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

Department of Veterans Administration Department of Defense

Update Version 2.0b- 2004

Prepared by:

THE MANAGEMENT OF HYPERTENSION IN THE PRIMARY CARE SETTING

Working Group

With support from:

The Office of Quality and Performance, VA, Washington, DC

&

Quality Management Directorate, United States Army MEDCOM

Version 1.0 – 1999

Update Version 2.0b -2004 Last revised 7/05

Based on evidence reviewed until December 2003

VA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF HYPERTENSION

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INTRODUCTION

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

The guideline was developed under the auspices of the Veterans Health Administration (VHA) and the Department of Defense (DoD) pursuant to directives from the Department of Veterans Affairs. VHA and DoD define clinical practice guidelines as:

"Recommendations for the performance or exclusion of specific procedures or services derived through a rigorous methodological approach that includes the following:

- 1. Determination of appropriate criteria, such as effectiveness, efficacy, population benefit, or patient satisfaction; and
- 2. Literature review to determine the strength of the evidence in relation to these criteria."

Blood pressure control at VA clinics is improving, but slowly. A study of data on hypertension patients in the VA healthcare system indicates that blood pressure control has improved significantly and substantially over time, but that many patients have less than optimal blood pressure control (Borzecki et al., 2003). The authors point out that the gap between hypertension guideline recommendations and achieved blood pressure control is still wide. They attribute this to both patient- and provider-related reasons, although they note that failure of providers to initiate or intensify therapy when needed is a prominent problem and that improvement in providers' adherence to hypertension guidelines is still needed.

Even so, the trend in VA showing improvement in blood pressure control has continued since the first version of the HTN CPG in 1999. Data from the VA External Peer Review Program (EPRP) is illustrated in the following figure 1 and, as can be seen, further improvement is indeed necessary.

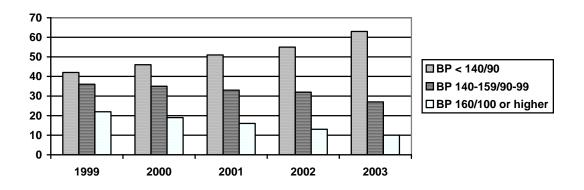


Figure 1: Blood Pressure Control In Veterans with Hypertension: 1999 to 2003

Since the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the largest hypertension trial, were announced at the end of 2002, there has been a deluge of revised national guidelines. These include those by the World Health Organization (WHO), American Society of Hypertension (ASH), Canadian Hypertension Education Program (CHEP) European society for hypertension and the National Heart Lung and Blood Institutes' Joint National Committee's Seventh Report (JNC 7).

The complete version of JNC 7 re-emphasizes the key messages that:

- Among individuals aged > 50 years, SBP > 140 mm Hg is a more important cardiovascular disease risk factor than DBP.
- Beginning at 115/75 mm Hg, the risk of cardiovascular disease doubles for each increment of 20/10 mm Hg.
- People who are normotensive at 55 years of age will have a 90% lifetime risk of developing hypertension.
- Prehypertensive individuals (SBP 120-139 mm Hg or DBP 80-89 mm Hg) require healthpromoting lifestyle modifications (LSM) to prevent the progressive rise in blood pressure and cardiovascular disease.
- For uncomplicated hypertension, a thiazide-type diuretic should be used in most cases, either alone or combined with drugs from other classes.
- Specific high-risk conditions are compelling indications for the use of other antihypertensive drug classes (ACE inhibitors, angiotensin-receptor blockers, beta-blockers, calcium channel blockers).
- Two or more antihypertensive medications will be required to achieve goal blood pressure (< 140/90 mm Hg) or < 140/80 mm Hg for patients with diabetes.
- For patients whose blood pressure is > 20 mm Hg above the SBP goal or > 10 mm Hg above the DBP goal, initiation of therapy using 2 agents, 1 of which usually will be a thiazide diuretic, should be considered, regardless of therapy or care.
- Hypertension will be controlled only if patients are motivated to stay on their treatment plan.
- Positive experiences, trust in the clinician, and empathy improve patient motivation and satisfaction.

This VA/DoD guideline for Hypertension update is generally in concordance with most other revised national and international guidelines though some differences remain, where noted. It emphasizes the need to screen our patient population for elevated blood pressure – a precursor to hypertension and a major risk factor for cardiovascular morbidity and mortality. The guideline is intended for primary care providers, practitioners, nurses, and other members of the primary health care team.

This version has updated the blood pressure classification since the previous guidelines published in 1999. The working-group accepted the category of "prehypertension," as introduced in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). The premise behind the new classification is that people with high-normal blood pressure levels are likely to develop hypertension with aging and that lifestyle modification is appropriate for such individuals to slow the progression. Advice on lifestyle modifications is recommended for everyone with high, borderline, or high-normal blood pressure.

This guideline also provides specific recommendations about which drugs should be used in which patients:

The revised guideline recommends initiation of drug treatment in all patients with sustained systolic blood pressure (SBP) \geq 140 mm Hg or sustained diastolic blood pressure (DBP) \geq 90 mm Hg, or sustained DBP 80-89 mm Hg in patients with diabetes. Optimal goals of treatment are < 140/<90 mm Hg. In people with diabetes the goals of treatment are < 140/< 80 mm Hg.

Several studies in recent years have shown that population blood pressure is not controlled sufficiently, as recommended by the evidence guidelines. One explanation suggests that physicians may not be aggressive enough with the management of hypertension. The poor rates of blood pressure control can be attributed to the predominant use of monotherapy. To address this issue, the current guideline recommends initiation of combination therapy (two agents) for patients at higher risk, most notably those with higher blood pressure $(\geq 160/100)$.

This guideline, along with other VA/DoD guidelines, support the view that physicians should not focus solely on blood pressure measurements, but should assess total risk of CVD and should implement multi factorial interventions, including lifestyle modification, aspirin, lipid lowering therapies and screening and management of diabetes when appropriate.

Although this guideline represents the best evidence-based practice on the date of its publication, it is certain that medical practice is evolving and that this evolution will require continuous updating of published information. In addition, the reader is reminded that this document is intended as a guideline and should not supersede the clinical judgment of the health care provider.

Guideline Development

The development process of this update follows a systematic approach described in "Guideline-for-Guideline," an internal working document of VHA's National Clinical Practice Guideline Counsel. Appendix E clearly describes the guideline development process.

KEY ELEMENTS

- 1. Screen blood pressure in adults annually since BP rises with increasing age.
- 2. Encourage patients with prehypertension to engage in lifestyle changes to reduce risk of proceeding to hypertension.
- 3. Explain to patients that blood pressure control reduces CV risks over a lifetime.
- 4. Once hypertension is diagnosed, take aggressive action to reduce blood pressure.
- 5. Include lifestyle modifications for all patients, as appropriate.
- 6. Use thiazide-type diuretics, alone or in combination with other agents, as first line therapy.
- 7. Choose other agents based on evidence for reduction of mortality and morbidity. These agents include (in alphabetical order): ACEIs, ARBs, beta-blockers, and long-acting calcium channel blockers.
- 8. Strongly consider starting therapy with a combination of two drugs for patients with Stage 2 hypertension.
- 9. Target blood pressure goals appropriately for each patient and titrate therapy to achieve that goal through:
 - a. Informing patients about their blood pressure (BP)
 - b. Follow-up closely until goal achieved
 - c. Adjustinging medication as necessary at each visit
 - d. Keeping the medication regimen as simple as possible
 - e. Educating and involve patients in their care plan
 - f. Using ancillary staff and available programs to support and help in reaching target goal.

Performance Measurement

The inability of consumers and health care purchasers to determine if medical care is appropriate and effective has given rise to the concept that the health care system should be held accountable for what is done and the outcomes achieved. This principle of accountability has resulted in the development of so-called "performance and outcome measures" which are administered through "report card" systems. Measures must be seen as fair and reasonable and must be achievable in various practice settings, when carried out either by providers or tobacco dependence treatment specialists.

Performance measures are indicators or tools to assess the level of care provided within systems of care to populations of patients who use tobacco products. The measures are constructed to best utilize the available evidence for assessing care or outcomes of care in systems where test reliability, patient characteristics, (co-morbidity), and compliance cannot be easily determined and taken fully into consideration (i.e., the measures are not case-mix adjusted). The current state of the art measurement system does not allow full adjustment for factors outside the control of the health care system.

The Working Group suggests that the following indicators be considered in establishing the performance measurement system:

• The percent of patients with a blood pressure of less than 140/90 mm Hg

GUIDELINE UPDATE WORKING GROUP

Peter Glassman, MBBS, MSc. (co-chairman)

VA

Paul R Conlin, MD

William Cushman, MD

Elaine Furmaga, PharmD

Leonard Pogach, MD

Thakor G. Patel, MD

DoD

Douglas, Kevin, MAJ, MD (co-chairman)

Robert Manaker, LtCol, MC, USAF

Angela Allerman, PharmD, BCPS

Vincent P. Fonseca, LtColMD, MPH

Doreen Lounsbery, COL, MD, MHA

Paul G. Welch, LTC, MC, USA

Bell Michael R MAJ USACHPPM

Angela Klar, RN, MSN, ANP, CS

FACILITATOR Oded Susskind, M.P.H.

COORDINATOR Joanne Marko, M.S., CCC-SLP

RESEARCH TEAM-EVIDENCE APPRAISAL REPORTS

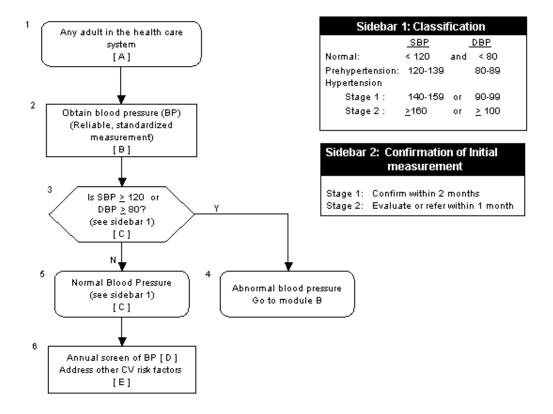
Center for Evidence-Based Practice State University of New York, Upstate Medical University, Department of Family Medicine

Lorne Becker, M.D. – Director R. Eugene Bailey, M.D. John Epling, M.D. William Grant, Ed.D. Jennifer Schultz, M.S.Ed. Sandra M. Sulik, M.D., M.S. **ACS Federal Healthcare, Inc.**

Diane Boyd, Ph.D. Sarah Ingersoll, R.N., M.B.A. Russell Smith, M.L.S. Lara Bainbridge Oneil Brown Sara Thomas

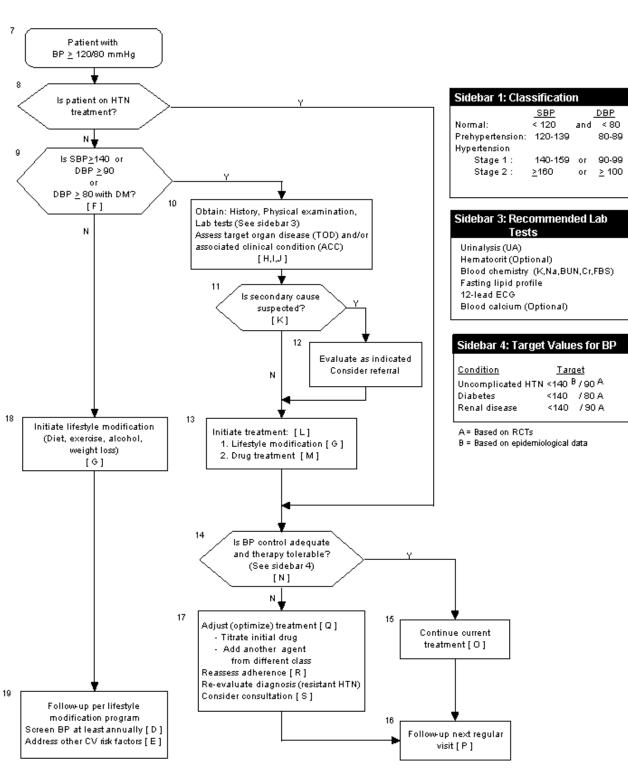
ALGORITHMS

MANAGEMENT OF HYPERTENSION Module A: Screening for Elevated Blood Pressure



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MANAGEMENT OF HYPERTENSION Module B: Management of Elevated Blood Pressure

ANNOTATIONS

A. Any Adult in the Health Care System

DEFINITION

In this document, an adult is defined as anyone 17 years of age or older.

This guideline is directed at screening for high blood pressure in adults, and management of chronic hypertension. It is not directed to the treatment of pregnant women who should be managed in consultation with appropriate specialists. This guideline is also not intended for patients presenting with acute illnesses and/or other urgent conditions involving high blood pressure as these patients should be managed according to their relevant diagnoses.

RECOMMENDATIONS

1. Screen adults for elevated blood pressure (BP)

DISCUSSION

Screening for hypertension to prevent CV disease:

A recent review of the evidence for the U.S. Preventive Services Task Force describes the rationale for blood pressure screening: (Sheridan et al., 2003)

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

For patients who are screened, estimates of the potential benefit of treatment can be improved both by carefully measuring the degree of blood pressure elevation and by assessing the contribution of other risk factors to global cardiovascular risk. " (Ferrucci et al., 2001; Ogden et al., 2000; Staessen et al., 2000)

The USPSTF found good evidence that blood pressure measurement can identify adults at increased risk for cardiovascular disease due to high blood pressure, and good evidence that treatment of high blood pressure substantially decreases the incidence of cardiovascular disease and causes few major harms. The USPSTF concludes the benefits of screening for, and treating, high blood pressure in adults substantially outweigh the harms. U.S. Preventive Services Task Force (2003)

B. Obtain Blood Pressure

BACKGROUND

Any primary care manager/provider (PCM/PCP) can obtain the BP of a patient in any health care setting, (e.g., clinic, doctor's office, emergency room, or hospital). Blood pressure readings may vary depending upon the instrument and technique used, the setting, and patient and provider characteristics.

RECOMMENDATION

- 1. Blood pressure should be measured with a technique using a properly calibrated and validated instrument:
 - Patient should be seated quietly for 5 minutes with back supported, feet on the floor, and arm bared, unrestricted by clothing, and supported at heart level. Measurement of BP in the standing position may be indicated for patients at risk for postural hypotension or at the discretion of the clinician.
 - Smoking, exercise, or caffeine ingestion should not have occurred within 30 minutes prior to the BP measurement.
 - The appropriate blood pressure cuff size should be chosen for the patient. The cuff should be wrapped snugly around the arm with the bladder centered over the brachial artery. The bladder should encircle at least 80% of the arm.

For Auscultatory Measurements Only:

- Palpated radial pulse obliteration pressure should be used to estimate the systolic BP (SBP). The cuff should then be inflated 20-30 mm Hg above this level for the auscultatory determinations.
- Position the stethoscope over the brachial artery and rapidly inflate the cuff. Deflate the cuff at a rate of 2 to 3 mm Hg per second, listening for Phase 1 and Phase 5 Korotkoff sounds. The first appearance of sound (Phase 1) is used to record the SBP. Phase 5, at the disappearance of sound, is the diastolic BP (DBP) in adults. Listen 10 to 20 mm Hg below Phase 5 for any further sound then deflate the cuff completely.
- The BP should be recorded in even numbers with the patient's position, arm used, and cuff size documented.
- BP readings should be repeated in the same arm and averaged, if different. Two minutes should elapse before repeating the BP measurement. If the readings differ by more than 5 mm Hg, additional measurements should be obtained.
- 2. Measurements can be taken with a mercury sphygmomanometer, but a recently calibrated aneroid manometer or a validated electronic device is an acceptable alternative.

DISCUSSION

The recommendations for blood pressure measurements follow the methods used in the many randomized trials that have established the benefits of antihypertensive therapy (e.g., SHEP, ALLHAT). Using these methods allows the provider to accurately risk stratify patients, since epidemiological studies (e.g., Framingham) used the same measurement techniques.

Ambulatory Measurement

Office measurement of blood pressure is most commonly done with a sphygmomanometer. Due to variability in individual blood pressure measurements (occurring as a result of instrument, observer, and patient factors), it is recommended that hypertension be diagnosed only after 2 or more elevated readings are obtained on at least 2 visits over a period of 1 to several weeks, unless there is evidence of hypertension target organ damage (see annotations H and I).

Office blood pressure measurement (using an appropriate upper arm cuff with either mercury, calibrated aneroid, or validated electronic sphygmomanometer) is the standard screening test for hypertension. When performed correctly, sphygmomanometers provide a measure of blood pressure that is highly correlated with intra-arterial measurement and highly predictive of cardiovascular risk (Reeves, 1995). However, office blood pressure measurements can in some cases exhibit great variability and may not represent the patient's usual blood pressure outside the clinical setting.

However, ambulatory blood pressure measurement is subject to many of the same errors as office blood pressure measurement.

Ambulatory blood pressure monitoring that provides average blood pressure over 24 hours, as opposed to the isolated values obtained in office checks, may better predict cardiovascular outcomes than clinic-based measurements. Two recent reviews of good quality found that ambulatory blood pressure measurements correlate better with left ventricular mass and cardiovascular disease than do office blood pressure measurements (McAlister, 2001; Myers et al., 1999). Ambulatory blood pressure measurement was found to be a better predictor of clinical cardiovascular outcome than clinic-based approaches (Verdecchia et al., 1994; Khattar et al., 1999; Staessen et al., 1999). Another review found blood pressure measurements obtained through ambulatory devices more closely predictive of risk for target end organ damage than self-or office blood pressure measurements (Appel, 1997). However, ambulatory measurements are also subject to similar errors to office based measurements and, as well, are difficult to complete for many patients since the device must be worn continuously. Hence, at this time such devices cannot be routinely recommended although they may assist in the diagnosis for selected patients.

Another option that may selectively assist in diagnosing, and in some cases managing, hypertension is home blood pressure monitoring. Recent studies indicate that self-monitoring may help in differentiating white-coat hypertension (i.e., temporarily elevated blood pressure above desired levels) from chronically high blood pressure readings and/or may provide additional readings in patients who are already being treated for hypertension but who also have a white-coat component (i.e., control is better at home than in the office setting) (Staessen, 2004; Bobrie, 2004; Little 2002). However, while there is some suggestive evidence that home blood pressure monitoring has good prognostic efficacy for predicting cardiovascular events (Bobrie, Ohktubo 1998), Staessen et al. recently noted that patients who were on antihypertensive treatment and utilized home monitoring instead of office monitoring of blood pressure had less control, although self-measurement identified patients with white-coat hypertension (Staessen 2004). Interestingly, home blood pressure monitoring may assist in finding patients who have good blood pressure in the office but not at home (so-called "masked" hypertension) (Bobrie 2004).

Home (or out-of-office) blood pressure readings should be used judiciously due to the potential inaccuracy of self-report and because studies demonstrating the benefit of antihypertensive therapy used office readings. The evidence is insufficient to assume that home blood pressure readings, in patients already being treated for hypertension, may be substituted for office-based readings. On the other hand, providers may wish to utilize information from home-based readings for selected patients to help determine a diagnosis of hypertension when white-coat hypertension is suspected, assuming there is no evidence of target organ damage, or when masked hypertension is suspected (i.e., control is worse outside the office). From a practical standpoint, it may be helpful for patients to bring in their self-monitoring device to clinic in order to calibrate it against an office manometer.

