"> Minor methodological concerns <p>Consistency:</p> <ul style="list-style-type: none"> For SR/MA, no major conflict in results (consider heterogeneity) For individual studies, no major conflict in results <p>Relevancy</p> <ul style="list-style-type: none"> No compelling reason not to generalize the published work to the target KP population
Grade INSUFFICIENT	<p>Type and number of studies</p> <ul style="list-style-type: none"> Single RCT of lower quality or insufficient size Cohort study <p>Quality</p> <ul style="list-style-type: none"> Major methodological concerns (i.e., lack of concealed allocation, inadequate blinding, no ITT analysis) <p>Consistency</p> <ul style="list-style-type: none"> Studies that are well-designed and conducted (Good or Fair) but with major conflict in results SR/MA with major conflict in results (consider heterogeneity) <p>Relevancy</p> <ul style="list-style-type: none"> Compelling reasons why the results do not apply to the target KP population 	<p>Type and number of studies</p> <ul style="list-style-type: none"> Single cross-sectional study of lower quality Case-control study <p>Quality</p> <ul style="list-style-type: none"> Major methodological concerns (non-consecutive, poor or non-independent gold standard) <p>Consistency</p> <ul style="list-style-type: none"> Studies that are well-designed and conducted (Good or Fair) but with major conflict in results <p>Relevancy</p> <ul style="list-style-type: none"> Compelling reasons why the results do not apply to the target KP population 	<p>Type and number of studies</p> <ul style="list-style-type: none"> Single prospective cohort study of lower quality Retrospective cohort study Untreated control arm of RCT Case series <p>Quality</p> <ul style="list-style-type: none"> Major design or methodological concerns (sampling bias, high dropout, non-blinded outcome assessment, lack of adjustment for confounders) <p>Consistency</p> <ul style="list-style-type: none"> Studies that are well-designed and conducted (Good or Fair) but with major conflict in results <p>Relevancy</p> <ul style="list-style-type: none"> Compelling reasons why the results do not apply to the target KP population

*Evidence is graded with respect to the degree it supports the specific clinical recommendation. For example, there may be good evidence that Drugs 1 and 2 are effective for Condition A, but no evidence that Drug 1 is more effective than Drug 2. If the recommendation is to use either Drug 1 or 2, the evidence is good. If the recommendation is to use Drug 1 in preference to Drug 2, the evidence is insufficient.

Appendix B: Supporting Documentation

Screening for Hypertension

Problem Formulation

Clinical Question:	Should adults be screened for hypertension?	
Population:	All adult members who are not diagnosed with hypertension.	
Health Problem:	Complications of undiagnosed hypertension.	
Health Intervention:	<ul style="list-style-type: none"> ◆ Screening. ◆ No screening 	
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ Angina ◆ Myocardial Infarction ◆ Stroke ◆ End Stage Renal Disease 	<ul style="list-style-type: none"> ◆ Heart Failure ◆ Coronary Artery Disease ◆ Deaths ◆ Cardiovascular Deaths

For Evidence Search and Evidence Summary see USPSTF as of July, 2003.

For most recent search see: <http://www.ahrq.gov/clinic/uspstf/uspshyp.htm>

Problem Formulation

Clinical Question:	At what interval should adults be screened for hypertension?	
Population:	All adult members.	
Health Problem:	Complications of Hypertension.	
Health Intervention:	Screening at the following intervals: <ul style="list-style-type: none"> ◆ Every visit ◆ 1 year ◆ 2 years ◆ No Screening 	
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ Angina ◆ Myocardial Infarction ◆ Stroke ◆ End Stage Renal Disease 	<ul style="list-style-type: none"> ◆ Heart Failure ◆ Coronary Artery Disease ◆ Deaths ◆ Cardiovascular Deaths

For Evidence Search and Evidence Summary see USPSTF as of July, 2003.

For most recent search see: <http://www.ahrq.gov/clinic/uspstf/uspshyp.htm>

Treatment of Hypertension

Problem Formulation

Clinical Question:	When treating hypertension, what is the appropriate time to begin pharmacotherapy?
Population:	Nonpregnant adults with hypertension who do not have diabetes, heart failure, renal insufficiency, or known coronary heart disease.
Health Problem:	Essential hypertension
Health Intervention:	Early use of antihypertensive medication(s) after diagnosis Delayed use of antihypertensive medication(s) after diagnosis
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ All-cause mortality ◆ CV mortality ◆ Stroke ◆ Nonfatal myocardial infarction ◆ Heart failure

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension were included. Selection was limited to studies that randomized participants to head-to-head trials using a step-care approach consisting of various antihypertensive agents.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed	Hypertension[MESH] AND Algorithms[Text Word]	Meta-analysis, Adult, English, Human	1965 - 04/06/07	0/0
		Randomized Controlled Trial, Adult, English, Human	1965 - 04/06/07	0/158
	Hypertension[MESH] AND Clinical Protocols[MESH]	Meta-analysis, Adult, English, Human	1965 - 04/06/07	0/0
		Randomized Controlled Trial, Adult, English, Human	1965 - 04/06/07	0/95
Cochrane	Hypertension and Weight Loss	Systematic reviews	06/13/05	0/52
	Hypertension and Physical Activity	Systematic reviews	06/13/05	0/56
	Hypertension and Alcohol	Systematic reviews	06/13/05	0/98
PubMed	Hypertension[MESH] AND Diet[MESH] OR Diet Therapy[MESH]	Meta-analysis	1966 - 04/06/07	0/49
		Randomized Controlled Trial	1966 - 04/06/07	1/2061
	Hypertension[MESH] AND (Exercise/Physiology[MESH] OR Exercise/Therapy[MESH])	Meta-analysis	1966 - 04/06/07	1/11
		Randomized Controlled Trial	1966 - 04/06/07	2/160
	Hypertension[MESH] AND Alcohol Drinking[MESH]	Meta-analysis	1966 - 04/06/07	0/0
		Randomized Controlled Trial	1966 - 04/06/07	1/50

* Note: "No. Included" refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. "Total Retrieved" refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Appropriate Office-Based Target Blood Pressure For Hypertension*

Problem Formulation

Clinical Question:	<ul style="list-style-type: none"> ◆ What is the appropriate target blood pressure for nonpregnant adults with hypertension who do not have diabetes, heart failure, chronic kidney disease, or known coronary artery disease? ◆ What is the appropriate target blood pressure for patients with a prior diagnosis of stroke?
Population:	Nonpregnant adults with hypertension who do not have diabetes, heart failure, renal insufficiency, or known coronary heart disease.
Health Problem:	Essential hypertension
Health Intervention:	<ul style="list-style-type: none"> ◆ Use a target blood pressure of $\leq 139 / \leq 89$ mm Hg for patients with hypertension. ◆ Use a different target blood pressure for patients with hypertension.
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ All-cause mortality ◆ CV mortality ◆ Stroke ◆ Nonfatal myocardial infarction ◆ Heart failure

* In nonpregnant adults who do not have diabetes, heart failure, chronic kidney disease, or known coronary heart disease.

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension were included. Selection was limited to studies that randomized participants to head-to-head trials using a step-care approach of various antihypertensive agents.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed	((hypertension[MESH] OR Hypertension[Text Word]) AND target[All Fields])	Meta-analysis, English, Human	1965 - 3/11/05	0/11
		Clinical Trial, English, Human	1965 - 3/10/05	0/418
	Hypertension AND Target blood pressure	RCT, English, Human	1965 - 2/23/05	1/237
	Hypertension AND Target blood pressure	Meta-analysis, Clinical Trial, RCT, English, Human	2/24/05 - 4/1/2007	0/14
	Hypertension/drug therapy[MESH] AND Cerebrovascular accident [MESH] AND secondary prevention	Meta-analysis, Randomized Controlled Trial, Clinical Trial, Review, Adult, English, Human	1966 - 3/1/2007	0/23

* Note: “No. Included” refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. “Total Retrieved” refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Home Blood Pressure Monitoring for Diagnosis and Management

Problem Formulation

Clinical Questions:	<ul style="list-style-type: none"> ◆ What is the role of home blood pressure monitoring in determining a diagnosis of hypertension? ◆ What is the role of home blood pressure monitoring in the management of hypertension?
Population:	Nonpregnant adults with hypertension who do not have diabetes, heart failure, chronic kidney disease, or known coronary heart disease.
Health Problem:	Essential hypertension
Health Intervention:	Blood pressure measured in the medical office Self-measurement of blood pressure at home
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ All-cause mortality ◆ Cardiovascular mortality ◆ Fatal and nonfatal stroke ◆ Fatal and nonfatal myocardial infarction ◆ Heart failure

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes were included. When possible, studies were included if they were primarily concerned with participants without significant comorbid conditions.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
Cochrane	Hypertension	Systematic reviews	01/11/05	0/104
PubMed	Blood Pressure Monitoring, Ambulatory	All types, English, Human	01/01/1994 - 6/21/2005	3/2833
	Blood Pressure Determination	All types, English, Human	01/01/1995 - 6/21/2005	4/4420
	Sustained Hypertension	All types, English, Human	01/01/1994 - 6/21/2005	1/1155
	Blood Pressure Monitoring, Ambulatory OR Blood Pressure Determination OR Sustained Hypertension	All types, English, Human	6/22/2005 - 3/1/2007	0/348

* Note: “No. Included” refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. “Total Retrieved” refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

First-Line Treatment of Hypertension

Problem Formulation

Clinical Question:	What class of medication is the most effective first-line therapy for reducing the rates of serious outcomes in hypertension?		
Population:	Nonpregnant adults with hypertension who do not have diabetes, heart failure, chronic kidney disease, or known coronary heart disease.		
Health Problem:	Essential hypertension		
Health Intervention:	<ul style="list-style-type: none"> ◆ Beta-blockers ◆ Thiazide diuretics ◆ Calcium channel blockers ◆ ACEIs ◆ Angiotensin receptor blockers ◆ No treatment 		
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ All-cause mortality ◆ Cardiovascular mortality ◆ Fatal and nonfatal stroke ◆ Fatal and nonfatal myocardial infarction ◆ Heart failure 		

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension who were randomized to head-to-head trials of first-line antihypertensive agents were included. When possible, studies were included if they were primarily concerned with participants without significant comorbid conditions.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
Cochrane	Hypertension AND medication	Systematic reviews	02/15/03	0/134
PubMed	Hypertension[MESH] AND (Adrenergic beta-Antagonists[MESH] OR angiotensin-converting enzyme inhibitors[MESH] OR Adrenergic alpha-Antagonists[MESH] OR calcium channel blockers[MESH] OR Diuretics[MESH])	Meta-analysis, English, Human	06/01/01 - 02/15/03	3/28
		English, Randomized Controlled Trial, Human	06/01/01 - 02/15/03	4/366
Cochrane	Hypertension AND medication	Systematic reviews	12/14/04	0/204
PubMed	Hypertension[MESH] AND (Adrenergic beta-Antagonists[MESH] OR angiotensin-converting enzyme inhibitors[MESH] OR calcium channel blockers[MESH] OR Diuretics[MESH])	Meta-analysis, English, Human	10/25/02 - 09/15/04	2/10
		English, Randomized Controlled Trial, Human	10/25/02 - 09/17/04	1/137
	Blood Pressure[MESH] AND (Adrenergic beta-Antagonists[MESH] OR angiotensin-converting enzyme inhibitors[MESH] OR calcium channel blockers[MESH] OR Diuretics[MESH])	Meta-analysis, English, Human	1990 - 09/17/04	0/131
		English, Randomized Controlled Trial, Human	1990 - 09/17/04	0/1466
PubMed	Blood Pressure[MESH] AND (Adrenergic beta-Antagonists[MESH] OR angiotensin-converting enzyme inhibitors[MESH] OR calcium channel blockers[MESH] OR Diuretics[MESH])	Meta-analysis, Randomized Controlled Trial, Review, English, Human	09/17/04 - 3/1/2007	7/547

* Note: "No. Included" refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. "Total Retrieved" refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Initial Combination Treatment of Hypertension*

Problem Formulation

Clinical Questions:	<ul style="list-style-type: none"> ◆ Which is the most effective first-line therapy for reducing the rates of serious outcomes in hypertension – monotherapy or combination therapy? ◆ If combination therapy is best, which medications should be used? 		
Population:	Nonpregnant adults with hypertension who do not have diabetes, heart failure, chronic kidney disease, or known coronary heart disease.		
Health Problem:	Essential hypertension		
Health Intervention:	<ul style="list-style-type: none"> ◆ Monotherapy with thiazide diuretics, ACEI, beta-blockers, or calcium channel blockers ◆ Two-drug combination therapy with any two of the following medications: thiazide diuretics, ACEI, beta-blockers, or calcium channel blockers 		
Most Important Health Outcomes:	<table style="width: 100%; border: none;"> <tr> <td style="width: 50%;"> <ul style="list-style-type: none"> ◆ All-cause mortality ◆ Cardiovascular mortality ◆ Fatal and nonfatal stroke </td> <td style="width: 50%;"> <ul style="list-style-type: none"> ◆ Fatal and nonfatal myocardial infarction ◆ Heart failure </td> </tr> </table>	<ul style="list-style-type: none"> ◆ All-cause mortality ◆ Cardiovascular mortality ◆ Fatal and nonfatal stroke 	<ul style="list-style-type: none"> ◆ Fatal and nonfatal myocardial infarction ◆ Heart failure
<ul style="list-style-type: none"> ◆ All-cause mortality ◆ Cardiovascular mortality ◆ Fatal and nonfatal stroke 	<ul style="list-style-type: none"> ◆ Fatal and nonfatal myocardial infarction ◆ Heart failure 		

* In nonpregnant adults who do not have diabetes, heart failure, chronic kidney disease, or known coronary heart disease.

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension who were randomized to head-to-head trials of first-line antihypertensive agents were included. When possible, studies were included that were primarily concerned with participants without significant comorbid conditions.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
Cochrane	Hypertension AND Combination Therapy	Systematic reviews	01/11/03	0/104
PubMed	Hypertension OR high blood pressure AND (Drug Combinations OR Drug Therapy, Combination)	All types, English, Human	01/01/1965 - 3/16/2005	2/4453
PubMed	Hypertension/drug therapy[MeSH] AND Combination Therapy	Systematic reviews, English, Human	01/12/2003 - 3/17/2007	0/4
PubMed	Hypertension/drug therapy[MeSH] OR high blood pressure AND (Drug Combinations OR Drug Therapy, Combination)	Meta-analysis, Randomized Controlled Trial, Review, English, Human	3/16/2005 - 3/17/2007	0/147
PubMed RCT search	(Hypertension or "high blood pressure") AND ("drug therapy" OR Step Care OR Algorithms OR Clinical Protocols OR "combination therapy" OR dosage or Antihypertensive agents[MESH] OR antihypertensive agents [Pharmacological Action] OR Antihypertensive Agents[Text Word]) AND (("2007/03"[PDat] : "2009/01/29"[PDat]) AND (Humans[Mesh]))	Limits: Humans, Randomized Controlled Trial, English	03/2007 - 01/29/2009	1/667

* Note: “No. Included” refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. “Total Retrieved” refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed Meta-analysis Search	(Hypertension or "high blood pressure") AND ("drug therapy" OR Step Care OR Algorithms OR Clinical Protocols OR "combination therapy" OR dosage) AND (("2007/03"[PDat] : "2009/01/29"[PDat]) AND (Humans[Mesh]))	Humans, Meta-Analysis, English	03/2007 to 01/29/2009	0/7
Cochrane Database of Systematic Reviews	(Hypertension or "high blood pressure") AND ("drug therapy" OR Step Care OR Algorithms OR Clinical Protocols OR "combination therapy" OR dosage or Antihypertensive agents[MESH] OR antihypertensive agents[Pharmacological Action] OR Antihypertensive Agents[Text Word])		2007 to 2009	0/337
Cochrane Central Register of Controlled Trials"	(Hypertension or "high blood pressure") AND ("drug therapy" OR Step Care OR Algorithms OR Clinical Protocols OR "combination therapy" OR dosage or Antihypertensive agents[MESH] OR antihypertensive agents [Pharmacological Action] OR Antihypertensive Agents[Text Word])		2007 to 2008	0/830

Step-Care Therapy for Hypertension

Problem Formulation

Clinical Question:	When treating hypertension, what are the most effective pharmacological strategies when monotherapy is not successful?
Population:	Nonpregnant adults with hypertension who do not have diabetes, heart failure, renal insufficiency, or known coronary heart disease and whose hypertension has not responded to monotherapy.
Health Problem:	Essential hypertension
Health Intervention:	<ul style="list-style-type: none"> ◆ Treatment plan using diuretics, ACEI, beta-blockers, and calcium channel blockers in a sequence. ◆ Treatment plan using diuretics, ACEI, beta-blockers, and calcium channel blockers in a different sequence.
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ All-cause mortality ◆ CV mortality ◆ Stroke ◆ Nonfatal myocardial infarction ◆ Heart failure

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension were included. Selection was limited to studies that randomized participants to head-to-head trials using a step-care approach of various antihypertensive agents. Evidence from published guidelines and 1 RCT of intermediate outcomes were included as supplemental evidence.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed	Hypertension[MESH] AND stepped-care[Text Word]	Meta-analysis, Adult, English, Human	1965 - 05/23/03	0/2
		Randomized Controlled Trial, Adult, English, Human	1965 - 05/23/03	0/201
	Hypertension[MESH] AND Stepped Care[Text Word]	Meta-analysis, Adult, English, Human	2002 - 01/21/05	0/0
		Randomized Controlled Trial, Adult, English, Human	2002 - 01/21/05	0/2
	Hypertension[MESH] AND Step Care[Text Word]	Meta-analysis, Adult, English, Human	2002 - 01/21/05	0/0
		Randomized Controlled Trial, Adult, English, Human	2002 - 01/21/05	0/3
	Hypertension[MESH] AND Algorithms[Text Word]	Meta-analysis, Adult, English, Human	2002 - 01/21/05	0/0
		Randomized Controlled Trial, Adult, English, Human	2002 - 01/21/05	0/11
	Hypertension[MESH] AND Clinical Protocols[MESH]	Meta-analysis, Adult, English, Human	2002 - 01/21/05	0/0
		Randomized Controlled Trial, Adult, English, Human	2002 - 01/21/05	0/12

* Note: "No. Included" refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. "Total Retrieved" refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed	Hypertension OR high blood pressure AND combination therapy	Meta-analysis, Adult, English, Human	2002 - 12/29/04	0/1
		Randomized Controlled Trial, Adult, English, Human	2002 - 12/29/04	0/52
PubMed	(Hypertension/drug therapy[MESH] AND (antihypertensive agents[MESH] OR antihypertensive agents[Pharmacological Action] OR Antihypertensive Agents[Text Word]) AND ((organization and administration[TIAB] NOT Medline[SB]) OR organization and administration[MESH] OR administration[Text Word]) AND dosage[All Fields]))	Randomized Controlled Trial, Adult, English, Human	2002 - 01/26/05	1/164
	Hypertension/drug therapy[MESH] AND Step Care OR Algorithms OR Clinical Protocols OR combination therapy OR dosage	Meta-analysis, Randomized Controlled Trial, Adult, English, Human	01/27/05 - 3/1/2007	1/198
PubMed RCT search	(Hypertension or "high blood pressure") AND ("drug therapy" OR Step Care OR Algorithms OR Clinical Protocols OR "combination therapy" OR dosage OR Antihypertensive agents[MESH] OR antihypertensive agents[Pharmacological Action] OR Antihypertensive Agents[Text Word]) AND (("2007/03"[PDat] : "2009/01/29"[PDat]) AND (Humans[Mesh]))	Limits: Humans, Randomized Controlled Trial, English	03/2007 - 01/29/2009	3/667