EVIDENCE

	Recommendation	Sources	QE	Overall Ouality	R
1	Use the standardized technique to measure blood pressure	SHEP ALLHAT	Ι	GOOD	Α

QE = Quality of Evidence; R = Recommendation (see Appendix E)

C. Is SBP \geq 120 or DBP \geq 80 mm Hg?

OBJECTIVE

Identify patients with abnormal elevated blood pressure.

BACKGROUND

Evidence from epidemiological studies suggests a linear relationship between blood pressure and vascular event rates, with risk rising from approximately 120/80 mm Hg (Collins, 1994; MacMahon, 1990; Prospective Studies Collaboration, 2002). Furthermore, Vasan et al. demonstrated in the Framingham cohort that there was an increasing risk of cardiovascular events as blood pressure rose through what was then considered the normal (120-129 mm Hg systolic or 80-84 mm Hg diastolic) and high normal range of blood pressures (130-139 mm Hg systolic; 85-89 mm Hg diastolic) (Vasan et al., 2001). In addition, blood pressure increases with age such that 90% of persons with normal blood pressure at age 55 are diagnosed with hypertension later in their lifetime (Vasan, et al., 2002). Indeed, overall prevalence of hypertension now approaches 50 million persons in the United States (Hajjar, 2003). For these reasons, it is prudent to begin education and other health-related interventions in a so-called prehypertension stage, defined as a blood pressure greater than 120 mm Hg systolic or 80 mm Hg diastolic but under the definitional threshold for hypertension. In other words, consider a blood pressure of 120/80 mm Hg or higher as greater than optimal for vascular events.

RECOMMENDATION

1. Screen adults for elevated blood pressure, defined as a systolic blood pressure 120 mm Hg and above or a diastolic blood pressure 80 mm Hg and above.

DISCUSSION

The USPSTF concluded the following from the evidence on screening adults for elevated blood pressure:

"The risk for adverse events associated with hypertension is continuous and graded (Kannel, 1996; Prospective Studies Collaboration, 2002). SBP predicts cardiovascular risk better than DBP (Benetos, 2002). Even modest elevations of blood pressure in young adulthood are associated with increased risk for cardiovascular events in middle age (Miura, 2001). The absolute risk for cardiovascular events, however, varies depending on the presence of other cardiovascular risk factors, including smoking, diabetes, and abnormal blood lipid levels, as well as the duration of blood pressure elevation (Ferruci, 2001; USPSTF, 2003).

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Blood pressure measurement can identify adults at increased risk for cardiovascular disease due to high blood pressure	USPSTF, 2003	Ι	Good	Α
2	The treatment of high blood pressure substantially decreases the incidence of cardiovascular disease and causes few major harms	USPSTF, 2003	Ι	Good	Α
3	SBP > 120 mm Hg or DPB > 80 mm Hg is higher than optimal in terms of vascular risks	Collins et al., 1999 Prospective Studies Collaboration, 2002 Vasan et al., 2001	Ι	Fair to Good	В

QE = Quality of Evidence; R = Recommendation (see Appendix E)

D. Annually Screen For Blood Pressure

OBJECTIVE

Screen for future elevation of blood pressure

BACKGROUND

Incidence and prevalence of hypertension increases with age, and hence periodic screening for elevated blood pressures is recommended. The US Preventive Services Task Force (USPSTF, 2003) found "good evidence that blood pressure measurement can identify adults at increased risk for cardiovascular disease due to high blood pressure, and good evidence that treatment of high blood pressure substantially decreases the incidence of cardiovascular disease and causes few major harms."

Evidence is lacking to recommend an optimal interval for screening adults for high blood pressure. A reasonable timeframe can be inferred based on age, baseline blood pressure, and cardiovascular risks but as a general recommendation, it seems prudent and most straightforward to assess at yearly intervals since most people, especially those over the age of fifty, require an annual assessment or follow-up for other medical issues.

RECOMMENDATION

- 1. Blood pressure screening should occur periodically.
- 2. Blood pressure screening is recommended annually for adults 50 years of age and older and/or for those who have prehypertension and/or other cardiovascular risk factors.
- 3. Blood pressure screening is recommended at indeterminate intervals, preferably annually. This may occur at the time of routine preventive care or routine health assessments.

DISCUSSION

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

Table 1. Incluence Kates of Hypertension at 1,2 and 5 Tears					
Baseline BP Category	Age 35-64 Years	Age 65-94 Years			
% hypertension at 1 year (95 CI)*					
Optimum BP	1.3 (1.1-1.6)	4.3 (3.1-5.7)			
Normal BP	4.7 (4.0-5.5)	7.1 (5.5-9.0)			
High Normal BP	11.0 (9.6-12.6)	15.7 (13.0-18.8)			
% hypertension at 2 year (95 CI)*					
Optimum BP	2.7 (2.2-3.2)	8.3 (6.2-11.1)			
Normal BP	9.2 (7.9-10.7)	13.7 (10.8-17.2)			
High Normal BP	20.8 (18.3-23.5)	28.9 (24.2-34.0)			
% hypertension at 3 year (95 CI)*					
Optimum BP	4.0 (3.3-4.8)	12.2 (9.2-16.1)			
Normal BP	13.5 (11.6-15.7)	19.8 (15.7-24.6)			
High Normal BP	29.6 (26.2-33.1)	40.1 (34.0-46.4)			
* D 100 1 1	1.0 1.1				

Table 1. Incidence Rates of Hypertension at 1,2 and	3 Years
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* Rates are per 100, and are adjusted for sex, age, body-mass index, baseline examinations, and baseline systolic and diastolic BP.

Nonetheless, the optimal screening intervals have not been determined in clinical studies. However, most patients over 50 years old routinely seek care at least annually for either medical conditions or for other preventive care (e.g., colorectal cancer screening and vaccinations), and it is clinically appropriate to also screen for hypertension at that time. In addition, consideration should be given to annual screening for those patients of any age who have cardiovascular risks such as those who smoke or are overweight or have lipid disorders since these patients are already at risk for future vascular events. Younger patients without risk factors have a lower incidence of hypertension in the short term, but, if possible, annual screening –which is relatively easy to perform when patients attend clinics for preventive care (e.g., vaccinations) or routine health assessments – should be considered.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Blood pressure screening should occur periodically	Sheridan et al., 2003	II-1	Fair	В
2	Blood pressure screening annually for adults older than 50 and/or for adults with prehypertension and/or other cardiovascular risk factors	Vasan et al., 2001 Franklin et al., 1997	II-2 II-3	Fair	В
3	Annual screening for healthy adults	Experts Consensus	III	Poor	Ι

QE = Quality of Evidence; R = Recommendation (see Appendix E)

E. Address other cardiovascular risk factors

OBJECTIVE

Evaluate and address all modifiable cardiovascular risk factors.

BACKGROUND

The relationship between SBP and DBP and cardiovascular risk is continuous and graded but clearly blood pressure is not the sole factor in determining cardiovascular and cerebrovascular disease risks. To that end, all modifiable cardiovascular risk factors should be evaluated and addressed and a healthy lifestyle should be emphasized. Clinicians should consider the patient's overall cardiovascular risk profile, including smoking, diabetes, abnormal blood lipids, age, sex, sedentary lifestyle, and obesity.

RECOMMENDATION

- 1. Screening lipid profile should be done per the VA/DoD Guideline [VA/DoD Guideline for Management of Dyslipidemia]
- 2. Screening for diabetes mellitus should be done per the VA/DoD Guideline [VA/DoD Guideline for Management of Diabetes Mellitus]
- 3. Reduction/cessation of the use of tobacco and cigarette should be addressed per the VA/DoD Guideline [VA/DoD Guideline for Management of Tobacco Use]
- 4. A heart-healthy lifestyle including optimum weight maintenance (and/or weight loss, when needed), diet rich in fruits, vegetables and low fat dairy products and an exercise program emphasizing daily or near daily aerobic activity, should be recommended.
- 5. Aspirin should be recommended to patients who have hypertension and diabetes mellitus (see the VA/DoD Guideline for Diabetes) or IHD (see the VA/DoD Guideline for IHD) and should be recommended to patients who already have vascular disease (e.g., cerebrovascular disease or cardiovascular disease).

DISCUSSION

There is some evidence that patients with treated hypertension but without evidence of vascular disease may benefit from aspirin therapy (Hayden, 2002; Hansson 1998) but, a discussion of the risks and benefits is nevertheless important when aspirin therapy is considered in this group. Aspirin (or another oral antiplatelet drug) is protective in most types of patients at increased risk of occlusive vascular events, including those with an acute myocardial infarction, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischemia, peripheral arterial disease, or atrial fibrillation (Antithrombotic trialists, 2002). It is unclear whether or to what extent a benefit may accrue for patients with poorly controlled hypertension but the risk of hemorrhagic stroke generally precludes use in that group (Hayden, 2002). As a general rule of thumb, the higher the vascular event risk, the more likely aspirin will have benefit.

F. SBP \ge 140 or DBP \ge 90 or DBP \ge 80 with DM?

BACKGROUND

The relationship between BP and risk of CVD events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater is the chance of heart attack, heart failure, stroke, and kidney disease. For individuals 40 to 70 years of age, each increment of 20 mm Hg in systolic BP or 10 mm Hg in diastolic BP doubles the risk of CVD across the entire BP range from 115/75 to 185/115 mm Hg

(Lewington, 2002). Based primarily on epidemiological studies, showing linear increases in risk as blood pressure rises, as well as selected intervention studies, discussed above, the threshold for diagnosing hypertension is considered to be a SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher. However, in selected populations (e.g., Diabetes Mellitus) DBP above 80 mm Hg may require intervention. Nonetheless, since the diagnosis requires lifetime treatment and/or monitoring, it should be carefully considered over time (typically over 2 visits), unless there are other factors that suggest the need to treat earlier (e.g., target organ damage).

RECOMMENDATION

- 1. The diagnosis of hypertension should be determined by BP readings on two separate patient visits. A minimum of two BP measurements should be performed during a patient visit:
 - Patients with SBP \geq 140 or DBP \geq 90 (Stage 1 hypertension) or with DBP \geq 80 mm Hg and concomitant diabetes mellitus or chronic kidney disease should have their blood pressure confirmed generally within 1 to 2 months.
 - Patients with SBP \geq 160 or DBP \geq 100 (Stage 2 hypertension) should be appropriately evaluated by a healthcare provider, typically within 1 month -- or sooner if the clinical situation warrants.

DISCUSSION

Classification

As stated earlier, defining abnormally high blood pressure is somewhat arbitrary because the relationship between systemic arterial pressure and morbidity appears to be linear from around 120/80 mm Hg, and because there is insufficient evidence to determine which threshold goal(s) are optimal for reducing risk. Nonetheless, a classification system is essential for making decisions about aggressiveness of treatment or therapeutic interventions. Thus, based on recommendations of JNC 7, the classification of blood pressure (expressed in mm Hg) for adults aged 17 years or older is as follows:

	SBP * mm Hg	DBP * mm Hg	Follow-up
Normal	< 120	< 80	Recheck in 1 year
Prehypertension	120-139	80-89	Recheck in 1 year **
Stage 1 Hypertension	140-159	90-99	Confirm within 1-2 months
Stage 2 Hypertension	<u>≥</u> 160	<u>≥</u> 100	Evaluate or refer to source of care immediately or within 1 month, or sooner, depending on clinical situation

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

* If systolic and diastolic categories are different, follow recommendations for the higher measurement. (e.g. 160/86 mm Hg is considered Stage 2 hypertension and thus should be evaluated or referred to source of care within 1 month).

** Modify the scheduling of follow-up according to reliable information about past blood pressure measurements, other comorbidities, or target organ disease.

• Due to the limitations in the reliability of blood pressure measurements, experts commonly recommend that clinicians diagnose hypertension only after obtaining 2 or more elevated readings at 2 or more office visits at intervals of 1 to several weeks (McAlister, 2001; JNC 7, 2002).

- Normal blood pressure with respect to cardiovascular risk is less than 120/80 mm Hg. However, unusually low readings should be evaluated for clinical significance.
- Prehypertension, a new category designated in the JNC 7 report, emphasizes that patients with prehypertension are at higher risk for progression to hypertension (see Table 1 annotation D) and for CVD than people with normal BP, and that lifestyle modifications are important preventive strategies. Prehypertension is not a disease category. Rather it is a designation chosen to identify individuals at high risk of developing hypertension, so that both patients and clinicians are alerted to this risk and encouraged to intervene and prevent or delay the disease from developing.
- Hypertension may be either essential (primary) or secondary. Essential hypertension is diagnosed in the absence of an identifiable secondary cause. Approximately 95% of American adults have essential hypertension, while secondary hypertension accounts for fewer than 5% of the cases.

Prehypertension

Observational data show the risk of cardiovascular events and mortality doubling with 20 mm Hg increases in SBP and 10 mm Hg increases in DBP beginning with a BP of 115/75 mm Hg. The relative risk increases are similar but absolute risk is higher for persons with diabetes mellitus or chronic kidney disease.

The incidence of hypertension among people with SBP 130-139 mm Hg or DBP 85-89 mm Hg is approximately 8-13%. For all people \geq 55 years of age without hypertension, the incidence of hypertension is approximately 5% per year.

Those with SBP 130–139 mm Hg or DBP 85–89 mm Hg are at twice the risk to develop hypertension and twice the risk for CVD events as those with lower values. Even people with SBP 120-129 or 80-84 mm Hg are at 30-50% higher risk for CVD risk than those with BP < 120/80 mm Hg.

Recognizing these relationships, the JNC 7 report added a new category designated as "prehypertension" (SBP 120-139 mm Hg or DBP 80-89 mm Hg), in order to signal the need for increased education of health care professionals and the public to promote or initiate lifestyle modifications to prevent the development of hypertension and reduce CVD risk in those with prehypertension, which is 22% of the adult population.

Mortality/Morbidity:

In the Framingham Heart Study, the age-adjusted risk of congestive heart failure was 2.3 times higher in men and 3 times higher in women when highest blood pressure was compared to the lowest. Multiple Risk Factor Intervention Trial (MRFIT) data showed that the relative risk for coronary heart disease mortality varied from 2.3- 6.9 times higher for persons with mild-to-severe hypertension compared with normal blood pressure.

The relative risk for stroke ranged from 3.6-19.2. The population attributable risk percentage for coronary artery disease varied from 25.6-2.3%, whereas the population attributable risk for stroke ranged from 40.0-6.8%.

Race: Blacks have a higher prevalence and incidence of hypertension than whites. The prevalence of hypertension was increased by 50% in African Americans. In Mexican Americans, the prevalence and incidence of hypertension is similar to or lower than in whites. The National Health and Nutrition Examination Survey (NHANES) III reported an age-adjusted prevalence of hypertension in adults at 20.6% in Mexican Americans and 23.3% in non-Hispanic whites.

Sex: The age-adjusted prevalence of hypertension in adults was 34%, 25.4%, and 23.2% for men and 31.0%, 21.0%, and 21.6% for women among African Americans, whites, and Mexican Americans,

respectively. In the NHANES III study, the prevalence of hypertension was 12% for white men and 5% for white women aged 18-49 years. However, the age related blood pressure rise for women exceeds that of men. The prevalence of hypertension was reported at 50% for white men and 55% for white women aged 70 years or older.

Age: A progressive rise in blood pressure with increasing age is observed. The third NHANES survey reported that the prevalence of hypertension grows significantly with increasing age in all sex and race groups. The age-specific prevalence was 3.3% in white men (aged 18-29 years); this increased to 13.2% in the group aged 30-39 years. The prevalence further increased to 22% in the group aged 40-49 years, to 37.5% in the group aged 50-59 years, and to 51% in the group aged 60-74 years. In another study, the incidence of hypertension appeared to increase approximately 5% for each 10-year interval of age. Age-related hypertension appears to be predominantly systolic rather than diastolic. The systolic blood pressure rises into the eighth or ninth decade, while the diastolic blood pressure remains constant or declines after age 40 years (Cornoni-Huntley, 1989).

G. Initiate Lifestyle Modification

OBJECTIVE

Provide dietary and lifestyle changes to help treat HTN and assist in reducing risk factors for cardiovascular disease.

BACKGROUND

Clinicians should begin by prescribing lifestyle modifications (LSM) in all patients with prehypertension or HTN. Certain lifestyle modifications have been shown to decrease blood pressure in randomized clinical trials; other lifestyle modifications are also important in decreasing cardiovascular risk. These non-pharmacologic measures can be sufficient to control BP or to decrease the amount of required medication (World Hypertension League, 1991; The multiple Risk Factor Intervention Group, 1990). Hence, the importance of lifestyle modifications cannot be emphasized enough and these continue to be a cornerstone in the management of hypertension.

Effective implementation of lifestyle measures depends on many factors but, at least from the clinicians standpoint, should involve education of patients and perhaps relevant family members, periodic discussion with and/or motivations to patients including consistent advice on the benefit of a healthy diet and general fitness and how to attain those goals.

RECOMMENDATIONS

- 1. Lifestyle modifications aimed at controlling hypertension should be recommended in all cases. These methods can be used by themselves or in combination with drugs. (B)
- 2. Individual LSM are effective however, addressing multiple modifications may have a greater effect on reducing blood pressure. (B)
- 3. Successful implementation will require multiple visits, and close follow-up. (B)
- 4. Education may take place in either individual or group settings involving allied health professionals. (B)
- 5. Clinician empathy increases patient trust, motivation, and adherence to therapy.
- 6. Physicians should consider their patients' cultural beliefs and individual attitudes in formulating therapy.

DISCUSSION

Patients with HTN should receive counseling on the following lifestyle modifications:

Intervention	Lifestyle Modification or Change	Systolic BP
		Reduction (range)
Daily sodium intake	Maximum of 100 meq/L day (2.4 g sodium or 6 gms sodium chloride)	2-8 mm Hg
Weight loss	Reduce to and/or maintain normal body weight (e.g.,	5-20 mm Hg per
	Body Mass Index, 18.5-24.9)	10-kg wt loss
Alcohol consumption	Limit to no more than 2 drinks per day for men, and no more than 1 drink per day in women and light weight persons	2-4 mm Hg
Exercise	Aerobic exercise for at least 30 minutes, most days of week	4-9 mm Hg
DASH Diet	Dietary Approaches to Stop Hypertension (DASH) diet rich in fruits, vegetables, and low-fat diary products, with overall reduced saturated and total fat content	8-14 mm Hg

Table 3. Impact of Lifestyle Therapies on BP in Hypertensive Adults*

*Modified from JNC 7

WEIGHT REDUCTION - Overweight patients should reduce their weight to within 10 percent of their ideal body weight. However, reduction even of 5 to 10 pounds can be helpful in controlling HTN (Langford et al., 1991; Schotte and Stunkard, 1990; Hypertension Prevention Trial Research Group, 1990; World Hypertension League, 1991; Hypertension Prevention Trial Research Group, 1990; Klatsky et al., 1977). Weight-reducing diets in overweight hypertensive persons can affect modest weight loss in the range of 3-9% of body weight and are probably associated with modest blood pressure decreases of roughly 3 mm Hg systolic and diastolic. Weight-reducing diets may decrease dosage requirements of persons taking antihypertensive medications (Murlow et al., 2003 [Cochrane report]).