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed Meta-analysis Search	(Hypertension or "high blood pressure") AND ("drug therapy" OR Step Care OR Algorithms OR Clinical Protocols OR "combination therapy" OR dosage) AND ((2007/03"[PDat] : "2009/01/29"[PDat]) AND (Humans[Mesh]))	Humans, Meta-Analysis, English	03/2007 - 01/29/2009	1/70
Cochrane Database of Systematic Reviews	(Hypertension or "high blood pressure") AND ("drug therapy" OR Step Care OR Algorithms OR Clinical Protocols OR "combination therapy" OR dosage or Antihypertensive agents[MESH] OR antihypertensive agents[Pharmacological Action] OR Antihypertensive Agents[Text Word])		2007 - 2009	1/337
Cochrane Central Register of Controlled Trials"	(Hypertension or "high blood pressure") AND ("drug therapy" OR Step Care OR Algorithms OR Clinical Protocols OR "combination therapy" OR dosage or Antihypertensive agents[MESH] OR antihypertensive agents[Pharmacological Action] OR Antihypertensive Agents[Text Word])		2007 - 2009	3/830

Discrete Populations – Hypertension Treatment for Women of Childbearing Potential

Problem Formulation

Clinical Questions:	What class of medication is the most effective therapy for reducing the rates of serious outcomes in hypertensive women of childbearing potential?		
Population:	Women who are pregnant or using less effective birth control (pills or barrier) with hypertension who do not have diabetes, heart failure, chronic kidney disease, or known coronary heart disease.		
Health Problem:	Essential hypertension		
Health Intervention:	Treatment plan using ACEI		
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ Birth defects ◆ All-cause mortality ◆ Cardiovascular mortality 	<ul style="list-style-type: none"> ◆ Fatal and nonfatal stroke ◆ Fatal and nonfatal myocardial infarction ◆ Heart failure 	

Search Strategy

Only studies with clinical outcomes that studied pregnant individuals with hypertension and pregnancy outcomes were included.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed	Hypertension/drug therapy[MESH] AND pregnancy OR abnormalities [MESH]	Meta-analysis, Randomized Controlled Trial, Clinical Trial, Review, Adult, English, Human	1966 to 3/1/2007	1/115
Cochrane Systematic Reviews	Antihypertensives/hypertension drug therapy AND women of child birth potential OR pregnancy AND birth defects OR pregnancy complications	Systematic reviews, clinical trials	1966 to May 2009	1/6
PubMed	Hypertension/drug therapy [MESH] AND women of child birth potential OR pregnancy OR birth defects [MESH] ACEIs AND women of child birth potential OR pregnancy; thiazides AND women of child birth potential OR pregnancy; calcium channel blockers AND women of child birth potential OR pregnancy; beta blockers AND women of child birth potential OR pregnancy	RCTs, meta-analyses, systematic reviews, human, English	1966 to May 2009	4/5
OVID	Hypertension/drug therapy [MESH] AND women of child birth potential OR pregnancy OR abnormalities [MESH] ACEIs AND women of child birth potential OR pregnancy; thiazides AND women of child birth potential OR pregnancy; calcium channel blockers AND women of child birth potential OR pregnancy; beta blockers AND women of child birth potential OR pregnancy	RCTs, meta-analyses, systematic reviews, cohort studies, human, English	1966 to May 2009	0/0
Other www.FDA.gov	Antihypertensives/hypertension drug therapy AND women of child birth potential OR pregnancy AND birth defects OR pregnancy complications	Medical alerts, advisories, guides		1/2

* Note: "No. Included" refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. "Total Retrieved" refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Discrete Populations – Post-Stroke Treatment of Hypertension

Problem Formulation

Clinical Questions:	What is the most effective therapy for reducing the rates of serious outcomes in prehypertension or hypertension for patients who are post-stroke?
Population:	Patients who have survived a stroke or transient ischemic attack
Health Problem:	Essential hypertension
Health Intervention:	Treatment plan using diuretics, ACEI, ARBs, and CCBs
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ Fatal and nonfatal stroke ◆ All-cause mortality ◆ Cardiovascular mortality

Search Strategy

Only RCTs, clinical trials, systematic reviews, or meta-analyses with clinical outcomes that studied individuals with a prior diagnosis of stroke or TIA who were randomized to head-to-head trials of antihypertensive agents were included.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed	Hypertension/drug therapy[MESH] AND Cerebrovascular accident [MESH] AND secondary prevention	Meta-analysis, Randomized Controlled Trial, Clinical Trial, Review, Adult, English, Human	1966 - 3/1/2007	2/23

* Note: “No. Included” refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. “Total Retrieved” refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Behavioral Change – Supplementary Treatment of Uncomplicated Hypertension with Lifestyle Modifications

Problem Formulation

Clinical Question:	Should behavioral change measures be recommended to supplement antihypertensive medications?		
Population:	Nonpregnant adults with hypertension who do not have diabetes, heart failure, renal insufficiency, or known coronary heart disease.		
Health Problem:	Essential hypertension		
Health Intervention:	<ul style="list-style-type: none"> ◆ Low intake of sodium ◆ Calorie and fat restriction for weight reduction ◆ Increased intake of fruits and vegetables ◆ Limited intake of alcohol ◆ Increased physical activity ◆ No change 		
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ All-cause mortality ◆ CV mortality ◆ Stroke ◆ Nonfatal myocardial infarction ◆ Heart failure 		

Search Strategy

Initially, only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension who were treated with antihypertensive medications and were randomized to intervention vs. control groups were searched for. There were no studies with hard outcomes and few with treated populations, so the intermediate outcome of blood pressure was used, as were some studies with untreated populations.

Diet: Systematic review covered articles through December 2001.
 PubMed search updated the SR from October 2001 – April 2003.

Weight Loss: Systematic review covered articles through November 1997.
 PubMed search updated the SR from September 1997 – April 2003.

Alcohol: No appropriate systematic review was found.
 PubMed search covered 1966 – April 2003.

Exercise: PubMed search covered 1966 – 2003. It yielded one meta-analysis (of some aspects of the problem), which included studies published up to August 1998.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
Cochrane	Hypertension AND diet	Systematic reviews	05/21/03	1/41
	Hypertension AND weight loss	Systematic reviews	05/21/03	1/27
	Hypertension AND alcohol	Systematic reviews	05/21/03	0/55
	Hypertension AND physical activity	Systematic reviews	05/21/03	0/28
PubMed	Hypertension[MESH] AND (Diet[MESH] OR Diet therapy[MESH])	Meta-analysis, English, Human	10/01 - 04/23/03	0/9
		English, Randomized Controlled Trial, Human	10/01 - 04/23/03	2/16
	Hypertension[MESH] AND (Diet[MESH] OR Diet therapy[MESH])	Meta-analysis, English, Human	4/24/03 - 4/15/05	0/2
		English, Randomized Controlled Trial, Human	4/24/03 - 4/15/05	0/13

* Note: “No. Included” refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. “Total Retrieved” refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed	Hypertension[MESH] AND (Weight loss[MESH])	Meta-analysis, English, Human	9/1997 - 04/23/03	0/1
		English, Randomized Controlled Trial, Human	9/1997 - 04/23/03	3/5
		Meta-analysis, English, Human	4/24/03 - 4/15/05	0/2
		English, Randomized Controlled Trial, Human	4/24/03 - 4/15/05	0/6
	Hypertension[MESH] AND (Alcohol drinking[MESH])	Meta-analysis, English, Human	1966 - 04/23/03	0/3
		English, Randomized Controlled Trial, Human	1966 - 04/23/03	4/38
		Meta-analysis, English, Human	4/24/03 - 4/15/05	0/1
		English, Randomized Controlled Trial, Human	4/24/03 - 4/15/05	0/4
	Hypertension[MESH] AND (Exercise[MESH])	Meta-analysis, English, Human	1966 - 04/23/03	1/11
		English, Randomized Controlled Trial, Human	1966 - 04/23/03	1/117
		Meta-analysis, English, Human	4/24/03 - 4/15/05	0/1
		English, Randomized Controlled Trial, Human	4/24/03 - 4/15/05	0/8

Behavioral Change – Adherence to Medications and Lifestyle Modifications

Problem Formulation

Clinical Question:	What are the most effective strategies to achieve medication and lifestyle adherence in adults with hypertension?
Population:	Nonpregnant adults with hypertension who do not have diabetes, heart failure, renal insufficiency, or known coronary heart disease.
Health Problem:	Essential hypertension
Health Intervention:	<ul style="list-style-type: none"> ◆ Medication and lifestyle adherence ◆ Daily dosage frequency
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ All-cause mortality ◆ CV mortality ◆ Stroke ◆ Nonfatal myocardial infarction ◆ Heart failure

Search Strategy

Initially, only RCTs, systematic reviews, or meta-analyses with clinical outcomes that studied nonpregnant individuals with hypertension who were treated with antihypertensive medications and were randomized to intervention vs. control groups were searched for. There were no studies with hard outcomes and few with treated populations, so the intermediate outcome of blood pressure was used, as were some studies with untreated populations.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
Cochrane	Hypertension AND diet	Systematic reviews	05/21/03	1/41
	Hypertension AND weight loss	Systematic reviews	05/21/03	1/27
	Hypertension AND alcohol	Systematic reviews	05/21/03	0/55
	Hypertension AND physical activity	Systematic reviews	05/21/03	0/28
PubMed	Hypertension[MESH] AND (Diet[MESH] OR Diet therapy[MESH])	Meta-analysis, English, Human	10/01 - 04/23/03	0/9
		English, Randomized Controlled Trial, Human	10/01 - 04/23/03	2/16
		Meta-analysis, English, Human	4/24/03 - 4/15/05	0/2
		English, Randomized Controlled Trial, Human	4/24/03 - 4/15/05	0/13