ALCOHOL INTAKE - Alcohol intake should be limited to no more than one ounce (24 ounces of beer; or 10 ounces of wine; or 3 ounces of 80-proof whiskey) per day for men or 0.5 ounces of alcohol per day for women and for lighter weight persons (Puddey et al., 1987; National High Blood Pressure Program Working Group, 1993; Law et al., 1991).

SODIUM INTAKE - Sodium intake in the patient with HTN should be limited to no more than 100 mmol/day (2.4 g of sodium or 6 g of sodium chloride). (Blair et al., 1989; Trials of Hypertension Prevention, Collaboration Research Group, 1992; Morris et al., 1980).

A recent Cochrane review (Hooper, 2003) questions the consistency of data, and the degree of blood pressure reduction, concerning the effect of reducing intake of salt on blood pressure. However, as the review notes, there may be varying effects by individual and by level of diet though it is not clear that the BP reductions are directly associated with the degree of salt restriction. Nonetheless, while the data are not perhaps definitive, there is sufficient data from various studies such as DASH (DASH-sodium 2001), as well as other studies (PREMIER, 2003) of varying methodological merit, to encourage patients to reduce salt intake as part of their overall effort to decrease blood pressure.

A recent Cochrane review has concluded that reduction of sodium intake reduces blood pressure in the short-term only (Cooper, 2003). Reduced sodium intake in Caucasians with elevated blood pressure has a useful effect to reduce blood pressure in the short-term. The results suggest that the effect of low versus high sodium intake on blood pressure was greater in Black and Asian patients than in Caucasians. However, the number of studies in black (8) and Asian patients (1) was insufficient for different recommendations. There is not enough evidence to conclude that reduction in sodium intake can decrease the blood pressure of a population and thereby reduce cardiovascular mortality and morbidity (Jurgen, 2003).

EXERCISE - The target for aerobic exercise should be 30 to 45 minutes per session, at least four or five times per week (or daily) if possible (Shepherd et al., 1995; Trials of Hypertension Prevention, 1992).

DIET - An adequate dietary intake of potassium, calcium, and magnesium can be obtained from fresh fruits and vegetables. Other dietary advice should include a heart-healthy diet such as the DASH Diet.

DASH diet

THE DASH "COMBINATION DIET" lowers blood pressure and is rich in fruits, vegetables, and low-fat dairy foods. It is low in saturated and total fat, low in cholesterol but high in dietary fiber, potassium, calcium, and magnesium; and moderately high in protein. The DASH eating plan shown above is based on 2,000 calories a day. Depending on energy needs, the number of daily servings in a food group may vary from those listed.

Detail on the DASH diet is available at: http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf

TOBACCO USE CESSATION - Counsel to stop tobacco use and offer smoking cessation classes or other aids to quit (see VA/DoD Clinical Practice Guideline for the Management of Tobacco Use).

Adherence to Lifestyle Modification

Although lifestyle modifications can have a profound positive impact on blood pressure, cardiovascular risk, overall health, and functioning, helping patients adopt a healthier lifestyle is often difficult. One method is to use the USPSTF "5 A's" approach to clinical counseling. This approach can be used with any of the lifestyle modifications (e.g., physical activity, eating habits, weight loss, tobacco use or drinking habits) (Whitlock et al., 2002).

- 1. Assess: the patient's current knowledge, attitudes, practices and readiness to change. Based on your evaluation of the patient's status, you may then assess readiness to change with "Do you intend to change your ______ in the next month?"
- 2. Advise: A strong, personalized message serves to increase motivation by enhancing the perceived importance (why change?) and confidence (how will I succeed?) related to the lifestyle change. A useful mnemonic to construct this message is the 5 R's: Relevance to the patient's personal situation; Risks-both short-term and long-term; Rewards-benefits of change; Roadblocks-discuss potential barriers and solutions; and Repetition of motivational intervention. Explore perceived importance and build confidence without judgment or confrontation. You can only start where the patient is and they set the pace. By exchanging information and gradually reducing resistance the patient may increase their readiness to change. Continue to use motivational interventions until the patient self-expresses importance of, and readiness to change.
- 3. **Agree**: When patients are ready to change, use a collaborative approach to designing realistic objectives and strategies. Usually it is better to successfully take small steps and to build upon those successes. "Progress not perfection."
- 4. **Assist**: In developing the specifics of the lifestyle modification plan. Anticipate challenges and realistic solutions. Classes may be helpful in acquiring the "skill power" and social support to accompany the willpower.
- 5. **Arrange**: Schedule follow-up to support the patient by congratulating them and building upon their successes, discussing difficulties, and adjusting the plan to provide ongoing support (both social and clinical).

	Recommendation	Sources	QE	Overall Quality	R
1	Initiate LSM for prehypertension	TOHP I, II TONE DASH (Obarzanek, 2003)	Ι	Good	А
2	Addressing multiple modification	PREMIER, 2003 DEW-IT (Miller, 2002) TOHP-2	Ι	Fair	В
3	Reduce Sodium intake	PREMIER 2003 Hooper, 2003 Jurgen, 2003	Ι	Fair	В
4	Limit alcohol consumption	XIN 2001	Ι	Fair	В
5	Reduce / maintain body weight (BMI < 25)	Neter, 2003 Murlow, 2003	Ι	Fair	В
6	Daily exercise	Whelton 2002 Kelley 2000 Shepherd et al., 1995; Trials of Hypertension Prevention, 1992	Ι	Fair	В
7	Dietary Approaches rich in fruits, vegetables, and low-fat diary products, with overall reduced saturated and total fat content	Stamler et al., 1997 Cappuccio et al., 1995 Appel et al., 1997	Ι	Fair	В
8	DASH Diet	DASH, 1997 DASH sodium 2001	Ι	Fair	В

EVIDENCE

QE = Quality of Evidence; R = Recommendation (see Appendix E)

H. Obtain History

OBJECTIVE

Elicit historical features that may influence clinical decision-making.

BACKGROUND

Evaluation of patients with hypertension has 3 objectives: (1) to assess lifestyle and identify other cardiovascular risk factors or concomitant disorders that may affect prognosis and guide treatment, (2) to reveal identifiable causes of high BP; and (3) to assess the presence or absence of target-organ damage and cardiovascular disease. The data needed are acquired through medical history, physical examination, routine laboratory tests, and other diagnostic procedures.

RECOMMENDATIONS

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

- 1. Duration, levels, and nature of BP elevation.
- 2. History or symptoms to rule out coronary heart disease (CHD), heart failure, cerebrovascular disease, peripheral vascular disease, renal disease, DM, dyslipidemia, and gout.
- 3. Survey for baseline symptoms of sexual dysfunction, depression, cough, and angioedema.
- 4. Family history of hypertension, premature CHD, cerebrovascular accident (CVA), DM, dyslipidemia, or renal disease.

- 5. Other symptoms suggesting other causes of elevated BP.
- 6. Results and adverse effects of any previous antihypertensive therapy.
- 7. History of recent change in weight, physical activity, tobacco use.
- 8. Dietary assessment, including intake of sodium, saturated fat, and caffeine.
- 9. History of all prescribed and over-the-counter medications, herbal remedies, and dietary supplements, some of which may raise blood pressure or interfere with the effectiveness of antihypertensive medications.
- 10. History of alcohol and illicit drug use (especially cocaine and other stimulants).
- 11. Psychosocial and environmental factors (e.g., family situation, employment status and working conditions, level of comprehension) that may influence HTN control.

The following major risk factors are the components of cardiovascular risk in patients with hypertension: (JNC 7)

- 1. Tobacco use
- 2. Dyslipidemia
- 3. Diabetes Mellitus
- 4. Obesity [body mass index (BMI) \geq 30]
- 5. Physical inactivity
- 6. Microalbuminuria or estimated glomerular filtration rate (GFR) < 60 mL/min
- 7. Age (> 55 years for men, > 65 years for women)
- 8. Family history of cardiovascular disease for women younger than 65 or men younger than 55

DISCUSSION

All hypertensive patients should have a thorough history and physical examination, but need only a limited number of routine investigations. It is beyond the scope of these guidelines to discuss every detail of the clinical evaluation, but it may be useful to summarize the aims, which are to elicit and document:

- Causes of hypertension, e.g., renal disease, endocrine causes;
- Contributory factors, e.g., obesity, salt intake, excess alcohol intake;
- Complications of hypertension, e.g., previous stroke, left ventricular hypertrophy, IHD, chronic kidney disease (CKD), HF
- Cardiovascular risk factors, e.g., smoking, family history; Note: Increased risk begins at approximately 55 and 65 for men and women, respectively. Adult Treatment Panel III used earlier age cutpoints to suggest the need for earlier action.
- Relative or absolute contraindications to specific drugs, e.g., asthma (beta-blockers), gout (thiazides), angioedema (ACEIs).

Initial evaluation of the hypertensive patient

Secondary Causes of hypertension:

- Medications (NSAID's, oral contraceptive, steroids, licorice)
- Sympathomimetics, ie., decongestants
- Renal disease (present, past or family history: palpable kidney(s) polycystic, hydronephrosis or neoplasm)
- Renovascular disease (abdominal or femoral bruit)
- Pheochromocytoma (paroxysmal symptoms)
- Hyperaldosteronism (tetany, muscle weakness, polyuria)
- Coarctation (delayed or weak femoral pulses)
- Cushings (general appearance)
- Hyperparathyroidism
- Hyperthyroidism
- Sleep apnea
- Other (licorice, some illicit drugs including cocaine, methamphetamine).

Contributory factors:

- Overweight
- Excess alcohol (>2 drinks/day for men, >1 drink/day for women))
- Salt intake
- Lack of exercise
- Complications of hypertension/target organ damage:
 - o Stroke, TIA, dementia
 - o Left ventricular hypertrophy (LVH), heart failure
 - o Myocardial infarct, angina, coronary artery bypass graft (CABG) or angioplasty
 - Peripheral vascular disease
 - Fundal hemorrhages or exudates
 - o Proteinuria
 - o Renal impairment

Table 4: Categories of associated clinical conditions and target organ disease, as 'markers' for those at high or very high absolute risk of a primary or secondary cardiovascular event.

Associated Clinical Conditions (ACC)	Target Organ Disease (TOD)
Diabetes Cerebrovascular disease Ischemic stroke Cerebral hemorrhage Transient ischemic attack	 Left ventricular hypertrophy (LVH) (electrocardiogram, echocardiogram) Microalbuminuria ≥30 µg/min and/or proteinuria ≥200 mg/day and/or glomerular filtration rate (GFR) < 60 mls/min
 <i>Heart disease</i> Myocardial infarction Angina Coronary revascularization Chronic heart failure <i>Chronic kidney disease</i> Diabetic nephropathy Glomerulonephritis Hypertensive renovascular disease <i>Aortic disease</i> Dissecting aneurysm Fusiform aortic aneurysm 	 Ultrasound or radiological evidence of atherosclerotic plaque (aorta, carotid, coronary, femoral and iliac arteries) Hypertensive retinopathy (Grade II or more)
Peripheral arterial disease	
Modified from: Guidelines Subcommittee of th management of hypertension. J Hypertens 199	he WHO-ISH: 1999 WHO-ISH guidelines for the 99, 17:151-183.

I. Perform Physical Examination

OBJECTIVE

Elicit physical signs that may influence clinical decision-making.

RECOMMENDATION

A physical exam should evaluate for signs of secondary HTN or hypertensive organ damage. At a minimum, vital signs should include height, weight, and two or more blood pressure readings with the patient seated.

If the patient is at risk for postural hypotension or has symptoms of orthostasis, a standing blood pressure should also be measured in addition to seated or supine. The two blood pressure measurements should be separated by 2-minute intervals.

A focused examination should include the following:

- 1. Fundoscopy
 - a. Arteriovenous (AV) nicking or arterial narrowing
 - b. Hemorrhages
 - c. Exudates
 - d. Papilledema

2. Neck

- a. Carotid bruits and pulses
- b. Jugular venous distention
- c. Thyromegaly

3. Heart

- a. Normal rate and regular rhythm
- b. Apical impulse
- c. Precordial heave
- d. Clicks, murmurs, third or fourth heart sounds

4. Lungs

- a. Crackles
- b. Wheezes or rhonchi
- 5. Abdomen
 - a. Masses, e.g., aortic aneurysm, polycystic kidneys
 - b. Bruits
- 6. Extremities
 - a. Peripheral arterial pulses
 - b. Femoral bruits
 - c. Edema
- 7. Central and peripheral nervous systems
 - a. Signs of prior CVA
 - b. Signs or symptoms of dementia

Target organ damage associated with clinical cardiovascular diseases includes:

- 1. Heart diseases
 - a. Left ventricular hypertrophy

- b. Angina or prior myocardial infarction
- c. Prior coronary revascularization
- d. Heart failure
- 2. Stroke or transient ischemic attack
- 3. Chronic kidney disease (nephropathy)
- 4. Peripheral arterial disease
- 5. Retinopathy

DISCUSSION

Treatment of hypertension with drugs in clinical trials has reduced stroke incidence by 35% to 40%; myocardial infarction by 20% to 25%; and HF by more than 50% (Neal et al., 2000). In patients with stage 1 hypertension (SBP 140-159 mm Hg and/or DBP 90-99 mm Hg) and additional CV risk factors, a sustained 12 mm Hg reduction in SBP over 10 years has been estimated to prevent 1 death for every 11 patients treated. In the presence of CVD or target organ damage, only 9 patients would require such BP reduction to prevent 1 death (Ogden et al., 2000).

Presence of any target organ damage or history or evidence of a previous cardiovascular event substantially increases the risk of subsequent events in hypertensive patients. Examples of target organ damage include left ventricular hypertrophy or dysfunction, hypertensive retinopathy, chronic renal insufficiency, cerebrovascular disease, and peripheral vascular disease. Antihypertensive drug therapy is usually as or more beneficial in the presence of target organ damage, although absolute risk for CVD with treatment is still higher than similarly treated patients who had not developed target organ damage. In SHEP, HF was reduced by 49% with drug treatment in all patients, while it was reduced by 81% in those with a prior myocardial infarction (MI) (SHEP, 1997).

J. Perform Laboratory and Other Diagnostic Procedures

OBJECTIVE

Determine the baseline data on patient's health status, the existence of secondary causes of HTN and the risk factors contributing to the disease process.

BACKGROUND

Routine laboratory tests help to determine the presence of target organ damage, some risk factors, and the suggestion of secondary causes of hypertension. Optional tests may be used, depending on findings obtained in the history and physical examination and previously known comorbidities. A greater, more inclusive assessment, e.g., cardiovascular anatomy and function, can be determined by ad hoc specialized testing.

RECOMMENDATION

Routine laboratory tests for the investigation of all patients with hypertension

- 1. Urinalysis (UA)
- 2. Blood chemistry (potassium, sodium, blood urea nitrogen [BUN], creatinine, fasting glucose)
- 3. Fasting lipid profile (TC, HDL-C, LDL-C, TG)
- 4. 12-lead electrocardiography

Optional laboratory tests*

- 1. Hematocrit, Complete Blood cell Count
- 2. GFR estimated by MDRD (Modification of Diet in Renal Disease Study Group) equation)**

- 3. Blood calcium
- 4. Urinary protein excretion (24-hour urine collection or spot urine for protein/creatinine ratio)
- 5. Uric acid
- 6. Glycosylated hemoglobin (HbA1c)
- 7. Thyroid-stimulating hormone (thyrotropin) (TSH)
- 8. Transthoracic echocardiography to determine the presence of left ventricular hypertrophy

* May have clinical utility in certain instances

** Calculators and modeling aids. Available at: http://www.nkdep.nih.gov/healthprofessionals/tools/gfr_adults.htm

Estimation of proteinuria and Clcr may be done by single urine and blood tests instead of collecting 24hour urines. To estimate urinary protein excretion, obtain a single urine specimen for protein concentration (in mg/dL) and creatinine concentration (in mg/dL). The protein-to-creatinine ratio (protein concentration divided by the creatinine concentration) estimates the 24-hour protein excretion in grams per day.

Example:

A patient is found to have 3+ protein on urinalysis. Urine specimen sent for protein creatinine ratio revealed a protein concentration of 150 mg/dL and creatinine concentration of 75 mg/dL. The estimated **urinary protein excretion** is 2 grams per day.

There are now several formulas available to estimate Clcr. One of the simplest uses the patient's age, serum creatinine (Scr), weight in kilograms, and sex, to estimate Clcr. Normal Clcr is >100 cc/min, but diminishes with age. The estimation formula is $(140\text{-}age)/\text{Scr} \times \text{wt}/72 \times 1.0$ (if male) or 0.85 (if female).

Examples:

A 72 year-old female weighing 50 kilograms with a serum creatinine of 1.6 has significant renal failure.

Estimated Clcr = (140-72)/1.6 x 50/72 x 0.85 = 25 cc/min.

A 51 year-old male weighing 80 kg with Scr of 1.8 **Estimated Clcr** = $(140-51)/1.8 \times 80/72 = 55$ cc/min.

DISCUSSION

Routinely Recommended Tests

Urinalysis is useful in the detection of overt proteinuria. Blood chemistry may be helpful in identifying underlying kidney disease, diabetes, and baseline electrolyte abnormalities. Fasting lipid profiles may assist in global risk factor modification. Twelve-lead ECGs are recommended to assist in the identification of LVH or ischemic heart disease.

The optional tests listed may be of clinical utility in certain circumstances.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	Routine tests: Urinalysis, Blood chemistry, Fasting Lipid Profile, ECG	JNC-7	III	POOR	Ι

QE = Quality of Evidence; R = Recommendation (see Appendix E)

K. Is a Secondary Cause Suspected?

OBJECTIVE

Detect underlying disease(s) responsible for secondary HTN using additional laboratory tests.

RECOMMENDATION

An early discussion or consultation with an appropriate specialist is encouraged when a patient is suspected of having secondary hypertension.

DISCUSSION

Although fewer than five percent of patients have secondary hypertension, clinicians should constantly be alert to secondary causes of HTN. Referral to appropriate experts as needed may lead to the most accurate and cost-effective workup if an underlying cause of HTN is diagnosed.