* Note: “No. Included” refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. “Total Retrieved” refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed	Hypertension[MESH] AND (Weight loss[MESH])	English, Randomized Controlled Trial, Human	9/1997 - 04/23/03	3/5
		Meta-analysis, English, Human	4/24/03 - 4/15/05	0/2
		English, Randomized Controlled Trial, Human	4/24/03 - 4/15/05	0/6
PubMed	Hypertension[MESH] AND (Weight loss[MESH])	Meta-analysis, English, Human	4/16/05 - 03/05/07	0/2
		English, Randomized Controlled Trial, Human	4/24/03 - 4/15/05	0/6
PubMed	Hypertension[MESH] AND (Alcohol drinking[MESH])	English, Randomized Controlled Trial, Human	1966 - 04/23/03	4/38
		Meta-analysis, English, Human	4/16/05 - 03/05/07	0/1
		English, Randomized Controlled Trial, Human	4/16/05 - 03/05/07	0/4
		Meta-analysis, English, Human	4/16/05 - 03/05/07	0/0
		English, Randomized Controlled Trial, Human	4/15/05 - 03/05/07	0/0

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed	Hypertension[MESH] AND (Exercise[MESH])	Meta-analysis, English, Human	1966 - 04/23/03	1/11
		English, Randomized Controlled Trial, Human	1966 - 04/23/03	1/117
		Meta-analysis, English, Human	4/24/03 - 4/15/05	0/0
		English, Randomized Controlled Trial, Human	4/24/03 - 4/15/05	0/8
PubMed	Hypertension AND patient adherence	Meta-analysis, English, Human	04/16/05 - 03/15/07	1/1
		English, Randomized Controlled Trial, Human	04/16/05 - 03/15/07	0/0

Use of Aspirin in Hypertensive Patients Receiving Antihypertensive Medications

Problem Formulation

Clinical Question:	Should aspirin be recommended for patients with hypertension receiving antihypertensive medication?		
Population:	Nonpregnant adults with hypertension who do not have diabetes, heart failure, renal insufficiency, or known coronary heart disease who are taking antihypertensive medications.		
Health Problem:	Essential hypertension		
Health Intervention:	<ul style="list-style-type: none"> ◆ Aspirin ◆ No aspirin 		
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ All-cause mortality ◆ Cardiovascular mortality ◆ Stroke 	<ul style="list-style-type: none"> ◆ Nonfatal myocardial infarction ◆ Heart failure 	

Search Strategy

Only RCTs, systematic reviews, or meta-analyses with clinical outcomes were included. When possible, studies were included that were primarily concerned with participants without significant comorbid conditions.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
Cochrane	aspirin, hypertension, and antihypertensive	Systematic reviews	CD-ROM, Issue 3, 2001	0/2
	Hypertension, aspirin, acetylsalicylic acid, ASA, blood pressure	Randomized Controlled Trials (RCT)	12/09/02	0/74
	Hypertension, aspirin, acetylsalicylic acid, ASA, blood pressure	Systematic reviews	12/09/02	0/39
Clinical Evidence	Hypertension, blood pressure, aspirin	Systematic reviews and RCTs	Vol. 5, 2001, evidence through Dec. 2000 (Hand search through Vol. 5 for SRs of antihypertensive tx), June 2002 issue	0/1
PubMed	(((((hypertension[MESH] OR hypertension[Text Word]) AND (aspirin[MESH] OR aspirin[Text Word]))) AND (antihypertensive agents[MESH] OR antihypertensive agents[Text Word]))) AND (((clinical trial[pt] OR randomized controlled trial[pt]) OR meta-analysis[pt]) OR review[pt])) AND English[la] AND human[MESH]) AND (1966[dp]: 2001/10/31[dp]))	Meta-analysis, Randomized Controlled Trial, Adult, English, Human	1966 through October 2001	0/89

* Note: “No. Included” refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. “Total Retrieved” refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed	((hypertension[MESH] OR hypertension[Text Word]) AND adverse[All Fields]) AND ((aspirin[MESH] OR aspirin[Text Word]) OR (acetylsalicylic[All Fields] AND (acids[MESH] OR acid[Text Word]))))	Randomized, controlled trial or Clinical Trial or Meta-Analysis, All Adult: 19+ years, English, Human	11/01/01 to 12/06/02	1/1
PubMed	((antihypertensive agents[MESH] OR antihypertensive[Text Word]) AND ((aspirin[MESH] OR aspirin[Text Word]) OR (acetylsalicylic[All Fields] AND (acids[MESH] OR acid[Text Word]))))	Randomized, controlled trial or Clinical Trial or Meta-Analysis, All Adult: 19+ years, English, Human	11/01/01 to 12/06/02	0
Pre-Medline	Hypertension AND adverse AND (aspirin OR acetylsalicylic acid)		12/12/02	0
	antihypertensive AND (aspirin OR acetylsalicylic acid)		12/12/02	0
Medline	Hypertension AND adverse AND (aspirin OR acetylsalicylic acid)		2002	0
	antihypertensive AND (aspirin OR acetylsalicylic acid)		2002	0
Cochrane Database	Aspirin and hypertension	Systematic reviews	2005	1
PubMed	Aspirin[MESH] AND Cardiovascular Diseases[MESH]	Meta-analysis, English, Human	12/6/02 - 4/25/05	1
		Randomized Controlled Trial, English, Human	12/6/02 - 4/25/05	1

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
PubMed	Aspirin[MESH] AND Cardiovascular Diseases[MESH]	Meta-analysis, English, Human	4/25/05 - 03/20/07	2
		Randomized Controlled Trial, English, Human	4/25/05 - 03/20/07	1

Use of Antilipemic Therapy in Hypertensive Patients Taking Antihypertensive Medications

Problem Formulation

Clinical Question:	Should antilipemic therapy be recommended for patients with hypertension receiving antihypertensive medication?		
Population:	Nonpregnant adults with hypertension who do not have diabetes, heart failure, renal insufficiency, or known coronary heart disease.		
Health Problem:	Essential hypertension		
Health Intervention:	<ul style="list-style-type: none"> ◆ Statins ◆ Vytorin (Ezetimide/simvastatin) ◆ Gemfibrozil ◆ Fibrates ◆ No treatment 		
Most Important Health Outcomes:	<ul style="list-style-type: none"> ◆ All-cause mortality ◆ Cardiovascular mortality ◆ Stroke ◆ Nonfatal myocardial infarction ◆ Heart failure 		

Search Strategy

No appropriate Cochrane or Clinical Evidence Systematic Reviews were found on statin use in hypertensive patients. PubMed was searched from 1965 to 03/07.

Database:	Search Terms:	Article Type and Other Limits:	Search Date	No. Included / Total Retrieved*
Cochrane	Statins, hypertension, and blood pressure	Systematic reviews (SR)	12/09/02	0/5
		Controlled trials (CT)	12/09/02	0/7
Clinical Evidence	Statins, hypertension, and blood pressure	Systematic reviews and RCTs	June 2002	0/1
PubMed	Various combinations of MESH and Text Words: Hypertension, blood pressure, antihypertensives, HMG CoA reductase inhibitors, antilipemics, lipid lowering, cholesterol reduction, adverse events	Meta-analysis, Randomized Controlled Trial, Adult, English, Human	1965 - 12/18/02	1/414
	Hypertension AND Hydroxymethylglutaryl-CoA Reductase Inhibitors	Meta-analysis, English, Human	12/6/02 - 4/19/05	0/4
		Randomized Controlled Trial, English, Human	12/6/02 - 4/19/05	1/44
	Hypertension AND Hydroxymethylglutaryl-CoA Reductase Inhibitors	Meta-analysis, English, Human	4/19/05 - 03/20/07	1/1
		Randomized Controlled Trial, English, Human	4/19/05 - 03/20/07	0/5
	Hypertension AND Vytorin, Ezetimibe, gemfibrozil, fibrates	Meta-analysis, English, Human	4/19/05 - 03/20/07	0/0
		Randomized Controlled Trial, English, Human	4/19/05 - 03/20/07	0/0

* Note: "No. Included" refers to studies that are relevant to the problem formulation and, therefore, are included in this analysis of the evidence. "Total Retrieved" refers to the number of studies retrieved in the search, regardless of relevance. Because individual studies can be captured in multiple databases, they may be counted more than once in the number included.

Appendix C

Assessment of the Importance of Hypertension Control in Kaiser Permanente (KP)

Joel Handler, MD, SCPMG and Paul Barrett, MD, MSPH, CMI
September, 2007

Summary: In this analysis we estimate that modest improvements in identification, initiation of treatment and maintenance of long term control of the Northern California (NCal) and Southern California (SCal) KP (herein after KP California) adult members with high blood pressure (hypertension) **can prevent 1,324 strokes (CVAs) and 970 myocardial infarctions (MIs)** over the next five years. These results are based on numbers needed to treat (NNTs) of **63 for CVAs and 86 for MIs**, for all adults. The NNT is 36 for the combined end-point of CVA plus MI for all adults. Extending the NNTs for CVA and MI to the other KP Regions adds another 437 and 320, respectively, to the total benefits of controlling hypertension. We also call attention to data from KP and major competitors that suggests that **proactive planning is needed right now** if we are to **Maintain the recent gains** that KP California has made in controlling hypertension.

Analysis of the appropriateness of applying published estimates of number needed to treat (NNT) to prevent selected cardiovascular outcomes

In this paper we apply the results of a meta-analysis by Mulrow, et al. of the impact of successfully controlling hypertension¹ to the combined membership of the Northern California (NCal) and Southern California (SCal) (KP California). That study combined the results of many large, high quality, randomized clinical trials (RCTs) of antihypertensive agents to calculate the number needed to treat (NNT) to prevent one CVA or MI.

Our analysis considers several issues that might invalidate the use of these NNTs in KP California, including demographics, the prevalence of hypertension in the KP population, a goal for the completeness of ascertainment of hypertensives, the current proportion of patients whose hypertension is under control and a goal for the proportion whose hypertension is under control under a successful population-based disease management program.

Age demographics from the California KP hypertension registries are depicted in Table 1, the corresponding age-based NNTs from the Mulrow meta-analysis are seen in Table 2 and the calculation of KP NNTs in Table 3. The actual KP NNTs could either be higher or lower than those of Mulrow, depending on a number of factors, including the KP mix of un- and under-treated members relative to the mix of placebo-controlled vs. “usual-care-controlled” studies in Mulrow’s analysis. We assume for the purposes of this analysis that those relative relationships are similar so that the NNTs need not be adjusted for use in KP on that account.