Disease	Features	Recommended Test/Referral
Cushing's syndrome and other glucocorticoid excess states including chronic steroid therapy	Amenorrhea Increased dorsal fat Diabetes mellitus Edema Hirsutism Moon facies Purple striae Truncal obesity	History 24- hour urine for free cortisol Dexamethasone suppression test
Hyperparathyroidism	Hypercalcemia Polyuria/polydipsia Renal stones	Serum calcium and parathyroid hormone (PTH) level
Hyperthyroidism	Anxiety Brisk reflexes Hyperdefecation Heat intolerance Tachycardia Tremor Weight loss Wide pulse pressure	Thyroid Stimulating Hormone (TSH) Free T4
Pheochromocytoma	Labile BP Orthostatic hypotension Paroxysms (headaches, palpitations, sweating, pallor) Tachycardia	Plasma metanephrines or 24-hour urine for metanephrines and/or catecholamines Consider referral to specialist

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

Disease	Features	Recommended Test/Referral	
Primary hyperaldosteronism	K ⁺ ≤ 3.5 mEq/l in patients not on diuretic therapy; or K ⁺ ≤ 3 mEq/l in patients on diuretic therapy Muscle cramps Polyuria Weakness	Plasma aldosterone and plasma renin activity24 hour urinary aldosterone level on a high sodium diet	
Kidney disease	Abnormal urine sediment Elevated serum creatinine Hematuria on two occasions or structural renal abnormality (e.g., abdominal or flank masses) Proteinuria	Urinalysis; estimation of urinary protein excretion and creatinine clearance by using a single random urine test; renal ultrasound may also be considered (See annotation H.) Consider referral to nephrology	
Renovascular disease	Abdominal bruits over the renal arteries Abrupt onset of severe HTN Diastolic BP ≥ 115 mm Hg Initial onset age ≥ 50 years old Worsening BP control when previously stable Evidence of atherosclerotic vascular disease	 There are a variety of screening tests for renovascular HTN, depending on equipment and expertise in institutions. Magnetic resonance Angiography, renal artery Doppler, and post-captopril renograms are used. However, there is no single best test for renovascular HTN, and consultation with experts in your institution is recommended. Intravenous pyelogram is relatively contraindicated in diabetes and no longer recommended as screening test for renovascular disease. 	
Sleep apnea	Daytime somnolence Fatigue Obesity Snoring or observed apneic episodes	Referral for sleep study	
Aortic Coarctation	Weak or delayed femoral pulses	Computerized tomography angiography	

Disease	Features	Recommended Test/Referral
Drug or substance Induced	NSAIDs, including Cox-2 Inhibitors Sympathomimetics (e.g., decongestants, anorectics) Oral contraceptives Adrenal steroids Erythropoietin Cyclosporine, tacrolimus Cocaine, amphetamines Excessive alcohol use Licorice Selected dietary supplements (e.g., ma huang, ephedra, bitter orange)	History Urine toxicology as indicated.

L. Initiate Treatment for Hypertension

OBJECTIVE

Select the most effective therapy to control blood pressure.

BACKGROUND

Adoption of healthy lifestyles by all individuals is critical for the prevention of high BP and an indispensable part of the management of those with hypertension. Lifestyle modifications decrease BP, enhance antihypertensive drug efficacy, and decrease cardiovascular risk. Several clinical trial outcome data prove that lowering BP with several classes of drugs will all reduce the complications of hypertension. Determining the most appropriate therapy regimen is based on available evidence and patient adherence to treatment and tolerance to the drug therapy, and other patient's conditions.

RECOMMENDATIONS

PHARMACOTHERAPY (see also annotation M)

- 1. According to the baseline blood pressure and the presence or absence of complications, it appears reasonable to initiate therapy either with a starting dose of a single agent or with starting-doses of two agents. (See Appendix B Recommended Dosage for Selected Hypertension Drug Therapy).
- 2. To reach target blood pressure, it is likely that a large proportion of patients will require combination therapy with more than one agent.
- 3. Drug therapy should be initiated in conjunction with LSM.
- 4. Initial combination therapy with two drugs particularly low-dose combinations is more effective in achieving target level BP.
- 5. Initial combination therapy with two drugs maybe preferable for patients in STAGE 2 HTN.

NON-PHARMACOLOGIC THERAPY (see also annotation G)

1. Prescribe lifestyle modifications in all patients with prehypertension or HTN. Certain lifestyle modifications have been shown to decrease blood pressure in randomized clinical trials; other lifestyle modifications are also important in decreasing cardiovascular risk. These non-pharmacologic measures can be sufficient to control BP or to decrease the amount of required medication.

- 2. If patients with stage 1 HTN do not adhere to LSM or are adherent to LSM and show no improvement in blood pressure level for 3-6 months **initiate drug therapy.**
- 3. In addition to lifestyle modifications, drug therapy should be considered in patients with prehypertension and DM.
- 4. Additional compelling indications should be considered in determining non-pharmacologic, as well as pharmacologic treatment.

BP Classification*	SBP	DBP	LSM	Initial Drug Therapy
Prehypertension	120-139	80-89	Yes	Consider for those with DM when BP 140/80 or greater
Stage 1 Hypertension	140-159	90-99	Yes	Thiazide-type diuretic unless contraindicated or not tolerated (Consider ACEI, ARBs, BB, CCB) For compelling indication see Table 8.
Stage 2 Hypertension	<u>≥</u> 160	<u>≥</u> 100	Yes	Drug therapy with 2 drugs for most patients. This should include a thiazide-type diuretic unless contraindicated or not tolerated (Consider ACEIs, ARBs, BB, CCB) For compelling indication see Table 8

Table 6. Management of Elevated Blood Pressure for Adults

M. Drug Treatment

OBJECTIVE

Determine the most appropriate drug therapy regimen based on available evidence and patient comorbidities.

BACKGROUND

The recommendations for most patients with hypertension also apply to patients with selected comorbid conditions for which—based on outcomes—there are only minor cautions or modifications to standard therapy. For more detail on dosages and contraindications please refer to Appendix B - Recommended Dosage for Selected Hypertension Drug Therapy.

RECOMMENDATIONS

- 1. **Thiazide-type diuretics** are recommended as first line therapy for drug treatment of hypertension either as monotherapy or in combination with other agents. (A)
- 2. The following may be used as alternative or supplementary therapy:
 - a. ACEIs (A)
 - b. ARBs (A)
 - c. Beta-blockers ,A)
 - d. Long-acting calcium channel blockers (A)

Other Supplemental Agents:

3. **Reserpine** can be used as supplemental therapy when other agents are not provide clinical adequate response (A)

- 4. Other agents may be used as additional therapy in refractory hypertension or as supplementary therapy when other drugs are contraindicated or limited by adverse effects. These include:
 - a. Centrally acting drugs (e.g. clonidine, methyldopa) (B)
 - b. Vasodilators (e.g. hydralazine, minoxidil) (B)
 - c. Aldosterone antagonists (e.g., spironolactone, eplerenone) (B)
 - d. Combined alpha-beta blockers (B)
 - e. Alpha blockers (B)

Avoid use of:

- 5. Alpha-blockers should be avoided as monotherapy (D), may be used as supplemental therapy (B)
- 6. Short-acting calcium channel blockers should not be used as there is no evidence of benefit (D). Short-acting dihydropyridine (DHP) calcium channel blockers may cause harm (D)

Condition	Preferred	Alternate	Other agents	Comments
	agents	agents		
HTN - without compelling indications	Thiazide- type diuretic	ACEI ARB Beta-blocker CCB	Aldosterone antagonist Alpha-blocker Clonidine Reserpine Vasodilator	 Immediate-release nifedipine should not be used. An ARB may be considered in a patient who is intolerant to an ACEI. Alpha-blockers are useful in treating symptomatic BPH, but are not recommended as monotherapy for treating HTN.

 Table 7. Preferred Agents In Patients With Uncomplicated Hypertension

Compelling Indications for Individual Drug Classes

Recommendations for initial antihypertensive therapy in patients with HTN who also have certain compelling conditions may differ from other patients with HTN but in general, these patients should still be considered for thiazide-type diuretics -- in addition to the compelling medication -- based on the benefit seen in ALLHAT in patients on diuretics. More specifically, the recommendations in Table 8 include medications that have demonstrated improved outcomes or provided clinical improvement in the treatment of patients with certain conditions that may or may not be directly related to hypertension itself. These conditions addressed include: post-myocardial infarction, systolic heart failure (HF), kidney disease, diabetes, and stroke prevention.

Other specific recommendations are for choice of agent in treatment of pilots and patients whose work/duty require special consideration (pilots, and service person in extreme weather conditions.)

MOST COMPELLING INDICATIONS SHOULD INCLUDE A THIAZIDE-TYPE DIURETIC

	Preferred agents	Additional/Alternative	Other agents
DM †	Thiazide-type diuretic and/or ACEI	ARB CCB Beta-blocker	
Systolic HF	ACEI Beta-blocker	ARB Hydralazine-Nitrate Aldosterone antagonist	Diuretic (for treatment of volume overload) LADHP
CKD ‡	ACEI ARB Diuretic (thiazide or loop, based on kidney function)	Beta-blocker NCCB LADHP	
Post Stroke	Thiazide-type diuretic and ACEI		
Post – MI	Beta-blocker ACEI	NCCB Thiazide-type diuretic	LADHP

Table 8. Preferred Agents in Patients with Comorbidities

Table 9: Other Special Populations

	Preferred agents	Alternate agents	Comments
African Americans	Thiazide-type diuretic ACEI		Differences in efficacy are not as apparent when diuretics are added to ACEIs and beta -blockers
High ambient temp and/or extreme conditions	ACEI / ARB CCB	Low dose Thiazide-type diuretic	For patient already deployed consider CCB (LADHP)

 For patients with Diabetes Mellitus, please refer to the VA/DoD Clinical Practice Guideline, Management of Diabetes Mellitus in the Primary Care Setting, at <u>www.oqp.med.va.gov/cpg/cpg.htm</u>.
 For patients with Kidney Disease, refer to the VA/DoD Clinical Practice Guideline, Management of Pre-ESRD in the Primary Care Setting, at <u>www.oqp.med.va.gov/cpg/cpg.htm</u>

ACEI = angiotensin- converting enzyme inhibitor; ARB = angiotensin receptor blocker; NCCB = nondihydropyridine calcium channel blocker; CKD = chronic kidney disease; LADHP = long-acting dihydropyridine calcium cannel blocker

DISCUSSION

Selection of Drugs

The recommendations for using a thiazide-type diuretic as preferred therapy are based primarily on the results from the ALLHAT study that enrolled a significant number of veteran patients and included numerous VAMCs (ALLHAT, 2002). Conclusions of ALLHAT are supported by numerous studies as referenced in a recent meta-analysis (Psaty et al., 2003). Results of ANBP-2 were also considered (ANBP-

2, 2003). However this trial included a patient population that differed from ALLHAT and the diuretic and ACEI arms of ALLHAT had 5-10 times more cardiovascular events. Recommendations for use of alternate agents (e.g., ACEIs, ARBs, beta-blockers, CCBs) are based on placebo-controlled or comparison trials and meta-analyses that have shown these agents to be beneficial in patients with hypertension, although none have been shown to be superior to a thiazide-type diuretic (refer to Appendix D: Outcome Trials of Antihypertensive Agents). Other agents listed may be beneficial in reducing blood pressure in an effort to achieve target levels although the long-term benefits of the majority of these agents have not been studied.

Patients with HTN often have a comorbid condition where an antihypertensive agent is indicated, regardless of its ability to lower blood pressure. The evidence for the use of antihypertensive medications in certain compelling indications is discussed in detail in the following appendices

Compelling Conditions;

DM See Appendix C1: Compelling Indications - Diabetes

HF See Appendix C2: Compelling Indications – Heart Failure

CKD See Appendix C3: Compelling Indications – Chronic Kidney Disease

Stroke See Appendix C4: Compelling Indications – Prevention of Stroke

In addition, special patient populations may require additional considerations in selecting the most appropriate antihypertensive drug therapy.

African Americans

The low-sodium DASH eating plan was associated with greater reductions in BP in African Americans than other demographic subgroups. In clinical trials, lowering BP prevents sequelae of hypertension in all racial or ethnic groups. Nonetheless, monotherapy with beta-blockers, ACEIs, or ARBs lowers BP to a somewhat lesser degree in African Americans than whites. In the ALLHAT trial with more than 15,000 blacks, the ACEI lisinopril was less effective in lowering blood pressure than either the thiazide-type diuretic chlorthalidone or the CCB amlodipine. There was a 40% greater risk of stroke, 32% greater risk of HF, and 19% greater risk of CVD in those randomized to the ACEI versus the diuretic. There were no differences in major CVD outcomes between the diuretic and the CCB in blacks, except for a 47% higher incidence of heart failure with the CCB. The interracial differences in BP-lowering observed with these drugs are abolished when they are combined with a diuretic. Racial differences in incidence of antihypertensive drug side effects may occur; African Americans and Asians have a 3- to 4-fold higher risk of angioedema and have more cough attributed to ACEIs than whites.

Aviators

Aviators (pilots, navigators, flight surgeons, or special duty personnel) are disqualified from aviation duty when diagnosed with hypertension or placed on hypertension medications. A waiver is required to be returned to flying duties. Certain drugs require a grounding trial only while others require more. Details are spelled out within the Ait Force Instructions (AFI). This AFI applies to active duty, Air National Guard, and AF Reserve aviators.

Hypertension and the treating agent are both disqualifying. In general, only those medications listed in aircrew medication list are waiverable. The underlying medical condition must be adequately controlled prior to waiver submission.

The USA Aeromedical Policy Letter may be downloaded from http://usasam.amedd.army.mil/_aama/policyLetter.htm. The USN Aeromedical Waiver Guide may be found at http://www.nomi.med.navy.mil/NAMI/WaiverGuideTopics/index.htm#text. The medications are specifically addressed in AFI 48-123, Medical Examinations and Standards, Attachment 7.32.

High Ambient Temperature And/Or Extreme Conditions

BACKGROUND

Conditions and physiologic responses may be different if patient with hypertension are exposed to high ambient temperature and/or extreme conditions (e.g., deployment conditions in the desert). In such condition the general recommendations for drug therapy need to be modified.

RECOMMENDATIONS

The following recommendations are based on consensus opinion that considers the available literature, experience in the field, and physiology.

- 1. Clinicians should discuss how deployment might affect blood pressure control and describe potential complications of treatment with their patients as part of pre-deployment processing.
- 2. For Active duty soldiers who might be going into an extreme temperature, or those who do extreme physical activity and are prone to dehydration, CCB or ACEI/ARB would be the preferred agents, rather than a diuretic.
- 3. If thiazide diuretics are to be used, they should be kept to low doses. If possible, the patient should be monitored for signs and symptoms of dehydration and adequate blood pressure control for the first 7-10 days of deployment while they are becoming acclimatized.
- 4. For Active duty soldiers who are diagnosed with hypertension during a deployment in areas with extreme ambient conditions, dihydropyridine CCBs would be the preferred agents. These agents are available in once a day formulations, do not limit heart rate, and do not require electrolytes to be checked after initiation.

For detailed considerations for treatment of hypertension in the deployed environment please see Appendix C-5: High ambient temp and/or extreme conditions.

N. Is BP Control Adequate and Therapy Tolerable?

OBJECTIVE

Assess adequacy of HTN control and adverse effects to treatment.

RECOMMENDATIONS

The primary objective in hypertension treatment is to decrease blood pressure to less than 140/90 mm Hg, or to lower goals in selected patient populations.

- 1. Patients should be seen within 1 month after the initiation of therapy to determine adequacy of HTN control, degree of patient adherence, and presence of adverse effects. (Allied health professional may be useful to conduct these follow-up visits).
- 2. Earlier follow-up may be necessary for patients:
 - a. Requiring blood tests
 - b. At increased risk for adverse outcomes from HTN due to very high BP or target organ damage
 - c. At risk for postural hypotension.
- 3. Assessment of blood pressure control should be based on measurement of BP in the clinic setting. Out of office measurements may provide useful clinical information.
- 4. Once the patient's BP is controlled, follow-up at 3 to 6 month intervals (depending on patient status) is generally appropriate.
- 5. Older persons, persons with diabetes, those with neurological disease and patients with postural symptoms should be evaluated for postural hypotension.
- 6. Target level for blood pressure are included in the following table:

Condition	Target	Level of	Resource
	(SBP/DBP mm	Evidence	
	Hg)	(QE,R)	
Hypertension	<140/90	<150/90 (I,A)	SBP: SHEP, Syst-Eur
		<140/90 (II,B)	DPB: HDFP, HOT
Diabetes	<140/80	(I,A)	UKPDS, HOT
DM + Nephropathy	<140/80	(I,A)	IDNT RENAAL
			MDRD
Chronic Kidney disease	<140/90	<140/90 (I,A)	AASK
		<130/80 (III,C)	
Proteinuria >1g/day	<125/75	(III,C)	Post analyses MDRD

Table 10: Target Values For HTN control (ADOPTED FROM JNC7)

QE = Quality of Evidence; R = Recommendation (see Appendix E)

The VA/DOD Hypertension Guideline recommends a **minimal** target threshold that is based on level IA evidence derived from randomized clinical trials. For persons with diabetes this is 140/80 mm/Hg, and for persons without diabetes 140/90 mm/Hg. The VA/DOD Hypertension Guideline also acknowledges that there are data from multiple observational studies, including pooled data from randomized clinical trials (level IIA evidence) demonstrating that lower blood pressure levels are associated with risk reduction for adverse outcomes; the relationship is linear without a threshold. Consequently, clinicians are encouraged to set target values for each patient **based upon their individual circumstances**, including tolerance of medications.

DISCUSSION

For patients with diabetes mellitus, the HOT trial suggested that clinical outcome might be improved if the diastolic blood pressure is lowered to ≤ 80 mm Hg. However, in these patients, systolic blood pressure was still >140 mm Hg. JNC 7, though, followed the lead of the American Diabetes Association, in recommending antihypertensive medication for patients with diabetes if BP is persistently greater than 130/80 mm Hg. The lower systolic blood pressure as a level for initiating medication is based on consensus opinion, and on epidemiological data, but not on evidence from randomized controlled trials. For this reason, VA/DoD recommends a slightly higher and more conservative level of systolic blood pressure (\geq 140 mm Hg) for initiating therapy.

When chronic kidney disease (any type) is present and protein excretion is greater than or equal to 1 g/day, a target BP around 125/75 mm Hg may slow the progression of kidney disease. Lowering the BP to 125/75 mm Hg should depend on the tolerance of medication and side effects of BP reduction. Based on a

consensus of experts, JNC 7 has recommended a policy of starting antihypertensive medication for patients with chronic kidney disease if BP is persistently greater than 130/80 mm Hg. In fact the MDRD and AASK studies did not demonstrate renal benefits for lower BP goals. For this reason, the VA/DoD uses 140/90 mm Hg as the threshold and goal for therapy.

1. What should the threshold and/or goal be for drug treatment?

The BP goal of treatment of hypertension is <140/90 mm Hg (<140/80 mm Hg for DM).

Observational data shows risk of cardiovascular events and mortality doubling with 20 mm Hg increases in SBP and 10 mm Hg increases in DBP beginning with a BP of 115/75 mm Hg. The relative risk increases are similar but absolute risk is higher for persons with diabetes mellitus or chronic kidney disease.

2. What is the evidence that DBP should be lowered to < 90 mm Hg?

Most "diastolic hypertension" randomized controlled morbidity trials included a DBP of 90 or 95 mm Hg as the lower end of the entry DBP range. The entry DBP range for the VA morbidity trial, which was the initial trial proving treating hypertension reduces cardiovascular events, was 90-129 mm Hg. The DBP 115-129 mm Hg "subgroup" (defined retrospectively) was stopped after a mean of 18 months of follow-up because of benefit. The DBP 90-114 mm Hg "subgroup" was stopped after a mean follow-up of 3 years because of benefit.

The Hypertension Detection and Follow-up Program (HDFP) showed benefit especially for the 90-94 (and 90-104) mm Hg prospectively identified subgroup. The Hypertension Optimal Treatment (HOT) trial showed no further benefit (nor harm) for lower goals of 80 mm Hg and 85 mm Hg, compared with 90 mm Hg. "On treatment" DBPs in HOT suggested similar risk between 70-90 mm Hg and higher risk <70 and >90 mm Hg. However, HOT was probably underpowered for the small differences achieved.

In the patients with diabetes in HOT (with 80 mm Hg DBP goal) and UKPDS (with combined "intensively treated" goal <150/85 mm Hg), achieved DBPs in intensively treated groups of approximately 81 and 82 mm Hg, respectively, were associated with lower cardiovascular risk compared with DBPs of 85 mm Hg and 87 mm Hg, respectively. In the Appropriate Blood Pressure Control in Diabetes (ABCD) study a lower DBP goal (<75 mm Hg) did not show benefit compared with <90 mm Hg, but this study was not adequately powered for cardiovascular outcomes.

3. What is the evidence that SBP should be lowered to < 140 mm Hg?

In observational studies, SBP 140 mm Hg is associated with as high or higher risk as DBP 90 mm Hg and has twice the cardiovascular risk as 120 mm Hg.

In several diastolic HTN drug treatment morbidity trials (e.g., HDFP) on-treatment achieved mean SBP was <140 mm Hg (131 vs 142 mm Hg). Even higher risk patients with DM (for CVD and microvascular disease) and CKD (for CVD and decline in renal function) are at much higher risk with SBP 140 mm Hg than levels of 120 mm Hg associated with lower risk.

Randomized controlled trials of isolated systolic hypertension (SHEP and Syst-Eur) used entry criterion of SBP >160 mm Hg and demonstrate reduced cardiovascular events with SBP goals of <150-160 mm Hg (goal SBP in SHEP was <160 mm Hg and at least 20 mm Hg reduction from baseline; goal SBP in Syst-Eur (and Syst-China) was <150 mm Hg). There has not been a completed trial in hypertension comparing a SBP goal <140 mm Hg (or lower) compared with a higher SBP goal.

In diabetes, participants in HOT (with only DBP goals) and UKPDS (with combined "intensively treated" BP goal <150/85 mm Hg) achieved SBP in intensively treated groups of 140 mm Hg and 144 mm Hg, respectively, were associated with lower CV risk vs 144 mm Hg and 154 mm Hg, respectively.

In CKD, although observational data suggest lower is better, MDRD and AASK failed to show that lower MAP goals (approximating 125-130/75-80 mm Hg) affected decline in renal function or development of ESRD. Retrospective subgroup analysis suggested benefit if urine protein >1 gm in MDRD.

ACCORD is testing (n=4,200) whether SBP goal <120 mm Hg reduces CVD (and microvascular disease) compared with a SBP goal <140 mm Hg.

ALLHAT, ACCORD, LIFE, and VALUE have used the combined goal <140/90 mm Hg in comparison of various drug treatments – usually achieving control in 2/3 of participants over several years (ALLHAT & CONVINCE).

	Recommendation	Sources	QE	Overall Quality	R
1	Treat for HTN if SBP ≥150 mm Hg	Prospective Studies Collaboration, SHEP,	II-2 I	Good Good	А
		Syst-Eur	Ι	Good	
2	Treat for HTN if SBP ≥140 mm Hg	Prospective Studies Collaboration,	II-2	Good	В
		JNC 7	III	Poor	
3	Treat for HTN if DBP <u>≥</u> 90 mm Hg	Prospective Studies Collaboration, Collins meta-analysis	II-2	Good	А
			Ι	Good	
4	Confirm SBP \geq 140 mm Hg or DBP \geq 90 mm Hg on 2 or more visits, unless there are other clinical reasons for beginning therapy immediately (e.g., if target organ damage)	U.S. Task Force, 2003 HM Perry 1992	III	Fair	С
5	Confirm and/or begin treatment within 1 month if SBP \geq 160 mm Hg or DBP \geq 100 mm Hg	SHEP	III	Fair	C
6	Classify SBP 120-139 mm Hg or DBP 80-89 mm Hg as "prehypertension"	JNC 7 Prospective Studies Collaboration Vasan, 2001	II-2	Good	В

EVIDENCE

QE = Quality of Evidence; R = Recommendation (see Appendix E)

O. Continue Current Treatment; Reinforce Lifestyle Modification; Follow up at Next Regular Visit

OBJECTIVE

Follow patients who attain the desired target BP.

BACKGROUND

Once an effective and well-tolerated regimen has been obtained periodic follow-up is important to the management of the hypertensive patient and should help to:

- Assess the long-term response and adherence to therapy
- Monitor the development of target organ damage
- Assess for adverse effect(s) of medication(s)

• Reinforce lifestyle modification.

RECOMMENDATION

- 1. Once the patient's BP is stabilized, follow-up at 3 to 6 month intervals (depending on patient status) is generally appropriate.
- 2. Decrease or cessation of antihypertensive drug therapy is possible in patients who are willing to do so, and whose BP is very well controlled. Cessation may be considered in patients well controlled on monotherapy. These patients should be closely followed-up.

DISCUSSION

There is no definitive evidence on what duration between follow-up visits helps maintain optimal blood pressure, although a recent study by Birtwhistle et al. suggested that 6-month visits yielded similar control to 3 month visits (Birtwhistle, 2004). However, in that study, because patients were free to visit their clinician at any time, the number of visits over the approximately 3 year study period was roughly similar (16.2 vs. 18.8) although statistically significant. Hence, any interval within that timeframe would generally be appropriate, though depending on clinical circumstances some patients may be seen earlier or later.

Similarly, it is unclear what follow-up testing is necessary but it is clinically prudent to assess renal function and potassium once or twice yearly (JNC 7) and lipid profile periodically, depending on initial level and/or on-going treatment (see VA/DoD Clinical Practice Guideline for Dyslipidemia).

In terms of step-down therapy, this is a relatively rare occurrence. Review of observational data from the ANBP-2 cohort suggests that those most likely to successfully withdraw from anti-hypertensive medication are patients whose blood pressures are controlled with monotherapy (Nelson, 2003). When withdrawal of therapy does occur, follow-up should generally be tailored to shorter durations at first to assure that blood pressure does not rise again.

	Recommendation	Sources	QE	Overall Quality	R
1	Follow-up visits may occur every three to six months	Birtwhistle, 2004	IIa	Good	В
2	Decrease or cessation of antihypertensive drug therapy	Nelson et al., 2003	Ι	Fair	В

EVIDENCE

QE = Quality of Evidence; R = Recommendation (see Appendix E)

P. Self monitoring

OBJECTIVE Assess and promote blood pressure control.

BACKGROUND

Providers often encourage home blood pressure monitoring to assist them in the management of their patient's hypertension.

RECOMMENDATIONS

1. Home blood pressures may be used as a supplement to, but should not wholly substitute for, obtaining clinic blood pressures to assess or promote blood pressure control.

- 2. If home blood pressure monitoring is used, a minimum of two measurements per day for at least two days should be obtained and then averaged in order to provide a reliable estimate of home blood pressure. *
- 3. In order to improve accuracy and interpretation of home blood pressure measurements, the use of a device with a memory function is recommended rather than relying on the patient's recall or diary.
- 4. Home blood pressure monitoring may assist in detecting a white coat effect or poorer control at home than in the office.

* Note: Patients enrolled in a formal Care Coordicantion\Telehealth (CC-TH) should follow the instructions of the CC-TH program.

DISCUSSION

In patients already being treated for hypertension, home blood pressure monitoring may assist in managing, hypertension by improving control in selected patients (Ebrahim, 1998; Boulware, 2001), and may help in identifying a white coat effect in a small proportion of treated patients (Staessen, 2004 ; Little, 2002), perhaps as well as 24-hour blood pressure readings (Stergiou, 1998). Home blood pressure monitoring may also help identify patients whose control is worse at home compared to clinical based readings (Bobrie, 2004). Some evidence suggests that home blood pressure monitoring has good prognostic efficacy for predicting cardiovascular events (Bobrie, Ohktubo, 1998), but other evidence suggests that treated patients who utilized home monitoring instead of office monitoring of blood pressure had poorer control (Staessen). Home blood pressures have not been utilized in large clinical trials showing mortality and morbidity benefits when treating hypertension.

Overall, then, the evidence is insufficient to assume that home blood pressure readings, in patients already being treated for hypertension, may be wholly substituted for office-based readings. Indeed, apart from a small minority of patients with a suspected or known white-coat effect, office-based readings should remain the standard for determining control and therapy.

When home blood pressures are used, however, one randomized controlled trial suggests that at least two days of monitoring is required for reproducibility of home blood pressure readings to provide reliable information (Stergiou, 1998) and that using devices with a memory function may increase accuracy and interpretation of home blood pressure measurement (Bachmann, 2002). From a purely practical standpoint, it may be helpful for patients bring in their self-monitoring device to clinic in order to calibrate it against an office manometer.

	Recommendation	Sources of Evidence	QE	Overall Quality	R
1	Home blood pressures may be used as an alternative to clinic blood pressures in	Ebrahim et al., 1998	Ι	Good	В
	improving blood pressure control.	Boulware et al., 2001			
2	If home blood pressure monitoring is used, a minimum of two measurements per day for at least two days should be obtained and then averaged in order to provide a reliable estimate of home blood pressure.	Stergiou et al., 1998b	Ι	Good	В
3	In order to improve accuracy and interpretation of home blood pressure measurements, the use of a device with a memory function is recommended rather than relying on the	Bachmann et al., 2002	Ι	Good	В

EVIDENCE

	patient's recall or diary.				
4	The use of home blood pressures may be used as a reliable alternative to 24-hour ambulatory blood pressure monitoring in the detection of the white coat effect.	Stergiou et al., 1998a	Ι	Good	В

Q. Adjust Therapy

OBJECTIVE

Modify drug therapy to help achieve BP control.

BACKGROUND

The barrier to blood pressure control is failure to appropriately titrate medications and/or initiate other interventions when BP remains above target control. Intensive follow-up to assess therapeutic response and adverse effects is most important. If the blood pressure continues to be elevated adjustment should be made to the patient's medication regimen. Substituting another agent is not a preferred strategy unless the patient is experiencing adverse effects. Rather, an increase in dose or addition of another agent may provide better benefit.

RECOMMENDATION

If the blood pressure continues to be elevated, clinicians may consider choosing one of the strategies that have proven effective in the treatment of HTN.

- 1. Increase the dose of the original medication.
 - Titrating the dose usually means doubling the dose. Be aware of the dose response that is
 not always linear although adverse effects may increase with higher doses.

2. Add another agent

- If a thiazide-type diuretic is not chosen as the initial drug, it should be used as the second agent, unless contraindicated or not tolerated, especially because it frequently enhances the effects of the initial agent and has the best cardiovascular outcome data. (IA)
- When using combination therapy select those agents that have been shown to reduce morbidity and mortality. (A)
- When using combination therapy select agents from different classes and provide benefit for comorbid condition or compelling indications if they exist. (C)
- Combination therapy includes a potential for drug-drug interactions, but these are uncommon.
- 3. Consider care management by pharmacist in the follow-up and adjustment of medication to improve blood pressure goal. (B)
- 4. Involving other allied health professionals in follow-up may as well improve blood pressure control. (,C)

DISCUSSION

Blood pressure goals in patients with hypertension are frequently unmet, and only a low proportion of patients controlled compared to the population that carries the diagnosis (Hyman, 2001; JNC-7, Berlowitz, 1998). Reasons for this are unclear but, in part, reflect provider skepticism about reducing mild systolic and diastolic elevations (Hyman, 2000; Oliveria, 2002) which in turn may represent the general lack of data

in the past about the benefit of treating such patients aggressively, even though the epidemiological data would suggest otherwise, as discussed earlier. However, the threshold goal of 140/90 mm Hg is now well established and there is an increasing amount of evidence to support lower population blood pressures. Hence, the burden is on clinicians to utilize all available means to control blood pressure to target goal and in that context are strongly encouraged to titrate medications as needed and to recommend lifestyle modifications to improve blood pressure management whenever blood pressure is persistently above recommended targets.

Increase Dosage:

However, only about 30 percent of patients can be controlled with a single agent, though most patients who achieve control with one medication are likely to be those with mild elevations.

Combination of drugs:

Combination therapy is increasingly common and recommended, especially for patients with high initial blood pressure. Fixed-dose combination products are also available.

Change drug:

Discontinuing the original medication and starting a new agent has also been studied in clinical trials, again with approximately 30 percent of patients controlled. This regimen offers similar advantages to the first, and may avoid adverse effects seen with higher-dose titration. The patient's initial BP, BP goal, outcome data, and concomitant conditions should be taken into account before considering discontinuation of the initial medication. Since adverse effects tend to be similar within classes, a medication from a different class is usually preferred.

	Recommendation	Sources	QE	Overall Quality	R
1	Add second agent	Materson, 1996 ALLHAT	Ι	Good	Α
2	Thiazide-type diuretic should be used as one of the agents in combination therapy	ALLHAT JNC7	Ι	Good	Α
3	When using combination therapy select agents from different classes	Group Consensus	III	Poor	С
4	Involving other allied health professionals in follow-up	Group Consensus	III	Poor	C
5	Consider care management by pharmacist in the follow-up		Ι	Fair	В

EVIDENCE

QE = Quality of Evidence; R = Recommendation (see Appendix E)

R. Reassess Adherence

OBJECTIVE

Identify causes of inadequate response to therapy following dose or stepwise titration.

BACKGROUND

Poor adherence to antihypertensive therapy remains a major therapeutic challenge. Aside from simple inadequacy of the chosen agent, the clinician should consider alternate explanations for inadequate response to drug therapy. These include medical or psychosocial conditions that undermine blood pressure

control. Poor patient response to the initial drug management strategy should always lead the primary care provider to explore important factors that may explain failure to achieve target blood pressure.

RECOMMENDATION

Adherence to an antihypertensive medication regimen can be improved by a multi pronged approach including:

- a) Address barriers for obtaining the medications (administrative, economic, etc.)
- b) Simplifying medication regimens incorporating patient's preference
- c) Coordinate with other health care team members to improve monitoring of adherence with prescriptions of pharmacological and lifestyle modification
- d) Educate patients and patients' families about their disease/treatment regimens
- e) Encourage greater patient responsibility/autonomy in monitoring their blood pressure and adjusting their prescriptions.

Non-adherence to therapy	See Table 12, below.		
Pseudo-resistance	"White Coat" hypertension or office elevation		
	Pseudohypertension in older patients		
	Use of regular cuff on large (>32 cm circumference) arm		
Volume overload	Excess salt intake		
	Progressive renal damage (nephrosclerosis)		
	Fluid retention from reduction of blood pressure		
	Inadequate diuretic therapy		
Drug-related causes	NSAID(non steroidal anti-inflammatory drugs), COX-2 inhibitors		
	Dose(s) too low		
	Wrong type of diuretic		
	Inappropriate combinations		
	Rapid inactivation (e.g., hydralazine)		
	Drug actions and interactions		
	Sympathomimetics		
	Nasal decongestants		
	Appetite suppressants		
	Cocaine and other illicit drugs		
	Caffeine		
	Oral contraceptives		
	Adrenal steroids		
	Cyclosporine, tacrolimus		
	Erythropoeitin		
	Antidepressants		

Table 11. Causes of Inadequate Response to Therapy

Associated conditions	Smoking			
	Obesity			
	Sleep apnea			
	Hyperinsulinemia			
	Ethanol intake more than 3 oz. (90 ml) per day			
	Anxiety-induced hyperventilation or panic attacks			
	Chronic pain			
	Intense vasoconstriction (arteritis)			
	Memory deficit)			
Identifiable secondary causes of HTN	See Table 5, Recommended Testing for Patients Suspected of Having Secondary Hypertension			

The primary care provider should employ measures that assist in improving patient adherence to treatment. Many of these measures are designed to engage the patient in his or her wellness. Table 12 lists several suggestions to improve the patient's adherence to therapy.

Table 12. Strategies to Improve Patient Adherence to Antihypertensive Therapy

1. Be aware of signs of patient non-adherence to therapy (e.g., missed appointments, missed refills).				
2. Establish the goal of therapy early: to reduce BP to non-hypertensive levels with minimal or no adverse effects.				
3. Educate patients about the disease, and involve them and their families in its treatment. Have them measure blood pressure at home.				
4. Maintain contact with patients.				
5. Integrate pill taking into routine activities of daily living.				
6. Prescribe medications that require no more than twice daily dosing if possible.				
7. Ask about adverse effects and adjust therapy to prevent, minimize, or ameliorate side effects.				
8. Enlist the support of pharmacist in adjusting medication with regular follow-up.				
9. Consider group visits for education				

DISCUSSION

Inadequate blood pressure control may be attributed to patients not adequately adhering to the medication regimen (Haynes, 1982) and successful treatment for HTN has been related to adherence (Haynes and Gibson et al, 1982, Eisen et al, 1987, Mallion et al, 1997, Flack et al, 1995). It has been reported that over half of patients who did not achieve blood pressure control were taking < 80% of their prescribed medication (Rudd 1998) and two-thirds of patients who received care for HTN did not take enough medication to control their blood pressure (Eraker et al, 1984).

Numerous reasons have been suggested to cause poor medication adherence including long-term therapy, cognitive impairment, number of medications prescribed, frequency of administration, complexity of the drug regimen, cost of medications, side effects, and factors related to the patient's health decision (i.e., acceptance of the disease, perceived severity, satisfaction with healthcare interaction, etc.) (Eraker et al, 1984). Other factors may include patient and/or caregiver education on the disease and its management, education of the healthcare practitioner on patient communication, the extent the patient is involved in self-management of HTN, and monitoring by the healthcare professional (Feldman et al, 1998). In a survey of older patients, it was found that 52% of patients did not adhere to the medication regimen because they felt that they did not need to take the medication at the dose prescribed. Four percent felt they required more

medication (Cooper et al, 1982). It is difficult to apply patterns of medication adherence with various diseases due to different belief models or motivating factors for adherence (e.g., acutely life-threatening disease, symptomatic illness vs. asymptomatic condition). Although in this survey, patients with HTN did not differ in their adherence rates or reasons for not taking their medication as prescribed compared to patients without HTN (Cooper et al 1982). In another survey of over 1,200 veteran patients, 4% felt they were taking too many medications. These patients also reported decreased compliance, more adverse reactions, and decreased health-related quality of life (Fincke, 1998). Patients may also skip a dose of their medication if they feel they do not have a serious disease. One study reported that 36% of patients on antihypertensive agents adjusted their medications to a lower dose or less medications, and this practice was more prevalent in patients experiencing problems with their medications (Wallenius, 1995).