Another issue is the accuracy of blood pressure measurement in KP compared with that of the studies used by Mulrow. The accuracy of blood pressure measurement in a high-quality RCT is clearly better than in a community practice, where the equipment and training of staff are variable. This variability would certainly not improve the NNT in KP but it is hard to know how much it would increase it.

A related issue is the validity of the NCal and SCal hypertension registries, since the determination of the degree of control of blood pressure in a population is dependent on the accuracy of the diagnosis. An independent review of the NCal hypertension registry demonstrated a positive predictive value of 97.1% for patients labeled as hypertensive in the registry.² Thus the validity of the registries is not a factor in our calculation of the benefits of controlling hypertension in KP California.

The completeness of ascertainment of hypertension in KP California can be estimated from the number of hypertensives in the KP California hypertension registry, 1,191,722, and the total number of hypertensives in the population. That number can be estimated by applying the prevalence of hypertension in American adults from 2004 NHANES data, 29.3%, to the KP California adult population.³ Using this denominator yields ascertainment of hypertension of 84.4% and 83.8% for NCal and SCal, respectively, for a combined average of 84.1%.

The degree of control of hypertension is a critical variable. Treatment trials usually differ from the community setting in two important ways: (1) the patients are more highly motivated to follow treatment protocols; (2) the intensity of monitoring and support of patient adherence, e.g., by means of monthly medication “up-titrations” of three or more drugs, is higher. Patient motivation may not be as large a factor as once thought because recent studies have shown that patient motivation has far less effect on medication adherence and control than physician factors and therapeutic inertia.⁴⁻¹⁰ By putting treatment of hypertension under a population-based management system, KP is addressing the issue of therapeutic inertia. And, while the frequency and method of monitoring blood pressure in KP is variable, newer KP guidelines do involve the use of three or four drugs, beginning with a combination product to reduce pill burden. Thus there are significant similarities between the treatment of hypertension in KP and in treatment trials. Therefore it is not surprising to see HEDIS blood pressure control rates of 73.5% and 74.9% in NCal and SCal, respectively, compared with blood pressure control rates of 65% to 70% in treatment trials. Consequently, while the degree of control for clinical trials and the KP membership are probably not fully comparable, the KP HEDIS results suggest that Mulrow’s NNT need not be adjusted upward significantly to account for any hypothetical loss of effectiveness in translating the results of treatment trials into KP practice.

Finally, one must confront the issue of turnover in the membership, which will dilute the benefit of the control of hypertension within the KP membership. However, while the turnover in the membership < 65 years of age is significant, the turnover in the Medicare membership (mostly over age 65) is quite low. Using this relationship as a proxy for the relative turnover in the under 60 and 60 and older KP California membership and accounting for the fact that about 80% of the MIs and CVAs prevented occur in the 60 and over membership (data not shown), we believe that turnover will have only a modest effect on our calculations. Therefore we have done no formal adjustment to account for it.

In summary, while Mulrow's NNTs are probably not directly applicable to KP California, we believe that they are a reasonable approximation of what can be achieved in KP California.

Calculation of the MIs and CVAs prevented by small improvements in the identification, initiation of treatment and maintenance of control of blood pressure in KP California hypertensives

The key measures of the success of a program to prevent the effects of hypertension are the proportion of the population that is identified and followed, e.g., through enrollment in a registry and population-based care program, the proportion of those hypertensives whose blood pressure is brought under control and the proportion that are under long term, stable control (maintenance).

We estimated, above, that 84.1% of hypertensives in KP California have already been identified. Based on this level of performance, we estimate that a goal of 85% to 90% ascertainment is reasonable.

In the hypertension treatment trials included in Mulrow's study a mean comparative blood pressure reduction of 10 to 12 / 4 to 5 mm Hg compared with usual therapy resulted in control rate of about 65%. The southeastern state region American Society of Hypertension (ASH) goal control rate is 70%.¹¹ The ALLHAT treatment trial site at South Bay in SCal achieved a control rate of 80% for 250 patients and received an award from the ALLHAT investigators for best control rate.¹² Northern Cal KP achieved a HEDIS 2007 Medicare control rate of 81%.¹² The 90th percentile national HEDIS hypertension control rate for the Commercial population is 68.13%.¹² Combination drug treatment for hypertension, as recommended in the KP National Hypertension Guidelines, appears to be an important factor leading to highest echelon control rates. Recently reported interim results of the first large combination drug treatment trial, ACCOMPLISH, showed total trial control of 76%, with the United States centers reporting 80% control.¹³ Therefore, a KP program hypertension control rate goal of 75 to 80% is reasonable.

Now, taking the current KP California performance as the baseline, and assuming modest improvements toward these goals we can apply Mulrow's NNTs to KP California. Doing so, and assuming a 5% absolute increase in the degree of hypertension control, to 78.5% in NCal and 79.9% in SCal, maintained over the next five years, yields estimates of 693 MIs and 946 CVAs that could be prevented. If, in addition, just 2% more hypertensives in KP California were identified and treated with the same degree of control, another 277 MIs and 378 CVAs could be prevented for a grand total of 970 MIs and 1324 CVAs prevented.

Finally, we consider the long term maintenance of blood pressure control in large systems of care. Maintenance of hypertension control for at least five years is necessary for the NNTs from Mulrow, et al. to become applicable, and maintenance of high control rates has proven difficult as seen in Figure 1. For example, the HEDIS 2004 KP Mid-Atlantic States hypertension control rate of 78.8% is compared with its HEDIS 2007 control rate of 65.1%. The HEDIS 2004 California Blue Cross hypertension control rate of 75% is compared with the HEDIS 2007 control rate of 60.0%. Analysis thus far suggests that programs and recommendations have not changed to account for these downturns, and that the causes, though multifactorial, may at least partially be explained by shifting attention, priorities, and resources. A natural consequence of the competitive environment where health plans are competing to achieve HEDIS superiority is to shift administrative attention from a successful HEDIS area to a less successful HEDIS area. Initiative fatigue at the primary care level is another consideration. Our challenge in KP, especially in the California Regions, which have just reached their highest levels of control, is to maintain the recent high level of performance, even as Regional priorities move on to other areas of underperformance.

Calculation of the impact of a similar degree of control of Hypertension in Regions Outside California

The first question in attempting to apply this approach to the Regions outside of California (ROC) is “Are the KP California hypertension registry patients comparable to those in Regions outside of California?” We know that the proportion of Regional membership who are over 65 years old is comparable in several of those Regions, e.g., Northwest, Ohio and Colorado. Thus the population with hypertension should be similar to that of the California Regions. We will assume this for the purposes of this discussion, pending gathering information about the hypertension registries in the ROC.

Without the registry information from the ROC we cannot estimate the ascertainment of hypertensives, so we are not able to calculate any projected reduction in MIs and CVAs due to an increase in ascertainment.

For the KP program containing approximately 6 million adult members nationwide, there is an expected hypertension prevalence of 1,750,000 members, or 550,000 more than in KP California. The control rate for the ROC in 2007 ranged from 56.9% to 65.7% and was higher than that by at least 8% in the recent past in all but one of them. Therefore, it is reasonable to assume that they, too, could increase their rate of control by at least 5%. Using the MI NNT of 86 and the CVA NNT of 63, expected MIs and CVAs prevented by five years of a 5% increase in hypertension control are 320 and 437, respectively. This would bring the total for the entire KP population to 1290 and 1761 for MI and CVA, respectively.

In summary we have justified using the NNTs from a high quality meta-analysis in the KP California population and in the ROC and made modest assumptions about potential improvements in care in KP California and KP Programwide to calculate the potential benefit in the prevention of two of the major outcomes caused by hypertension, MI and CVA. We have also highlighted the instability of increases in the quality of the care of hypertension in KP ROC and in other large national HMOs and emphasized the importance of maintaining the gains, especially in KP California where their highest rates of control of hypertension have been achieved in the past two years.

Table 1: Demographics of 2007 Q2 California KP Hypertension Registries, age 18 and over.

	Hypertension Registries		
	NCal	SCal	Total
< Age 60	245,756 (40.9%)	261,517 (44.3%)	507,273 (42.6%)
≥ Age 60	355,523 (59.1%)	328,926 (55.7%)	684,449 (57.4%)
All Adults	601,279 (100.0%)	590,443 (100.0%)	1,191,722 (100.0%)

Table 2: Mulrow, et al. meta-analysis number needed to treat (NNT)s for 5 years for the outcomes myocardial infarction (MI) and stroke (CVA).

Mulrow, et al.	NNT < Age 60	NNT ≥ Age 60
MI	184	61
CVA	168	43

Table 3. Calculation of age-adjusted NNT for 5 years for KP membership with Hypertension for the outcomes myocardial infarction (MI) and stroke (CVA).

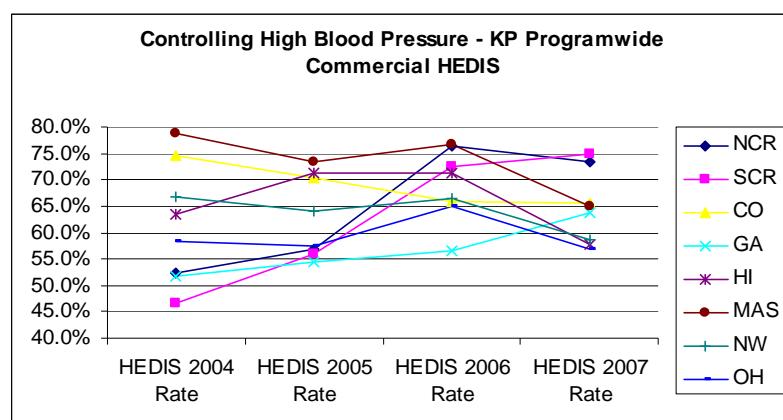
	Pop'n < 60	NNT < 60	Cases Prevented < 60	Pop'n ≥ 60	NNT ≥ 60	Cases Prevented ≥ 60	Total Cases Prevented	Total Pop'n	Age- Adj'd NNT
MI	507273	184	2757	684449	61	11220	13795	1,191,722	86
CVA	507273	168	3019	684449	43	15917	18936	1,191,722	63
CVA + MI	507273	88	5776	684449	25	27137	32731*	1,191,722	36

* The value for this cell as a row total is 32913, rather than 32731, because of the rounding that is inherent in calculating NNTs. The age-adjusted NNT is 36 either way.