Data have demonstrated that rates of adherence are related to the frequency of doses taken throughout the day. Researchers have found that compliance (defined as % days that the prescribed number of doses were removed from the pill container) was 83.6% on a once daily regimen, 74.9% on twice daily, and 59% with a regimen prescribed three times daily (P<0.05 daily or bid vs. tid; daily vs. bid did not show a statistically significant difference) (Eisen et al 1990). A review of the literature found that overall compliance was 76% (range 53-85%) in patients on once daily preparations (Cramer, 1998). Reducing the number of daily doses appears to be effective in increasing adherence to blood pressure lowering medication and should be tried as a first line strategy, although there is less evidence of an effect on blood pressure reduction. Some motivational strategies and complex interventions appear promising, but we need more evidence on their effect through carefully designed RCTs (Schroeder, 2003 [Cochrane review]).

With the evidence that patients have greater rates of adherence with simplified regimens, the majority of antihypertensive medications are now formulated as once daily preparations. In an effort to further improve adherence, two antihypertensive medications are now being combined into one dosage form. This has been demonstrated in some disease states (Eron, 2000) but not others (Braunstein, 1996).

Other methods to improve adherence and disease control should be considered. An intervention program consisting of a clinical pharmacist and nurse clinician was found to significantly improve drug documentation, compliance (Monson, 1981; Bond, 1984) and blood pressure control (Bond, 1984). Patients were compliant with 85% of their prescriptions at 9 months, and 88% at 4 years 9 months follow-up, compared to 33% in the control group. Compliance (assessed by refill pattern) was significantly correlated with BP control (P < 0.001) (Bond, 1984). Average BP was < 145/95 mm Hg in 69% of patients at 9 months, and 90% of patients at 4 years 9 months, compared to 29% in the control group. Reductions in cost were also associated with the intervention program (Bond, 1984). Other studies have also demonstrated an improvement in adherence and outcomes from an intervention program provided by healthcare practitioners (Logan, 1979).

Other recommendations to improve adherence in patients with HTN include providing written and verbal education on HTN and pharmacotherapy (especially since this is an often asymptomatic disease), combining behavior modification with simplifying the medication regimen (e.g., once daily medications taken at a time convenient for the patient), ensuring that the medication is affordable, and monitoring and discussing adherence upon follow-up (Chockalingam, 1998).

S. Consider Consultation

OBEJECTIVE

Determine appropriate point in time to consider consultation to improve hypertension management.

BACKGROUND

The two primary reasons for consultation are resistant hypertension, defined as failure to reach target goals with three appropriately titrated medications (one of which should be a thiazide-type diuretic unless contraindicated or not tolerated) and/or suspected secondary cause of hypertension (see

Annotation K). In general, when failing to reach target goal, an assessment of possible remedial causes should occur including, as examples, lack of adherence to medication or lifestyle regimens or use of other drugs prescribed or illicit) that might interfere with blood pressure control (other examples are given in annotation R).

RECOMMENDATION

From a clinical perspective, referral to or consultation with hypertension specialists or those with particular expertise in the relevant clinical area should be considered if there is:

- 1. Failure to achieve target blood pressure goals when on appropriate doses of three medications, one of which should typically be a thiazide-type diuretic and assuming that other remedial causes of inadequate response have been identified and addressed.
- 2. Suspected secondary cause for hypertension.

APPENDICES

APPENDIX A: ACRONYM LIST

- ACC Associated Clinical Conditions
- ACEI Angiotensin- converting enzyme inhibitor
- ARB Angiotensin II Receptor blocker
- BP Blood Pressure
- CCB Calcium Channel Blockers
- CHD Coronary Heart Disease
- CKD Chronic Kidney Disease
- CRI Chronic Renal Insufficiency
- CV Cardiovascular
- CVA Cerebrovascular Accident
- CVD Cardiovascular Disease
- DBP Diastolic Blood pressure
- DHCCB Dihydropyridine Calcium Channel Blockers
- DM Diabetes Mellitus
- GFR Glomerular Filtration Rate
- HDL -C High Density Lipoprotein Cholesterol
- HF Heart Failure
- HTN Hypertension
- IR Immediate Release
- LDL C Low-Density Lipoprotein Cholesterol
- LSM Lifestyle Modification
- LVEF Left Ventricular Ejection Fraction
- LVH Left Ventricular Hypertrophy
- MAOI Monoamine Oxidase Inhibitor
- MDRD Modification of Diet in Renal Disease Study Group
- NCCB Nondihydropyridine Calcium Channel Blockers
- PCM Primary Care Manager
- PCP Primary Care Provider
- QE Quality of Evidence
- R Recommendation
- SBP Systolic Blood Pressure
- Scr Serum creatinine
- SLE Systemic Lupus Erythematosus
- SR Sustained Release
- TG Triglycerides
- TOD Target Organ Damage

List of Studies Abbreviations

- AASK African American Study Of Kidney Disease And Hypertension
- HDFP Hypertension Detection and Follow-up Program
- HOT Hypertension Optimal Treatment
- IDNT Irbesartan in Diabetic Nephropathy Trial
- MDRD Modification of Diet in Renal Disease

RENAAL Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan

- SHEP Systolic Hypertension in the Elderly
- Syst-Eur Systolic Hypertension in Europe
- UKPDS United Kingdom Prospective Diabetes Study

APPENDIX B: DRUG TABLES

Recommended Dosage for Selected Hypertension Drug Therapy

Drug ^a	Usual Dose Range ^d	Comments ^g
Thiazide Diuretics		
Chlorthalidone ^b	12.5-25 mg daily	May cause hyperuricemia/gout
Hydrochlorothiazide ^b	12.5-50 mg daily	Monitor K+ levels
HCTZ/Triamterene ^b	12.5/18.75-50 mg/75 mg daily	May cause photosensitivity (rare)
Indapamide	1.25-2.5 mg daily	
Beta-blockers		
Noncardioselective		
Propranolol	IR: 80-160 mg/day (divided bid) SR: 80-160 mg daily	Discontinue with slow taper over 1 week
Cardioselective		Avoid combination with NCCB
Atenolol ^b	25-100 mg daily (adjust dose in CRI)	As doses increase, cardioselectivity decreases Beta-blockers should be used cautiously in
Metoprolol ^b	IR: 50-300 mg/day (daily or divided bid)	asthma
CCBs		Use CCBs with caution in patients with liver or kidney dysfunction
NCCBs		
Verapamil SR ^c	120-480 mg divided daily-bid	Verapamil may cause constipation; verapamil is contraindicated in AV node dysfunction (2nd or 3rd degree heart block), systolic HF and \downarrow LV function
Diltiazem SR ^b	120-540 mg daily	Diltiazem may ↓ sinus rate and cause heart block
DHPs		
Amlodipine ^f	2.5-10 mg daily	
Felodipine	2.5-10 mg daily	Monitor adverse effects (DHPs may cause ankle edema, dizziness, flushing, headache)
Nifedipine SR ^b	30-60 mg daily	unice edema, uzziness, nusining, neaudelie)

Drug ^a	Usual Dose Range ^d	Comments
ACEIs		Avoid in 2nd and 3rd trimesters of
Captopril ^{b,e}	25-100 ^f mg/day (divided bid)	pregnancy due to possible fetal and
Enalapril	5-40mg/day (daily or divided bid)	neonatal morbidity and death
Fosinopril	10-40 mg daily	Should not be used if history of angioedema
Lisinopril ^b	10-40 mg daily	Monitor K+ and kidney function; use
Ramipril ^{b,f}	2.5-20 mg/day (daily or divided bid) (10 mg daily for CV risk prevention)	caution if combined with ARB, K+ sparing diuretic, or K+ supplement
ARB s ^g		
Candesartan Eprosartan Irbesartan Losartan	8-32 mg daily 400-800mg/day (daily or divided bid) 150-300 mg daily	Contraindicated in 2nd and 3rd trimesters pregnancy due to potential for fetal and neonatal morbidity and death
Olmesartan Telmisartan Valsartan	25-100 mg/day (daily or divided bid) 20-40 mg daily 20-80 mg daily 80-320 mg daily	Monitor K+ and kidney function; use caution if combined with ACEI, K+ sparing diuretic, or K+ supplement
Alpha-blockers		
Doxazosin	1-16 mg daily	Initiate at low doses (1mg)
Prazosin ^b	2-20 mg/day (divided bid or tid)	Administer 1st dose at bedtime to avoid
Terazosin ^b	1-20 mg daily	syncope
Alpha-beta blockers		
Carvedilol ^f	12.5-50mg/day (divided bid)	Precautions for beta-blockers apply
Labetalol	200-800mg/day (divided bid)	
Centrally Acting		
Clonidine Tablet ^b	0.1-0.8 mg/day (divided bid)	Monitor for somnolence and dry mouth. Taper dose to discontinue
Clonidine Patch	0.1-0.3 mg patch weekly	Clonidine patches are costly but may be useful in selected patients
Methyldopa	500-2000mg/day (divided bid)	
Peripherally Acting		Monitor for sedation, nasal congestion,
Reserpine	0.1-0.25 mg daily	activation of peptic ulcer
Vasodilators		Should be used with a diuretic and beta- blocker to reduce edema and reflex tachycardia
Minoxidil	2.5-80 mg/day (daily or divided bid)	Monitor for hypertrichosis, pericardial effusions with minoxidil
Hydralazine ^b	50-200 mg/day (divided bid)	Monitor for headache and SLE (dose- related) with hydralazine

Aldosterone Antagonists		
Eplerenone	50-100 mg/day (daily or divided bid)	Monitor K+ and kidney function; use caution if combined with ACEI, ARB, K+ sparing diuretic, or K+ supplement
Spironolactone	25-50mg daily	May cause gynecomastia
Fixed-Dose Combinations		
Chlorthalidone/Atenolol	Available as 25/50mg, 25/100mg (dose as above)	
HCTZ/Lisinopril	Available as 12.5/10mg, 12.5/20mg, 25/20mg (dose as above)	Precautions apply as above

^a Partial list; for medications not included on this list, refer to JNC 7; refer to <u>www.vapbm.org</u> for items available on VANF

^b DoD BCF item; all BCF items are available through the DoD TMOP

^c Calan® SR, Isoptin® SR, and generic equivalents are on the DoD BCF ^dIR=immediate release; SR=sustained release, MAOI=monoamine oxidase inhibitor ^e Patients should take 1 hour prior to food ingestion (empty stomach)

^fVA criteria for use

^g For complete drug information, review the manufacturer's prescribing information.

APPENDIX C: HYPERTENSION AND COMORBID CONDITIONS

- C1. Compelling Indications Diabetes
- C2. Compelling Indications Chronic Kidney Disease
- C3. Compelling Indications Heart Failure
- C4. Compelling Indications Stroke Prevention
- C5 High ambient temp and/or extreme conditions

C1: DM – Hypertension

Management of Hypertension in Diabetes Mellitus

Patients with Diabetes with SBP >140 or DBP >80 mm Hg

BACKGROUND

The incidence of hypertension (HTN) among those with type 1 DM rises steadily from 5 percent at 10 years, to 33 percent at 20 years, and 70 percent at 40 years (Epstein & Sowers, 1992), and there is a correlation between the onset of HTN and the presence of diabetic nephropathy (DN). The association of HTN and DM is less strong among patients with type 2 DM, because up to 50 percent of patients have HTN before the onset of microalbuminuria. Therefore, early treatment of HTN in patients with diabetes, particularly type 2 DM, is important to delay the onset and/or retard the progression of cardiovascular disease and DM.

RECOMMENDATIONS

- 1. Patients with diabetes with hypertension (systolic BP \geq 140 or diastolic BP \geq -90 mm Hg) should:
 - Begin anti-hypertensive therapy with a diuretic or an angiotensin converting enzyme inhibitor (ACEI)
 - If ACEI induced side-effects occur, consider switching to an angiotensin receptor blocker (ARB)
 - Use other preferred agents (beta blockers, long acting calcium channel blockers) as necessary, depending on other co-morbid conditions or compelling indications to achieve a blood pressure <140/80 mm Hg
- Patients with diabetes with initial SBP <140 mm Hg and DBP 80 and 89 mm Hg (within the "prehypertensive" category identified by JNC 7) may benefit from lowering diastolic blood pressure to < 80 mm Hg. (A)
- 3. Individuals with diabetes whose blood pressures is <140/80 mm Hg who have clinical cardiovascular disease may benefit from ACEI therapy even without a reduction in blood pressure. (A)
- 4. In patients with diabetes with renal insufficiency (i.e., serum creatinine >1.5 mg/dL) and proteinuria (i.e., >1 g/24h) there are some data suggesting that further BP lowering (<125/75 mm Hg) may slow progression of renal disease. Lower BP should be achieved, if feasible and practical, depending on the tolerance of medications and side effects of BP lowering. (B)</p>

DISCUSSION

Blood Pressure Targets

Diabetics with HTN are at high-risk for cardiovascular disease. Lower BP, per se, reduces cardiovascular events (Gaede et al., 1999; Hansson et al., 1998; Lindholm et al., 2002; UKPDS 1998). However, despite using aggressive treatment protocols, clinical trials have been unsuccessful in achieving SBP <140 mm Hg. There are no published intervention studies in patients with diabetes in which achieved SBP was <130 mm Hg. Thus, there are no data on which to conclude that lower systolic levels will achieve further benefits. There have been a number of consensus based recommendations among professional societies and other national guideline panels recommending lower systolic BP targets. However, definitive scientific evidence as to whether or not systolic BP lowering from 140 mm Hg is beneficial will need to await the results of the ACCORD Trial, which includes a randomization of patients with diabetes to systolic BP of <140 mm Hg or <120 mm/Hg. Diastolic blood pressure (DBP) levels <80 mm Hg may be more readily controlled and there is evidence from clinical trials that <80 mm Hg is achievable and likely beneficial. In studies in which achieved DBP was 82 mm Hg or less diabetes-related outcomes were significantly improved (Brenner et al., 2001; Estacio et al., 2000; Hansson et al., 1998; Lewis et al., 2001; Lindholm et al., 2002; UKPDS, 1998.

Use of a thiazide-type diuretic (ALLHAT 2003) or blocking the renin-angiotensin system (Estacio et al., 2000; HOPE, 2000; Lewis et al., 1993) offer specific advantages in patients with diabetes and particularly when renal disease is present (Brenner et al., 2001; Lewis et al., 2001; Parving et al., 2001). Adding an ACEI to an existing medical regimen (even in the setting of BP <140/80 mm Hg) is associated with fewer cardiovascular events and delay in the progression of microalbuminuria to overt nephropathy (HOPE, 2000 and MICRO-HOPE 2000).

Pharmacotherapy

Patients with diabetes, particularly those with nephropathy, may have HTN that is difficult to control, often requiring combinations of several agents to achieve lower BP. ACEIs, ARBs, beta-blockers, diuretics, and nondihydropyridine calcium channel blockers (NCCB) may be used to treat hypertensive patients with DM.

ACEI

- 1. ACEIs have several advantages including protection against cardiovascular events, few adverse effects, and a safety track record. There is a compelling indication to use ACEIs for patients with type 1 DM and nephropathy, based on the reduced risk of doubling the serum creatinine and a 50 percent reduction in the risk of the combined endpoints of death, dialysis, and transplantation (Lewis et al., 1993).
- 2. ACEIs compared to placebo decreased the risk of combined MI, stroke, and cardiovascular death in hypertensive patients with type 2 diabetes with high-risk for cardiovascular disease (HOPE, 2000).
- 3. ACEIs may also be beneficial in normotensive patients with type 1 or 2 DM with microalbuminuria in decreasing morbidity and mortality (MICRO-HOPE) in addition to delaying progression of microalbuminuria (Laffel et al., 1995; Ravid et al., 1993; Viberti, 1994).

ARB

- ARBs appear to have similar short-term effects as ACEIs in patients with diabetes and nephropathy, with fewer side-effects (Anderson et al., 2000; Lacourciere et al., 2000; Muirhead et al., 1999; Nielsen et al., 1997). However, there are no long-term outcome trials comparing an ACEI to an ARB to determine if these agents provide similar long-term benefits in patients with DM.
- 2. ARBs are effective in patients with type 2 DM with nephropathy (Brenner et al., 2001; Lewis et al., 2001) or microalbuminuria (Morgensen et al., 2000: Parving et al., 2001). Treating patients with type 2 DM and nephropathy with an ARB resulted in a reduction in the composite endpoint

of doubling of serum creatinine, progression to end-stage renal disease, and all-cause mortality when compared to placebo (Brenner et al., 2001; Lewis et al., 2001).

- 3. Patients with HTN and type 2 DM with microalbuminuria experienced a significant reduction in the primary endpoint of time to onset of overt DN with an ARB compared to placebo (Parving et al., 2001).
- 4. Compared to treatment with a beta-blocker, an ARB reduced the composite endpoint of cardiovascular death, MI, and stroke in a subgroup of patients with DM, HTN and left ventricular hypertrophy (Lindholm et al., 2002).
- 5. Few studies have evaluated the effects of ARBs, ACEIs, or their combination. In one study of patients with HTN, type 2 DM, and microalbuminuria, BP and urinary albumin excretion were reduced with the ARB, the ACEI, and further reduced with the combination. However, there are no long-term safety or efficacy studies showing that this combination offers specific advantages over other combinations of anti-hypertensive medications in patients with nephropathy.

Calcium Channel Blockers (CCB)

- 1. For patients with type 1 or 2 DM with proteinuria, the NCCB reduce proteinuria and provide renoprotection (Bakris et al., 1996; Kasiske et al., 1993; Salvetti et al., 1999; Vivian & Goebig; 2001).
- 2. Combination ACEI and NCCB may provide additive protection in patients with inadequate response to an ACEI alone (Bakris et al., 1998; Vivian & Goebig; 2001).
- 3. Use of long-acting dihydropyridine calcium channel blockers (DHPCCB) in the absence of an agent that blocks the renin-angiotensin system may worsen proteinuria and/or progression of renal disease (Lewis et al., 2001).
- 4. Studies with a long-acting DHPCCB in patients with HTN and type 2 DM showed an increased risk of major vascular events (Tatti et al., 1998) and a higher incidence of fatal and nonfatal MI (Estacio et al., 1998) compared to patients treated with an ACEI (Opie & Schall, 2002; Pahor et al., 2000).

Beta-Blockers

- 1. Treatment with captopril versus atenolol in patients with HTN and type 2 DM had similar effects on preventing the primary endpoints of macrovascular and microvascular complications (UKPDS 1998).
- 2. Beta-blockers offer clear benefits in patients after a MI and in some patients with congestive heart failure. Small changes in insulin sensitivity induced by beta-blockers should not be considered a contraindication to their use in patients with diabetes.
- 3. Beta-blockers may worsen insulin resistance. In hypertensive non-diabetic patients this may be associated with an increased risk for developing type 2 diabetes when compared with no treatment, thiazides, CCBs, or ACEIs (Gress et al., 2000). Some of this adverse effect on insulin resistance is not seen with beta-blockers that also contain alpha-blocking properties.

Diuretic

- 1. Dietary salt restriction and/or diuretics may counteract the tendency for volume expansion in patients with diabetes and may enhance BP lowering.
- 2. Diuretics enhance the anti-hypertensive and anti-proteinuric effects of ACEIs and may reduce the occurrence of hyperkalemia with ACEI, ARBs and beta-blockers.
- 3. Treatment with a diuretic resulted in a reduction in major cardiovascular disease rate compared to placebo, in both patients with and without DM. The absolute risk reduction was twice as great in patients with DM compared to those who did not have DM (Curb et al., 1996).