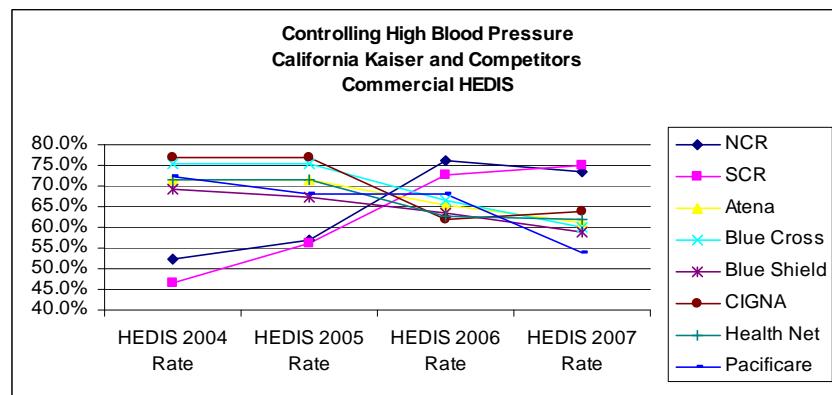
Table 4. Calculation of the number of MIs and CVAs prevented by a 5% absolute increase in the degree of control of Hypertension in KP California.

Region	Hypertensives newly controlled	MI's prevented	CVA's prevented
N California	30,064	350	477
S California	29,522	343	469
Total	59,586	693	946

Figure 1: HEDIS Commercial hypertension control trending 2004-2007 showing KP Regional comparisons (top graph), and California health plan competitors (bottom graph) depicting decline in the HEDIS 2004-2005 top performers as KP has improved.



HTN Commercial	HEDIS 2004 Rate	HEDIS 2005 Rate	HEDIS 2006 Rate	HEDIS 2007 Rate
NCR	52.3%	56.8%	76.27%	73.52%
SCR	46.5%	56.0%	72.51%	74.93%
CO	74.7%	70.3%	65.80%	65.69%
GA	51.6%	54.5%	56.45%	63.61%
HI	63.5%	71.3%	71.29%	57.73%
MAS	78.8%	73.3%	76.83%	65.09%
NW	66.7%	64.2%	66.42%	58.59%
OH	58.4%	57.4%	64.96%	56.93%



KP CA Competitor	HEDIS 2004 Rate	HEDIS 2005 Rate	HEDIS 2006 Rate	HEDIS 2007 Rate
NCR	52.3%	56.8%	76.27%	73.52%
SCR	46.5%	56.0%	72.51%	74.93%
Atena	72%	72%	65%	61%
Blue Cross	75%	75%	67%	60%
Blue Shield	69%	67%	63%	59%
CIGNA	77%	77%	62%	64%
Health Net	71%	71%	63%	62%
Pacificare	72%	68%	68%	54%

Please note that the measure specification changes in 2007 to expand the age band to 18-85, define adequate control as <140/90, and determine representative blood pressure, make results for this measure not trendable to prior years' results.

Center for Healthcare Analytics - HEDIS

Mulrow CD, Cornell JA, Herrera CR, et al. Hypertension in the elderly; implications and generalizability of randomized trials. *JAMA* 1994;272:1932-1938.

Woodling R. Specificity of northern California Kaiser Permanente hypertension registry inclusion by chart review 1999. internal Kaiser Permanente document, available on request

Ong KL, Cheung BMY, Yu BM, et al. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. *Hypertens* 2007; 49: 69-75.

Berlowitz DR, Ash AS, Hickey EC. Inadequate management of blood pressure in a hypertensive population. *NEJM* 1998; 339: 1957-1963.

Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. *NEJM* 2001; 345: 479-486.

Andrade SE, Gurwitz JH, Field TS, et al. Hypertension management: the care gap between clinical guidelines and clinical practice. *Am J Manag Care* 2004; 10: 481-486.

Phillips LS, Branch Jr WT, Cook CB. Clinical inertia. *Arch Intern Med* 2001; 135: 825-834.

Okonofua EC, Simpson KN, Jesri A, et al. Therapeutic inertia is an impediment to achieving the Health People 2010 blood pressure control goals. *Hypertens* 2006; 47: 345-351.

O'Connor PJ. Overcome clinical inertia to control systolic blood pressure. *Arch Int Med* 2003; 163: 2677-2678.

Hyman DJ, Pavlik VN. Poor hypertension control: let's stop blaming the patients. *Cleve Clinic J Med* 2002; 69: 793-799.

Jamerson KA. Exceptional early blood pressure control rates: the ACCOMPLISH trial. Presentation May 21, 2007 American Society of Hypertension (ASH) meetings, Chicago, Ill.

Internal KP data

Basile J. Presentation to American Society of Hypertension (ASH) Scientific meetings May 2006.

References

- (1) U.S.Preventive Services Task Force. Screening for High Blood Pressure, Topic Page. 2003. Rockville, MD, Agency for Healthcare Research and Quality. <http://www.ahrq.gov/clinic/uspstf/uspshyp.htm>
- (2) Staessen JA, Thijisq L, Fagard R, Celis H, Birkenhager WH, Bulpitt CJ et al. Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. *J Hypertens* 2004; 22(4):847-857. PM:15126928
- (3) Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr. et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42(6):1206-1252. PM:14656957
- (4) He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. *J Hum Hypertens* 2002; 16(11):761-770. PM:12444537
- (5) Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2002; 136(7):493-503. PM:11926784
- (6) Seals DR, Tanaka H, Clevenger CM, Monahan KD, Reiling MJ, Hiatt WR et al. Blood pressure reductions with exercise and sodium restriction in postmenopausal women with elevated systolic pressure: role of arterial stiffness. *J Am Coll Cardiol* 2001; 38(2):506-513. PM:11499745
- (7) Tsai JC, Yang HY, Wang WH, Hsieh MH, Chen PT, Kao CC et al. The beneficial effect of regular endurance exercise training on blood pressure and quality of life in patients with hypertension. *Clin Exp Hypertens* 2004; 26(3):255-265. PM:15132303
- (8) Ueshima H, Mikawa K, Baba S, Sasaki S, Ozawa H, Tsushima M et al. Effect of reduced alcohol consumption on blood pressure in untreated hypertensive men. *Hypertension* 1993; 21(2):248-252. PM:8428787
- (9) Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998; 351(9118):1755-1762. PM:9635947
- (10) Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360(9349):1903-1913. PM:12493255

- (11) Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. *JAMA* 2002; 287(8):1003-1010. PM:11866648
- (12) Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358(9287):1033-1041.
- (13) Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. *Stroke* 2003; 34(11):2741-2748.
- (14) Arima H, Chalmers J. Secondary prevention of stroke by blood pressure-lowering treatment. *Curr Hypertens Rep* 2006; 8(4):317-323.
- (15) Verberk WJ, Kroon AA, Kessels AG, de Leeuw PW. Home blood pressure measurement: a systematic review. *J Am Coll Cardiol* 2005; 46(5):743-751.
- (16) Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B et al. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004; 291(11):1342-1349. PM:15026401
- (17) Moser M, Franklin SS. Hypertension management: results of a new national survey for the hypertension education foundation: Harris interactive. *J Clin Hypertens (Greenwich)* 2007; 9(5):316-323.
- (18) Cappuccio FP, Kerry SM, Forbes L, Donald A. Blood pressure control by home monitoring: meta-analysis of randomised trials. *BMJ* 2004; 329(7458):145. PM:15194600
- (19) Appel LJ, Robinson KA, Guallar E, Erlinger T, Masood SO, Juhn M et al. Utility of blood pressure monitoring outside of the clinic setting. *Evid Rep Technol Assess (Summ)* 2002;(63):1-5. PM:15523745
- (20) Fagard RH, Staessen JA, Thijs L, Gasowski J, Bulpitt CJ, Clement D et al. Response to antihypertensive therapy in older patients with sustained and nonsustained systolic hypertension. *Systolic Hypertension in Europe (Syst-Eur) Trial Investigators*. *Circulation* 2000; 102(10):1139-1144. PM:10973843
- (21) Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension: a 10-year follow-up study. *Circulation* 1998; 98(18):1892-1897. PM:9799210
- (22) Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994; 24(6):793-801. PM:7995639

- (23) Staessen JA, Den Hond E, Celis H, Fagard R, Keary L, Vandenhoven G et al. Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: a randomized controlled trial. *JAMA* 2004; 291(8):955-964. PM:14982911
- (24) Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N et al. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens* 1998; 16(7):971-975. PM:9794737
- (25) Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005; 366(9496):1545-1553. PM:16257341
- (26) Bradley HA, Wiysonge CS, Volmink JA, Mayosi BM, Opie LH. How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and meta-analysis. *J Hypertens* 2006; 24(11):2131-2141.
- (27) Khan N, McAlister FA. Re-examining the efficacy of beta-blockers for the treatment of hypertension: a meta-analysis. *CMAJ* 2006; 174(12):1737-1742.
- (28) Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; 362(9395):1527-1535. PM:14615107
- (29) Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000; 356(9246):1955-1964. PM:11130523
- (30) Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA* 2003; 289(19):2534-2544. PM:12759325
- (31) Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997; 277(9):739-745. PM:9042847
- (32) Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991; 338(8778):1281-1285. PM:1682683
- (33) Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ* 1985; 291:97-104.

- (34) Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; 342(3):145-153. PM:10639539
- (35) MacMahon S, Sharpe N, Gamble G, Clague A, Mhurchu CN, Clark T et al. Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. PART-2 Collaborative Research Group. Prevention of Atherosclerosis with Ramipril. *J Am Coll Cardiol* 2000; 36(2):438-443. PM:10933355
- (36) Pitt B, O'Neill B, Feldman R, Ferrari R, Schwartz L, Mudra H et al. The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. *Am J Cardiol* 2001; 87(9):1058-1063. PM:11348602
- (37) Teo KK, Burton JR, Buller CE, Plante S, Catellier D, Tymchak W et al. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation* 2000; 102(15):1748-1754. PM:11023927
- (38) Wiysonge CS, Bradley H, Mayosi BM, Maroney R, Mbewu A, Opie LH et al. Beta-blockers for hypertension. *Cochrane Database Syst Rev* 2007;(1):CD002003.
- (39) Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA* 2001; 285(21):2719-2728. PM:11386927
- (40) Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288(23):2981-2997. PM:12479763
- (41) Black HR, Elliott WJ, Neaton JD, Grandits G, Grambsch P, Grimm RH, Jr. et al. Rationale and design for the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) Trial. *Control Clin Trials* 1998; 19(4):370-390. PM:9683312
- (42) Zanchetti A, Bond MG, Hennig M, Neiss A, Mancia G, Dal Palu C et al. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation* 2002; 106(19):2422-2427. PM:12417537
- (43) Malacco E, Gnemmi AE, Romagnoli A, Coppini A. Systolic hypertension in the elderly: long-term lacidipine treatment. Objective, protocol, and organization. SHELL Study Group. *J Cardiovasc Pharmacol* 1994; 23 Suppl 5:S62-S66. PM:7609510

- (44) Opie LH, Schall R. Evidence-based evaluation of calcium channel blockers for hypertension: equality of mortality and cardiovascular risk relative to conventional therapy. *J Am Coll Cardiol* 2002; 39(2):315-322. PM:11788225
- (45) Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000; 356(9227):366-372. PM:10972368
- (46) Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. National Intervention Cooperative Study in Elderly Hypertensives Study Group. *Hypertension* 1999; 34(5):1129-1133. PM:10567194
- (47) Rosei EA, Dal Palu C, Leonetti G, Magnani B, Pessina A, Zanchetti A. Clinical results of the Verapamil in Hypertension and Atherosclerosis Study. VHAS Investigators. *J Hypertens* 1997; 15(11):1337-1344. PM:9383184
- (48) Hansson L. STOP-Hypertension-2 and best practice for the future. *Heart* 2000; 84 Suppl 1:i2-i4. PM:10956309
- (49) Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000; 356(9227):359-365. PM:10972367
- (50) Pahor M, Psaty BM, Alderman MH, Applegate WB, Williamson JD, Cavazzini C et al. Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* 2000; 356(9246):1949-1954. PM:11130522
- (51) Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999; 353(9153):611-616. PM:10030325
- (52) Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003; 348(7):583-592. PM:12584366
- (53) Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000; 23 Suppl 2:B54-B64. PM:10860192
- (54) Lindholm LH, Hansson L, Ekbom T, Dahlof B, Lanke J, Linjer E et al. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. *J Hypertens* 2000; 18(11):1671-1675. PM:11081782

- (55) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ 1998; 317(7160):703-713. PM:9732337
- (56) Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, Faire U et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359(9311):995-1003. PM:11937178
- (57) Wilhelmsen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosie J et al. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPY trial. J Hypertens 1987; 5(5):561-572. PM:2892881
- (58) Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. BMJ 1992; 304(6824):405-412. PM:1445513
- (59) Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004; 363(9426):2022-2031. PM:15207952
- (60) Leenen FH, Nwachuku CE, Black HR, Cushman WC, Davis BR, Simpson LM et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Hypertension 2006; 48(3):374-384.
- (61) Yui Y, Sumiyoshi T, Kodama K, Hirayama A, Nonogi H, Kanmatsuse K et al. Nifedipine retard was as effective as angiotensin converting enzyme inhibitors in preventing cardiac events in high-risk hypertensive patients with diabetes and coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) subgroup analysis. Hypertens Res 2004; 27(7):449-456. PM:15302980
- (62) Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008; 359(23):2417-2428. PM:19052124
- (63) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 1991; 265(24):3255-3264. PM:2046107
- (64) Amery A, Birkenhager W, Brixko P, Bulpitt C, Clement D, Deruyttere M et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet 1985; 1(8442):1349-1354. PM:2861311

- (65) Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002; 288(23):2998-3007. PM:12479764
- (66) Wassertheil-Smoller S, Psaty B, Greenland P, Oberman A, Kotchen T, Mouton C et al. Association between cardiovascular outcomes and antihypertensive drug treatment in older women. JAMA 2004; 292(23):2849-2859. PM:15598916
- (67) Dezii CM. A retrospective study of persistence with single-pill combination therapy vs. concurrent two-pill therapy in patients with hypertension. Manag Care 2000; 9(9 Suppl):2-6. PM:11729417
- (68) Bangalore S, Sawhney S, Messerli FH. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. J Am Coll Cardiol 2008; 52(18):1482-1489. PM:19017516
- (69) Bangalore S, Wild D, Parkar S, Kukin M, Messerli FH. Beta-blockers for primary prevention of heart failure in patients with hypertension insights from a meta-analysis. J Am Coll Cardiol 2008; 52(13):1062-1072. PM:18848139
- (70) Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006; 113(9):1213-1225. PM:16476843
- (71) Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005; 366(9489):895-906.
- (72) Mancia G, De BG, Dominiczak A, Cifkova R, Fagard R, Germano G et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25(6):1105-1187. PM:17563527
- (73) National Institute for Health and Clinical Excellence. Hypertension: Management of hypertension in adults in primary care. National Institute for Health and Clinical Excellence . 2006. <http://www.nice.org.uk/>
- (74) Moser M, Setaro JF. Clinical practice. Resistant or difficult-to-control hypertension. N Engl J Med 2006; 355(4):385-392. PM:16870917
- (75) Epstein M, Calhoun DA. The role of aldosterone in resistant hypertension: implications for pathogenesis and therapy. Curr Hypertens Rep 2007; 9(2):98-105. PM:17442219

- (76) Ouzan J, Perault C, Lincoff AM, Carre E, Mertes M. The role of spironolactone in the treatment of patients with refractory hypertension. *Am J Hypertens* 2002; 15(4 Pt 1):333-339. PM:11991219
- (77) Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens* 2003; 16(11 Pt 1):925-930. PM:14573330
- (78) Goodfriend TL, Calhoun DA. Resistant hypertension, obesity, sleep apnea, and aldosterone: theory and therapy. *Hypertension* 2004; 43(3):518-524. PM:14732721
- (79) Vogt B, Bochud M, Burnier M. The association of aldosterone with obesity-related hypertension and the metabolic syndrome. *Semin Nephrol* 2007; 27(5):529-537. PM:17868790
- (80) Chapman N, Dobson J, Wilson S, Dahlof B, Sever PS, Wedel H et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 2007; 49(4):839-845. PM:17309946
- (81) Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003; 21(5):875-886. PM:12714861
- (82) Fox KM, Henderson JR, Bertrand ME, Ferrari R, Remme WJ, Simoons ML. The European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA). *Eur Heart J* 1998; 19 Suppl J:J52-J55. PM:9796841
- (83) van den Heuvel AF, van Gilst WH, van Veldhuisen DJ, de Vries RJ, Dunselman PH, Kingma JH. Long-term anti-ischemic effects of angiotensin-converting enzyme inhibition in patients after myocardial infarction. The Captopril and Thrombolysis Study (CATS) Investigators. *J Am Coll Cardiol* 1997; 30(2):400-405. PM:9247511
- (84) K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004; 43(5 Suppl 1):S1-290. PM:15114537
- (85) Mechanisms for the early mortality reduction produced by beta-blockade started early in acute myocardial infarction: ISIS-1. ISIS-1 (First International Study of Infarct Survival) Collaborative Group. *Lancet* 1988; 1(8591):921-923. PM:2895838
- (86) Roberts R, Rogers WJ, Mueller HS, Lambrew CT, Diver DJ, Smith HC et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. *Circulation* 1991; 83(2):422-437. PM:1671346
- (87) Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. The MIAMI Trial Research Group. *Eur Heart J* 1985; 6(3):199-226. PM:2863148

- (88) A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982; 247(12):1707-1714. PM:7038157
- (89) Pedersen TR. The Norwegian Multicenter Study of Timolol after Myocardial Infarction. Circulation 1983; 67(6 Pt 2):I49-I53. PM:6342838
- (90) Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002; 106(17):2194-2199. PM:12390947
- (91) The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999; 353(9146):9-13. PM:10023943
- (92) Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353(9169):2001-2007. PM:10376614
- (93) Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. BMJ 1998; 317(7160):713-720. PM:9732338
- (94) Franse LV, Pahor M, Di Bari M, Shorr RI, Wan JY, Somes GW et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). J Hypertens 2000; 18(8):1149-1154. PM:10954008
- (95) Liu L, Wang JG, Gong L, Liu G, Staessen JA. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. J Hypertens 1998; 16(12 Pt 1):1823-1829. PM:9869017
- (96) Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA 2003; 290(21):2805-2816. PM:14657064
- (97) Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. 1997; 350(9080):757-764. PM:9297994
- (98) Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ 2000; 321(7274):1440-1444. PM:11110735