EVIDENCE

	Recommendation	Sources	QE	Quality	R
	GENERAL RE	ECOMMENDATIONS			
1	Treatment of HTN in patients with diabetes to retard progression of macrovascular complications and DM.	Hansson et al., 1998 UKPDS , 1998 ALLHAT 2003	Ι	Good	A
2	Target BP of <140/80 mm Hg for patients with diabetes with HTN, due to high-risk for cardiovascular disease.	Group Consensus	III	Poor	С
3	Consideration of lower BP targets (<125/75 mm Hg) to slow the progression of renal disease for patients with diabetes with elevated serum creatinine and/or urinary protein excretion above 1 g/day.	Lazarus et al., 1997 UTIC RECOMMENDATIO	II-2	Fair	В
4			I	Good	٨
4	Antihypertensive therapy with thiazide diuretic or ACEI for patients with diabetes with BP >140/80 mm Hg. Switch to ARB if ACEI-induced side-effects occur, then use other agents to achieve BP target <140/80 mm Hg.	Anderson et al., 2000 Hansson et al, 1998 Investigators, 2000 Lacourciere et al., 2000 Lindholm et al., 2002 Mogensen et al., 2000 Muirhead et al., 1999 Nielsen et al., 1997	1	Good	A
	SPECIFIC THERAPE	UTIC RECOMMENDATION	NS	<u> </u>	
5	ACEI for normotensive patients with type 1 DM and proteinuria and for patients with type 2 DM and microalbuminuria or a high- risk for cardiovascular disease.	HOPE Study Investigators, 2000 Lewis et al., 1993	I	Good	A
6	Consideration of ACEI for normotensive patients with type 1 DM.	Laffel et al., 1995 Viberti et al., 1994	Ι	Fair	В
7	Treatment with ARBs for patients with type 2 DM and nephropathy, microalbuminuria, or HTN and left ventricular hypertrophy.	Brenner et al., 2001 Lewis et al., 2001 Lindholm et al., 2002 Mogensen et al., 2000 Parving et al., 2001	I	Good	A
8	Combination ACEI and NCCB to provide renal protection in patients with inadequate response to an ACEI alone.	Bakris et al., 1998 Vivian & Goebig, 2001	II-2	Fair	В
9	Diuretics to enhance the BP lowering effects of other antihypertensive agents.	Brenner et al., 2001 Curb et al., 1996 Lewis et al., 2001 Lindholm et al., 2002	Ι	Good	A
		UTIC CAUTIONS	•		
10	Use caution in prescribing long-acting DHCCBs without an ACEI or ARB because of the risk of less renal protection and/or adverse cardiovascular outcomes.	Estacio et al., 1998 Lewis et al., 2001 Opie and Schall, 2002 Pahor et al., 2000 Tatti et al., 1998	Ι	Good	A

QE = Quality of Evidence; R = Recommendation (see Appendix E)

C2: Kidney Disease

OBJECTIVE

To provide recommendations on pharmacologic therapy for renal preservation in patients kidney disease, regardless of blood pressure level.

BACKGROUND

Kidney disease is a recognized complication of HTN, which is the second most common cause of end-stage renal disease (ESRD) in the USA. Patients with CKD frequently have HTN and other comorbid conditions such as heart failure, diabetes, and atherosclerosis (USRDS 2003). CKD and HTN are both independent risk factors for cardiovascular events. Patients with CKD and HTN often require multiple blood pressure medications to achieve target blood pressure (Wright, 2000; Barkis, 2000). The general approach to managing these patients is found in the main body of this guideline. The purpose of section is to help providers preserve their patients' kidney function, slow progression of kidney failure, and reduce incidence of (ESRD), an important goal of Healthy People 2010. Patients with ESRD have reduced lifespan and higher rates of CV complications and hospitalization. Annual costs for dialysis exceed \$60,000 per patient, and the waiting list for kidney transplants continues to grow (USRDR, 2003). Although good cost effectiveness data are lacking, preserving kidney function may provide significant advantages in terms of patients' quality and duration of life, reduced health care costs, and reduced organ shortage.

RECOMMENDATION

- 1. ACEI may be preferred agent for patients with HTN and kidney disease (reduced kidney function with proteinuria). ARB may be substituted for patients with ACEI-induced cough.
- 2. In African Americans with hypertensive kidney disease, ACEI may be a first line therapy for treating HTN.
- 3. A diuretic should be used when a second blood pressure medication is needed, or if hyperkalemia occurs. Thiazide diuretic may be used if estimated GFR > 30 cc/min/1.73m², but loop diuretics are usually needed for lower kidney function. Potassium-sparing diuretics should be avoided in patients with CKD.
- 4. A stable increase of serum creatinine as much as 35% above baseline after ACEI or ARB initiation may be tolerated, as long as hyperkalemia does not occur. ACEI or ARB should be discontinued, or other potentially reversible causes of kidney failure investigated if progressive and rapid rise of serum creatinine continues. Since CKD is associated with progressive rise in creatinine over years, ACEI or ARB should not be discontinued for this situation, since these medications are renoprotective.
- 5. When treating HTN in patients with non-diabetic kidney disease, use of combined therapy with ACEI and ARB may offer more renoprotection than with either class of medication alone.
- 6. Avoid potential nephrotoxic medications such as NSAIDs, COX2 inhibitor, aminoglicosides, IV contrast, and excessive diuretic use.
- Monitor kidney function over time by estimating GFR or Clcr. Consider consulting with a nephrologist if a non-diabetic patient has nephrotic range proteinuria, or kidney function is < 30 cc/min/1.73m².

DISCUSSION

There is good evidence that certain classes of antihypertensive medications improve kidney outcomes in patients with DM type 1 (ACEI), DM type 2 (ARBs), and non-diabetic kidney disease with significant proteinuria (ACEI, ACEI/ARB combination). However, optimal doses or combinations have not been established in all types of kidney diseases. There is little experimental evidence that a lower BP target (<130/80 mm Hg) results in better kidney outcomes than the usual BP target (<140/90 mm Hg) in

hypertensive patients with renal disease. However, many consensus-based guidelines still recommend lower BP targets based on associative and subgroup analysis.

EVIDENCE

	Recommendation	Sources	QE	Overall Quality	R
1	ACEI for treating HTN. in African Americans patients	Wright et.al., 2002 [AASK]	Ι	Good	А
2	ACEI more effective in patients with HTN and kidney disease	REIN GISEN, 1997 Jafar et al., 2001	Ι	Good	А
3	ACEI and ARB may offer more renoprotection than with either class of medication alone in patient with nondiabetic kidney disease	COOPERATE	Ι	Good	A

QE = Quality of Evidence; R = Recommendation (see Appendix E)

Estimated Glomerular Filtration Rate (eGFR)

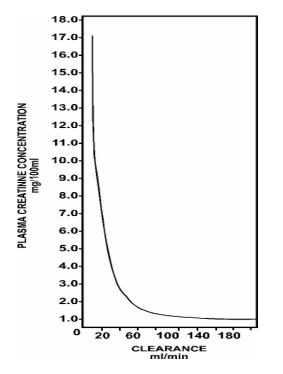
Serum creatinine level should be used to estimate the GFR to identify patients at risk and develop appropriate management plans.

Abnormalities of urinalysis or reduced renal function identify patients with kidney disease (see Table C-2.1). Patients with chronic kidney disease are at risk for progressive loss of kidney function. Most clinicians first identify patients with abnormal kidney function when serum creatinine (Scr) is elevated on routine laboratory testing. However, as Exhibit R2 demonstrates, significant reduction in kidney function is required before the Scr rises significantly. Also, patients with baseline Scr in the lower range of normal may lose significant amounts of kidney function before the Scr increases above the normal range (typically >1.2 mg/dL in females and > 1.5 mg/dL in males). Therefore, Scr alone is not a good test.

Table C-2.1. Definition of Chronic Kidney Disease Criteria

	Chronic Kidney Disease Criteria					
1.	Kidney damage for ≥ 3 months, as defined by structural or functional					
	abnormalities of the kidney, with or without decreased GFR, manifest					
	by either:					
	 Pathological abnormalities; OR 					
	• Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in					
	imaging tests					
2.	GFR <60 mL/min1.73m ² for \geq 3 months, with or without kidney					
	damage					

Exhibit C2. Creatinine Clearance Plotted Against Serum Creatinine Concentration Graph (Schrier, 1976)



The graph plots the creatinine clearance against serum creatinine concentration. It illustrates the lack of sensitivity of the serum creatinine level as a test for loss of renal function. For every 50 percent reduction in GFR (approximated by the creatinine clearance rate), the serum creatinine concentration approximately doubles. Waiting to aggressively treat the condition until the serum creatinine level rises is not likely to prevent end-stage renal disease, but rather just delay the need for dialysis a few more months (Bennett et al., 1995).

Measuring creatinine clearance (Clcr) or estimating Clcr or GFR by calculation formulas can be used to monitor abnormal kidney function. Measuring Clcr by 24-hour urine collection has been the traditional method for estimating GFR. However, collection inaccuracies and patient difficulties make this test unsatisfactory. Estimation of Clcr or GFR using routine clinical information is now recommended for estimating and monitoring kidney function. Cockroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) formulas are acceptable tools for estimating Clcr and GFR, respectively. CG is a simple formula that has been in use for over 2 decades. The MDRD formula is more precise, and online calculators are available.

Kidney Function Estimation Formulas:

- CG formula (estimated Clcr in cc/min): [(140 - age)/Scr (mg/dL)] x [wt (kg) /72] x 0.85 (if female)
- MDRD formula (estimated GFR in ml/min/1.73 m²):

Estimated GFR = $186 \text{ x} (S_{cr})^{-1.154} \text{ x} (Age)^{-0.203} \text{ x} (0.742 \text{ if female}) \text{ x} (1.210 \text{ if African - American})$

http://www.nkdep.nih.gov/healthprofessionals/tools/gfr_adults.htm

The National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI Clinical Practice Guidelines for Kidney Diseases) has developed a staging system for grading kidney disease (see table below). These stages can be used to monitor and educate patients, assess impact of management, and assist the primary provider in coordinating care with specialists and making plans for ESRD care.

Stage	Description	GFR	Action*	
_		$(mL/min/1.73m^2)$		
	At increased risk	<u>></u> 90	Screening,	
		(with CKD risk factors)	CKD risk reduction	
1	Kidney damage with	<u>></u> 90	Diagnosis and treatment,	
	Normal or \uparrow GFR		Treatment of comorbid conditions,	
			Slowing progression,	
			Cardiovascular disease risk reduction	
2	Kidney damage	60 - 89	Estimating progression	
	with Mild \downarrow GFR			
3	Moderate	30 - 59	Evaluating and treating complications	
4	Severe \downarrow GFR	15 - 29	Preparation for kidney	
			replacement therapy	
5	Kidney failure	<15	Replacement (if uremia present)	
		(or dialysis)		

Table C2-2. Chronic Kidney Disease (CKD): A Clinical Action Plan

Shaded area identifies patients who have chronic kidney disease; unshaded area designates individuals who are at increased risk for developing chronic kidney disease. Chronic kidney disease is defined as either kidney damage or GFR, <60 mL/min/1.73 m² for \geq 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. *Includes actions from preceding stages.

C3: Chronic Heart Failure (HF)

OBJECTIVE

To provide recommendations on pharmacologic therapy for patients with HTN and concomitant chronic heart failure (HF) due to systolic dysfunction.

BACKGROUND

Treatment of chronic heart failure (HF) is based upon the classification of HF into four stages: (Hunt et al., 2001) Stage A includes patients who are at high risk for developing HF, but do not have structural heart disease; Stage B are patients who do have structural damage to the heart, but have not developed symptoms; Stage C refers to patients with past or current HF symptoms and evidence of structural heart damage; and Stage D includes patients with end-stage disease, requiring special interventions. It is the intent of the recommendations to be used in conjunction with the NYHA functional classification that estimates the severity of disease based on patient symptoms.

Table C3.1. NYHA Functional Classification and Objective Assessment of HF^a

FUNCTIONAL CAPACITY
Class I No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina.
Class II: Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
Class IV: Unable to carry on any physical activity without discomfort. Symptoms are present atrest. With any physical activity, symptoms increase.

^a Adapted from the Criteria Committee of the American Heart Association. 1994 revisions to the classification of functional capacity and objective assessment of patients with disease of the heart. Circulation 1994;90:644-5.

The recommendations in this annotation refer to patients with Stage C HF (e.g., patients with past or current HF symptoms and evidence of structural heart damage).

Many of the classes of medications used to treat patients with hypertension have also been shown to provide benefit in patients with chronic heart failure. , If the patient continues to have an elevated blood pressure despite optimal treatment for HF based on the following recommendations, additional antihypertensive medications should be initiated (except for NCCBs or nifedipine) to achieve blood pressure goal.

RECOMMENDATIONS

- 1) A diuretic should be used in the treatment of patients with signs of fluid overload.
- All patients should be treated with an ACEI unless contraindicated or not tolerated. These agents improve HF symptoms, functional status, and quality of life, while decreasing frequency of hospitalization and mortality.
- 3) A beta-adrenergic blocker should be used in conjunction with an ACEI in all patients who are considered stable (i.e., minimal or no signs of fluid overload or volume depletion and not in an intensive care unit), unless contraindicated or not tolerated. These agents have been shown to reduce mortality and decrease the symptoms of HF.

- An ARB should be considered as an alternative to an ACEI in patients who are on a diuretic, betaadrenergic blocker, and usually digoxin and are unable to tolerate an ACEI due to cough or possibly, angioedema.
- 5) The combination of hydralazine and isosorbide dinitrate (HYD/ISDN) may be considered as an alternative to an ACEI in patients who are on a diuretic, beta-adrenergic blocker, and usually digoxin and are unable to tolerate an ACEI due to hypotension, renal insufficiency, or possibly, angioedema.
- 6) Digoxin (although not effective for the treatment of HTN) should be used in patients whose symptoms persist despite treatment with an ACEI, a beta-adrenergic blocker, and a diuretic. Digoxin reduces symptoms associated with HF and decreases the risk for hospitalizations due to HF but does not improve mortality.
- 7) Low dose spironolactone (an aldosterone antagonist) should be considered in patients with recent New York Heart Association (NYHA) Class IV HF and current Class III or IV symptoms and left ventricular ejection fraction (LVEF) ≤ 35%, provided the patient has preserved renal function and normal potassium levels. This therapy improves symptoms (as assessed by change in NYHA functional class), decreases hospitalizations for worsening HF, and decreases mortality.

	Recommendation	Sources	QE	Overall Quality	R
1	Diuretic in patients with signs of	Patterson et al 1994	Ι	Fair	В
	fluid overload	Parker 1993	Ι		
		Richardson et al 1987	Ι		
		Hunt et al 2001	III		
2	ACEI for all patients unless	Captopril-Digoxin 1988	Ι	Good	A
	contraindicated/not tolerated	SOLVD 1991	Ι		
		Cohn et al 1991	Ι		
		CONSENSUS 1987	I		
		Garg et al 1995	II-2		
		Hunt et al 2001	III		
3	Beta-adrenergic blocker in	MERIT-HF 1999	Ι	Good	A
	conjunction with an ACEI in all	CIBIS-II 1999	Ι		
	stable patients unless	Packer et al 1996	Ι		
	contraindicated/not tolerated	Packer et al 2001, 2002	Ι		
		Leizorovicz et al 2002	II-2		
		Shibata et al 2001	II-2		
		Hunt et al 2001	III		
4	ARB should be alternative to an	Cohn et al 2001	Ι	Good	Α
	ACEI in patients on a diuretic,	Granger et al 2003	Ι		
	beta-adrenergic blocker, and	McMurray et al 2003	Ι		
	usually digoxin and are unable to	Pfeffer 2003	Ι		
	tolerate an ACEI	Hunt et al 2001	III		
5	HYD/ISDN as alternative to an	Cohn 1986	Ι	Fair	В
	ACEI in patients on a diuretic,	Cohn 1991	Ι		
	beta-adrenergic blocker, and				
	usually digoxin and are unable to				
	tolerate an ACEI				
6	Digoxin in patients with	Digitalis Investigation	Ι	Good	А
	symptoms despite an ACEI, beta-	1997	Ι		
	adrenergic blocker, and diuretic	Captopril-Digoxin 1988	II-2		
		Jaeschke et al 1990			
7	Aldosterone antagonist in	Pitt et al (RALES) 1999	Ι	Good	Α
	patients with severe HF unless				
	contraindicated/not tolerated				

EVIDENCE

QE = Quality of Evidence; R = Recommendation (see Appendix E)

DISCUSSION

Goals of therapy for HF include improved symptoms, increased functional capacity, improved quality of life, slowed disease progression, decreased need for hospitalization, and prolonged survival.

Risk factor modification should be implemented in patients in Stage A (e.g., patients at high risk for developing HF, but do not have structural heart disease) to potentially reduce the development of HF.

In addition to risk factor modification, patients with HF in Stage B (e.g., patients who do have structural damage to the heart, but have not developed symptoms) should receive post-MI (refer to Annotation on Post-MI) treatment with an ACEI and beta-adrenergic blocker, regardless of the presence of left ventricular systolic dysfunction, to prevent future development of HF and improve overall survival. It is also recommended that patients with evidence of left ventricular systolic dysfunction who are without symptoms should be treated with an ACEI and beta-adrenergic blocker (Hunt et al, 2001).

The recommendations in this annotation refer to patients with Stage C HF (e.g., patients with past or current HF symptoms and evidence of structural heart damage). Patients with Stage D HF (e.g., patients with end-stage disease) require special interventions and should be referred to a specialist in the management of HF.

Diuretic Therapy

There have been no long-term controlled clinical trials evaluating the effectiveness of loop or thiazide diuretic therapy in patients with HF (Hunt et al, 2001). The majority of patients enrolled in long-term trials demonstrating a decreased morbidity or mortality with an ACEI or beta-adrenergic blocker therapy, were also receiving a diuretic (Hunt 2001).

Patients with HF may have symptoms that interfere with their daily activities and, therefore, impact on their quality of life. Patients with symptoms of fluid overload benefit from treatment with a diuretic in conjunction with an ACEI and beta-adrenergic blocker (Hunt 2001), and possibly digoxin (Young et al., 1998).

Loop diuretics are most commonly used for patients with HF and volume overload. They are effective in patients with renal insufficiency or creatinine clearance (CrCl) < 30 mL/min, whereas the effectiveness of thiazides are diminished in patients with CrCl < 30 mL/min (Hunt 2001, AHCPR 1994). Edema resistant to large doses of loop diuretics may intermittently require combined diuretic therapy (Hunt 2001)., although combination diuretic therapy requires close monitoring. Refer to PBM-MAP The Pharmacologic Management of Chronic Heart Failure at www.vapbm.org or http://www.oqp.med.va.gov for recommendations on dosing and monitoring of diuretics in patients with HF.

ACEIs

In addition to improving HF symptoms and functional status (Captopril Multicenter Research Group 1983, Sharpe et al 1984, Chalmers et al 1987, Lechat et al 1993), treatment with an ACEI has been shown to decrease the frequency of hospitalizations and mortality rate (Captopril-Digoxin Multicenter Research Group 1988, SOLVD Investigators 1991, Cohn et al 1991, CONSENSUS Trial Study Group 1987, Garg et al 1995).