- (99) Borhani NO, Mercuri M, Borhani PA, Buckalew VM, Canossa-Terris M, Carr AA et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). A randomized controlled trial. *JAMA* 1996; 276(10):785-791. PM:8769587
- (100) Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten B et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999; 354(9192):1751-1756. PM:10577635
- (101) The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997; 157(21):2413-2446. PM:9385294
- (102) Lindheimer MD, Taler SJ, Cunningham FG. ASH position paper: hypertension in pregnancy. *J Clin Hypertens (Greenwich)* 2009; 11(4):214-225. PM:19614806
- (103) Caton AR, Bell EM, Druschel CM, Werler MM, Lin AE, Browne ML et al. Antihypertensive medication use during pregnancy and the risk of cardiovascular malformations. *Hypertension* 2009; 54(1):63-70. PM:19433779
- (104) Lennestal R, Otterblad OP, Kallen B. Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. *Eur J Clin Pharmacol* 2009; 65(6):615-625. PM:19198819
- (105) Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2007;(1):CD002252. PM:17253478
- (106) Sibai BM, Mabie WC, Shamsa F, Villar MA, Anderson GD. A comparison of no medication versus methyldopa or labetalol in chronic hypertension during pregnancy. *Am J Obstet Gynecol* 1990; 162(4):960-966. PM:2183619
- (107) Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006; 354(23):2443-2451. PM:16760444
- (108) Kallen BA, Otterblad OP. Maternal drug use in early pregnancy and infant cardiovascular defect. *Reprod Toxicol* 2003; 17(3):255-261. PM:12759093
- (109) Sorensen HT, Czeizel AE, Rockenbauer M, Steffensen FH, Olsen J. The risk of limb deficiencies and other congenital abnormalities in children exposed in utero to calcium channel blockers. *Acta Obstet Gynecol Scand* 2001; 80(5):397-401. PM:11328214
- (110) The National Collaborating Centre for Chronic Conditions (NCC-CC). *Hypertension: management in adults in primary care: pharmacological update.* 2006. London, Royal College of Physicians. <http://www.nice.org.uk/nicemedia/pdf/HypertensionGuide.pdf>

- (111) Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004; 18(3):139-185. PM:14973512
- (112) FDA. Angiotensin-Converting Enzyme Inhibitor (ACE inhibitor) Drugs and Pregnancy. 6-8-2006.
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm102981.htm>
- (113) Boubred F, Vendemmia M, Garcia-Meric P, Buffat C, Millet V, Simeoni U. Effects of maternally administered drugs on the fetal and neonatal kidney. *Drug Saf* 2006; 29(5):397-419. PM:16689556
- (114) Bhatt-Mehta V, Deluga KS. Fetal exposure to lisinopril: neonatal manifestations and management. *Pharmacotherapy* 1993; 13(5):515-518. PM:8247923
- (115) Tabacova S. Mode of action: angiotensin-converting enzyme inhibition--developmental effects associated with exposure to ACE inhibitors. *Crit Rev Toxicol* 2005; 35(8-9):747-755. PM:16417042
- (116) Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006; 354(23):2443-2451. PM:16760444
- (117) Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005; 36(6):1218-1226.
- (118) Jurgens G, Graudal NA. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. *Cochrane Database Syst Rev* 2003;(1):CD004022. PM:12535503
- (119) Graudal NA, Galloe AM, Garred P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride: a meta-analysis. *JAMA* 1998; 279(17):1383-1391. PM:9582047
- (120) Grobbee DE, Hofman A. Does sodium restriction lower blood pressure? *Br Med J (Clin Res Ed)* 1986; 293(6538):27-29. PM:3089393
- (121) Cutler JA, Follmann D, Elliott P, Suh I. An overview of randomized trials of sodium reduction and blood pressure. *Hypertension* 1991; 17(1 Suppl):I27-I33. PM:1987008
- (122) Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? III--Analysis of data from trials of salt reduction. *BMJ* 1991; 302(6780):819-824. PM:1827353

- (123) Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996; 275(20):1590-1597. PM:8622251
- (124) Appel LJ, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effects of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). *Arch Intern Med* 2001; 161(5):685-693. PM:11231700
- (125) Vollmer WM, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Morton DG et al. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. *Ann Intern Med* 2001; 135(12):1019-1028. PM:11747380
- (126) Mulrow CD, Chiquette E, Angel L, Cornell J, Summerbell C, Anagnostelis B et al. Dieting to reduce body weight for controlling hypertension in adults. *Cochrane Database Syst Rev* 2000;(2):CD000484. PM:10796721
- (127) Jones DW, Miller ME, Wofford MR, Anderson DC, Cameron ME, Willoughby DL et al. The Effect of Weight Loss Intervention on Antihypertension Optimal Treatment (HOT) Study. *American Journal of Hypertension* 1999; 12:1175-1180.
- (128) Klatsky AL, Friedman GD, Armstrong MA. The relationships between alcoholic beverage use and other traits to blood pressure: a new Kaiser Permanente study. *Circulation* 1986; 73(4):628-636. PM:3948365
- (129) Cushman WC, Cutler JA, Bingham SF, Harford T, Hanna E, Dubbert P et al. Prevention and Treatment of Hypertension Study (PATHS). *American Journal of Hypertension* 1994; 7:814-823.
- (130) Lang T, Nicaud V, Darne B, Rueff B. Improving hypertension control among excessive alcohol drinkers: a randomised controlled trial in France. The WALPA Group. *J Epidemiol Community Health* 1995; 49(6):610-616. PM:8596098
- (131) Parker M, Puddey IB, Beilin LJ, Vandongen R. Two-way factorial study of alcohol and salt restriction in treated hypertensive men. *Hypertension* 1990; 16(4):398-406. PM:2210807
- (132) Puddey IB, Beilin LJ, Vandongen R. Regular alcohol use raises blood pressure in treated hypertensive subjects. A randomised controlled trial. *Lancet* 1987; 1(8534):647-651. PM:2882082
- (133) Arroll B, Beaglehole R. Salt restriction and physical activity in treated hypertensives. *New Zealand Medical Journal* 1995; 108:266-268.
- (134) Fagard RH. Exercise characteristics and the blood pressure response to dynamic physical training. *Med Sci Sports Exerc* 2001; 33(6 Suppl):S484-S492. PM:11427774

- (135) Appel LJ, Champagne CM, Harsha DW, Cooper LS, Obarzanek E, Elmer PJ et al. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA* 2003; 289(16):2083-2093. PM:12709466
- (136) Miller ER, III, Erlinger TP, Young DR, Jahn M, Charleston J, Rhodes D et al. Results of the Diet, Exercise, and Weight Loss Intervention Trial (DEW-IT). *Hypertension* 2002; 40(5):612-618. PM:12411452
- (137) Iskedjian M, Einarson TR, MacKeigan LD, Shear N, Addis A, Mittmann N et al. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. *Clin Ther* 2002; 24(2):302-316.
- (138) Schroeder K, Fahey T, Ebrahim S. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. *Cochrane Database Syst Rev* 2004;(2):CD004804.
- (139) Chodosh J, Morton SC, Mojica W, Maglione M, Suttorp MJ, Hilton L et al. Meta-analysis: chronic disease self-management programs for older adults. *Ann Intern Med* 2005; 143(6):427-438.
- (140) Boulware LE, Daumit GL, Frick KD, Minkovitz CS, Lawrence RS, Powe NR. An evidence-based review of patient-centered behavioral interventions for hypertension. *Am J Prev Med* 2001; 21(3):221-232.
- (141) Fahey T, Schroeder K, Ebrahim S. Educational and organisational interventions used to improve the management of hypertension in primary care: a systematic review. *Br J Gen Pract* 2005; 55(520):875-882.
- (142) Therapeutic control of blood pressure in the Hypertension Detection and Follow-up Program. Hypertension Detection and Follow-up Program Cooperative Group. *Prev Med* 1979; 8(1):2-13.
- (143) Ogedegbe G, Schoenthaler A, Richardson T, Lewis L, Belue R, Espinosa E et al. An RCT of the effect of motivational interviewing on medication adherence in hypertensive African Americans: rationale and design. *Contemp Clin Trials* 2007; 28(2):169-181.
- (144) Wang PS, Bohn RL, Knight E, Glynn RJ, Mogun H, Avorn J. Noncompliance with antihypertensive medications: the impact of depressive symptoms and psychosocial factors. *J Gen Intern Med* 2002; 17(7):504-511.
- (145) Morris AB, Li J, Kroenke K, Bruner-England TE, Young JM, Murray MD. Factors associated with drug adherence and blood pressure control in patients with hypertension. *Pharmacotherapy* 2006; 26(4):483-492.
- (146) Knight EL, Bohn RL, Wang PS, Glynn RJ, Mogun H, Avorn J. Predictors of uncontrolled hypertension in ambulatory patients. *Hypertension* 2001; 38(4):809-814.

- (147) Walsh JM, McDonald KM, Shojania KG, Sundaram V, Nayak S, Lewis R et al. Quality improvement strategies for hypertension management: a systematic review. *Med Care* 2006; 44(7):646-657.
- (148) Bartolucci AA, Howard G. Meta-analysis of data from the six primary prevention trials of cardiovascular events using aspirin. *Am J Cardiol* 2006; 98(6):746-750.
- (149) Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA* 2006; 295(3):306-313.
- (150) Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med* 1989; 321(3):129-135. PM:2664509
- (151) Magen E, Viskoper JR, Mishal J, Priluk R, London D, Yosefy C. Effects of low-dose aspirin on blood pressure and endothelial function of treated hypertensive hypercholesterolaemic subjects. *J Hum Hypertens* 2005; 19(9):667-673.
- (152) Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002; 136(2):161-172. PM:11790072
- (153) Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005; 352(13):1293-1304. PM:15753114
- (154) Lip GY, Felmeden DC. Antiplatelet agents and anticoagulants for hypertension. *Cochrane Database Syst Rev* 2004;(3):CD003186. PM:15266473
- (155) Bredie SJ, Wollersheim H, Verheugt FW, Thien T. Low-dose aspirin for primary prevention of cardiovascular disease. *Semin Vasc Med* 2003; 3(2):177-184. PM:15199480
- (156) Meade TW, Brennan PJ. Determination of who may derive most benefit from aspirin in primary prevention: subgroup results from a randomised controlled trial. *BMJ* 2000; 321(7252):13-17. PM:10875825
- (157) Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000; 321(7270):1183-1187. PM:11073508
- (158) Strazzullo P, Kerry SM, Barbato A, Versiero M, D'Elia L, Cappuccio FP. Do statins reduce blood pressure?: a meta-analysis of randomized, controlled trials. *Hypertension* 2007; 49(4):792-798.

- (159) Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Caulfield M et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003; 361(9364):1149-1158. PM:12686036
- (160) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360(9326):7-22. PM:12114036