It is recommended that an ACEI be offered to all patients with reduced left ventricular systolic dysfunction unless the patient has specific contraindications (Hunt 2001).

Doses should initially be low and then titrated upward over several weeks to the maximum dose tolerated, with the target doses based on those used in large scale clinical trials. Despite the overwhelming evidence in favor of treating HF patients with ACEIs and that a large majority of patients are able to tolerate high

doses, these agents are often underutilized, and frequently at low doses, although this may depend on the clinical setting.

Due to the strong evidence for the beneficial effects of ACEIs in patients with HF, every effort should be made to adjust the dosage before a patient is documented as intolerant. If the cough is not bothersome, the benefits of continuing the ACEI should be discussed with the patient.

Refer to PBM-MAP The Pharmacologic Management of Chronic Heart Failure at <u>www.vapbm.org</u> or <u>http://www.oqp.med.va.gov</u> for a discussion of the evidence for ACEI in patients with HF and for recommendations on dosing and monitoring.

Beta-Adrenergic Blockers

Numerous trials have shown the beneficial effects of beta-adrenergic blockers in reducing symptoms, hospitalization, and progression of disease in patients with HF due to systolic dysfunction (Hunt 2001, Waagstein et al 1993, CIBIS Investigators and Committees 1994, Colucci et al 1996, Australia/New Zealand Heart Failure Research Collaborative Group 1997, Packer et al 1996, Bristow et al 1996, Cohn et al 1997). However, more recent evidence has demonstrated a significant reduction in mortality with the use of beta-adrenergic blockers in this patient population (MERIT-HF Study Group 1999, CIBIS-II Investigators and Committees 1999, Packer et al 1996, Packer et al 2001, Packer et al 2002, Leizorovicz et al 2002, Shibata et al 2001). The beta-adrenergic blockers that have been studied for chronic HF and have demonstrated a clear reduction in mortality include bisoprolol, carvedilol and metoprolol. Other beta-adrenergic blockers may have similar benefit, however definitive studies evaluating other beta-adrenergic blockers are lacking. Patients with stable HF due to systolic dysfunction, with appropriate volume control and adequate afterload reduction, should receive therapy with a beta-adrenergic blocker unless contraindicated. It is important that patients with HF on a beta-adrenergic blocker are titrated carefully to a target dose as used in clinical trials or as tolerated.

The majority of patients included in the beta-adrenergic blocker trials received therapy with an ACEI. Survival benefit in the ACEI trials ranged from 12 to 33%, which was mainly a result of reduction in deaths from worsening HF. Meta-analyses of the beta-adrenergic blocker trials show a reduction in mortality of approximately 30 to 35% (Doughty et al 1997, Heidenreich et al 1997, Lechat et al 1998, Brophy et al 2001). It is felt that the use of an ACEI and beta-adrenergic blocker in patients with HF is synergistic and should be used in combination whenever possible (Hunt 2001).

Refer to PBM-MAP The Pharmacologic Management of Chronic Heart Failure at <u>www.vapbm.org</u> or <u>http://www.oqp.med.va.gov</u> for a discussion of the evidence for beta-adrenergic blockers in patients with HF and for recommendations on dosing and monitoring.

Angiotensin II Receptor Antagonists (AIIRAs)

The AIIRAs (also referred to as ARBs) have yet to be shown to be equivalent or superior to the ACEIs in patients with HF (Pitt et al 2000). According to a meta-analysis of 12,469 patients, the ARBs were not found to be superior to an ACEI in reducing mortality or hospitalizations. There was a trend toward improved mortality and hospitalizations with an ARB compared to placebo in patients not on an ACEI, and the combination of an ARB and ACEI significantly reduced the risk of hospitalizations compared to patients on an ACEI alone (Jong et al 2002). In a previous meta-analysis of 1,896 patients, an ARB contributed to a mortality benefit compared to a control group of either placebo or an ACEI, but this meta-analysis did not include the more recent outcome trials with an ARB in patients with HF (Sharma et al 2000).

In the Valsartan Heart Failure Treatment (Val-HeFT) trial of patients with HF receiving an ACEI (with approximately one-third on a beta-adrenergic blocker), overall mortality was similar in patients on an ARB compared to placebo. The combined primary endpoint of mortality and morbidity (i.e., cardiac arrest with resuscitation, HF hospitalization, or intravenous inotropic agents or vasodilators for over 4 hours) was

significantly lower in patients on an ARB. According to a subgroup analysis, there was an increased risk of mortality and a trend toward an increased risk of combined morbidity and mortality in patients receiving an ARB in conjunction with an ACEI and beta-adrenergic blocker. Patients who were not on an ACEI or beta-adrenergic blocker experienced a significant reduction in mortality. Patients on an ARB but not on an ACEI (with or without a beta-adrenergic blocker) had a lower risk of death and a lower risk of the combined endpoint (Cohn et al 2001). A subanalysis of the patients who were not on an ACEI showed that there was a significant decrease in all-cause mortality and combined morbidity and mortality (Maggioni et al 2002).

In another study with an ARB, the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program, use of an ARB decreased cardiovascular death and HF hospitalizations when used in patients who were ACEI intolerant (CHARM-Alternative) (Granger et al 2003). According to the results of CHARM-Added, where an ARB was added to therapy with an ACEI (with approximately half on a beta-adrenergic blocker), there was also a decrease in cardiovascular death and HF hospitalizations (McMurray et al 2003). All-cause mortality was not significantly reduced with an ARB in either of these studies (Granger et al 2003, McMurray et al 2003, Pfeffer 2003).

Since the benefits of an ACEI in conjunction with a beta-adrenergic blocker is well-defined, an ARB should not be prescribed prior to an ACEI but should considered if the patient is intolerant to an ACEI.

Refer to PBM-MAP The Pharmacologic Management of Chronic Heart Failure at <u>www.vapbm.org</u> or <u>http://www.oqp.med.va.gov</u> for a discussion of the evidence for ARBs in patients with HF and for recommendations on dosing and monitoring.

Hydralazine/Isosorbide Dinitrate

Patients with contraindications to or who cannot tolerate an ACEI present a dilemma since ACEIs are the preferred agents for afterload reduction. While no studies have specifically addressed the combination of HYD/ISDN in patients with HF who cannot tolerate ACEIs, treatment with HYD/ISDN has been shown to reduce mortality by two years compared to placebo (Cohn 1986). A similar mortality rate was found in another study in HF patients (majority with NYHA class II or III HF) treated with HYD/ISDN compared with an ACEI, although mortality after two years was lower in patients treated with an ACEI compared with patients on HYD/ISDN (Cohn 1991). Therefore it is reasonable to consider the combination HYD/ISDN as an alternative to an ACEI in patients who are on a diuretic, beta-adrenergic blocker, and usually digoxin and are unable to tolerate an ACEI due to hypotension, renal insufficiency, or possibly, angioedema.

Refer to PBM-MAP The Pharmacologic Management of Chronic Heart Failure at <u>www.vapbm.org</u> or <u>http://www.oqp.med.va.gov</u> for recommendations on dosing and monitoring HYD/ISDN in patients with HF.

Digoxin

Digoxin continues to have a role in the treatment of patients with HF by improving patient symptoms and decreasing hospitalizations and not adversely affecting survival (Digitalis Investigation Group 1997, Captopril-Digoxin Multicenter Research Group 1988). According to a meta-analysis, treatment with digoxin in patients with HF due to systolic dysfunction can reduce the incidence of clinical deterioration by 12% compared to patients on placebo (Jaeschke et al 1990). Two trials found that patients experienced worsening HF when treatment with digoxin was withdrawn (Packer et al 1993, Uretsky et al 1993).

Digoxin is recommended in patients with symptomatic HF, without bradycardia, to improve clinical status and thereby decrease the risk of hospitalization due to HF. Treatment is usually initiated in conjunction with a diuretic, ACEI, and beta-adrenergic blocker since these latter two classes of agents have been shown to improve survival in patients with HF (Hunt 2001). If there is no symptomatic improvement after one to two months of therapy, the risk vs. benefit of continued digoxin therapy should be considered.

Refer to PBM-MAP The Pharmacologic Management of Chronic Heart Failure at <u>www.vapbm.org</u> or <u>http://www.oqp.med.va.gov</u> for recommendations on dosing and monitoring digoxin in patients with HF.

Aldosterone Antagonists

Evidence has shown that addition of a low dose of an aldosterone antagonist in patients with severe HF (recent NYHA class IV HF and current class III or IV symptoms and LVEF $\leq 35\%$) who were already on treatment with an ACEI, resulted in a 30% reduction in the risk of death due to progressive HF and sudden death of a cardiac cause, and in a 35% decrease in hospitalizations due to worsening HF. Patients also experienced a significant improvement in symptoms resulting in some patients dropping into a lower NYHA class (Pitt et al 1999).

These are highly complex patients with a high mortality rate and should be cared for by a multidisciplinary HF team including a primary care provider in consultation with a cardiologist. The risk vs. benefit of using spironolactone in these patients needs to be determined. Spironolactone may contribute to serious hyperkalemia if not used properly in patients with HF. Potassium should be monitored closely in these patients.

Refer to PBM-MAP The Pharmacologic Management of Chronic Heart Failure at <u>www.vapbm.org</u> or <u>http://www.oqp.med.va.gov</u> for recommendations on dosing and monitoring spironolactone in patients with HF.

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C4: Stroke Prevention

BACKGROUND

Hypertension increases the risk for stroke, with observational studies on over 418 thousand persons noting a linear relationship between blood pressure and stroke risk (MacMahon, Lancet, 1990, Collins, Lancet 1990). These population studies demonstrated that each 5 mm Hg increase in diastolic blood pressure increases stroke risk by about one third (Collins, 1994). In randomized intervention trials, with nearly 48,000 individuals, the estimated overall reduction in stroke risk was slightly better, at about 38% (Collins 1994) for each 5 - 6 mm Hg decrease in blood pressure.

RECOMMENDATIONS

- 1. When an ACEI is used as principal therapy after stroke, a thiazide (or similar) diuretic should be used to assure maximal effect (A)
- 2. Diuretics remain a principal agent for risk reduction after stroke or TIA based on data on primary prevention studies and extrapolation from the PROGRESS trial on secondary prevention (Primary prevention of stroke A; Secondary prevention B)
- 3. Alternatives (in alphabetical order) include ACEI/ARB, beta-blockers, dihydropyridine (longacting) or diltiazem calcium channel blockers (Primary prevention I, A; Secondary prevention B).
- 4. In post-stroke patients with pre-hypertension, the addition of an ACEI may be considered but should be with a diuretic, as noted above (level of evidence for secondary prevention A). An ACEI may provide additional benefit to existing antihypertensive therapies or for patients who are not hypertensive for primary stroke protection (Primary prevention: A).

DISCUSSION

Patients who have had a stroke have a higher risk than those enrolled in primary prevention trials (Burn). Earlier non-randomized studies suggest that the relative risk of subsequent stroke is lowered by about 40% in patients who have their blood pressure reduced (Carter, 1970) with greater reductions in risk (50% to 75%) seen in patients with good control (Carter, 1970; Beevers, 1973, Alter). In the immediate stroke period, though, blood pressure is frequently elevated but unless considered clinically necessary, intervention in the peri- and early post-stroke period (within 1 to 2 weeks) should be avoided, as this may promote hypoperfusion (Lavin). Almost two-thirds of patients will normalize their blood pressure within about 10 days after a stroke (Harper, Wallace).

In terms of treatment regimens it is unclear if results from primary prevention trials are applicable to secondary prevention remains but there is no theoretical reason that that should not be the case. Unfortunately, evidence on post-stroke treatment of hypertension is generally lacking. Available studies include PROGRESS trial, and there are preliminary results available from the Post-Stroke Antihypertensive Trial or the PATS trial which took place in China (Anon. Abstract available, final results never published). The PROGRESS study, which actually randomized to 2 large patient groups (active treatment (n=3051), defined as combination therapy with perindopril and indapamide or single drug therapy with perindopril alone; and placebo treatment (n=3054), defined as placebo or double placebo), included 6105 patients with a history of stroke or TIA in the prior 5 years and who were clinically stable for at least 2 weeks following that event. They were followed for a mean of about 4 years. The study found that perindopril plus diuretics reduced stroke incidence compared to placebo from 14% to 8.5% with the relative risk of stroke reduced by 43% (95% CI, 30-54) whereas perindopril alone (compared to placebo) did not significantly reduce risk (95% CI of relative risk, -19 to 23). When the active treatment group (perindopril alone and perindopril plus indapamide groups, together) was compared to the placebo group (single and double placebo groups, together), the overall relative risk reduction on stroke was 28% (95% CI, 17-38%) or from 14% to 10% (absolute risk reduction of 4%). However, it appears that when the two subgroups were put together, the large positive effect from the combined therapy group overcame the non-effect in the single therapy group (i.e., an averaging out between effect and non-effect).

In PROGRESS, the authors concluded that combination therapy with the above agents should be "considered routinely for patients with a history of stroke or transient ischemic attack, irrespective of their blood pressure." There are two concerns with this conclusion: 1. since perindopril alone had no effect compared to placebo, one interpretation of the results is that the principal effect of combination was merely due to addition of a diuretic to the ACEI (Tirschwell); 2. the authors utilized a randomization scheme that could be construed as designing not one but two trials (randomizing first to active and placebo groups and then randomizing within groups to either one of two active treatments or one of two placebo subgroups), making comparisons across subgroups (e.g. combination therapy versus double placebo) concerning from a methodological standpoint (ACP Journal Club).

Other trials that support that the principal effect may be due to a diuretic rather than the ACEI including PATS (abstract available, final results never published) which included 5,665 patients randomized patients who had had stroke or transient ischemic attack to indapamide or placebo, with initial average systolic blood pressure (SBP) of 154 mm Hg and DBP of 93 mm Hg. Three year average SBP was 149 mm Hg for the placebo group and 144 mm Hg for the indapamide treatment group and three year DBP was 89 mm Hg and 87 mm Hg respectively. Three year incidence of fatal and non-fatal stroke was 12.3 vs. 9.4 per 100 patients with a relative risk reduction of 29% (P =0.0009) though mortality was not significantly impacted (RR =.91, P > 0.05). Most recently, ALLHAT found that diuretics reduced stroke by a relative risk of 15% (95% CI, 2 to 30%) compared to an ACEI (ALLHAT) with the absolute incidence over 6 years of 5.6 per 100 patients versus 6.3 per 100 patients. More generally, these results are supported by numerous primary prevention studies with diuretics (Collins, MacMahon, Messerli, Psaty). Furthermore, the Captopril Prevention Project (CAPPP) study that found that captopril did not have the same benefit on primary stroke reduction as diuretic/beta-blockers with an absolute risk increase from 2.7% to 3.4% (relative risk increase 25%, (95% CI 1- 55%).(Hansson 1999).

On the other hand, HOPE which added ramipril to existing regimens in high risk patients with vascular disease, found a risk reduction for stroke of 4.9% to 3.4% (relative risk reduction or RRR, 32%;95% CI, 56% to 84%) (Yusuf), though to some degree the effect is obscured by the additional blood pressure lowering in the ramipril group compared to the placebo group. Results from ANBP2 suggest that ACEI and diuretics had a non-significant difference in the rate for stroke of 9.2 versus 8.8 per 1000 patient years (P = .91) and STOP-2 found no difference in outcomes for stroke rates when using older drugs (diuretics and beta-blockers) or newer agents (ACEI and calcium channel blockers) (Hansson 1999). Finally, the LIFE trial results in patients with hypertension and left ventricular hypertrophy (LVH), with primary endpoint (composite CV death, MI, stroke, found that fatal and non-fatal stroke incidence was less with losartan than with atenolol with an absolute risk reduction (ARR) of 1.7% (P=0.001). However, it is somewhat contentious as to whether beta-blockers alone are sufficient for reduction in stroke mortality (versus diuretics) as Messerli and colleagues pointed out in their meta-analysis of 10 trials involving over 16,000 older (60 years of greater) patients. The findings suggested that diuretics were more effective in preventing cerebrovascular disease (odds ratio .61, 95% CI, 0.51 to 0.72) and fatal stroke (odds ratio 0.67, 95% CI, 0.49 to 0.90) (Messerli) which has also been supported by other recent meta-analyses by Psaty et al and by the Blood Pressure Lowering Treatment Trialists (Psaty, Blood Pressure Lowering Trialists).

Taken as a whole, the data for ACEIs are mixed and conflicting across subgroups and studies (and the data for ARBs, though promising, requires verification), and the benefit for primary prevention compared to diuretic therapy (or beta-blockers) is not clear, as noted in the overview by the Blood Pressure Lowering Treatment Trialists (Blood Pressure Lowering Treatment Trialists) and by Psaty et al (Psaty) in their meta-analysis More specifically, for secondary prevention, PROGRESS found that when an ACEI is considered for secondary prevention it should be used in combination with a diuretic.

For calcium channel blockers, the stroke rate in ALLHAT for the diuretic and long-acting dihydropyridine calcium channel blocker groups was similar (95% CI for relative risk reduction, .82-1.06) (ALLHAT). Apart from ALLHAT, there is some conflicting evidence on the benefit of calcium channel blockers for primary prevention of stroke. The Nordic Diltiazem Study (NORDIL) noted a marginally significant benefit of diltiazem for primary stroke prevention when compared to conventional therapies (diuretic, beta-blocker) with fatal and non-fatal stroke incidence of 6.4 events per 1000 patient-years in the diltiazem group and 7.9 events in the diuretic/beta-blocker group, for a relative risk reduction of 20% (95% CI, 1 to

35%, P = .04) (Hansson 1999) though the Controlled Onset Verapamil Investigation of cardiovascular End Points (CONVINCE) trial, which was stopped prematurely, found that verapamil did not demonstrate equivalence to diuretic and beta-blocker based therapy – with the difference in stroke rates not statistically significant (hazard ratio 1.15, 95% CI .90-1.48). (Black). An earlier randomized study found that in patients 60 years and older with isolated systolic hypertension (ISH), an active treatment group (n = 2398) utilizing nitrendipine (an intermediate-acting dihydropyridine calcium-channel blocker not available in the United States) alone or in combination with enalapril and/or hydrocholorthiazide reduced relative risk for stoke (non-fatal and fatal) compared to a group begun on placebo (but treatment commenced over time, using the same group of agents) by an absolute risk reduction of 5.8% (7.9 vs. 13.7), giving a relative risk reduction of 42%, though mortality did not differ between the groups (Staessen).

Overall, evidence on calcium channel blockers, especially dihydropyridine calcium channel blockers, suggests that benefits are similar to the benefits from diuretics for primary stroke prevention, as also noted by the Blood Pressure Lowering Treatment Trialists (Blood Pressure Lowering Treatment Trialists) and Psaty et al in their respective analyses. Data on secondary prevention is lacking.

Whether patients in pre-hypertension group require further blood pressure decreases is unknown although the HOPE trial suggested that primary stroke risk can be decreased by approximately 32% using an ACEI (ramipril). (HOPE). The PROGRESS trial findings on single drug therapy were not significant in non-hypertensives (95% CI for relative risk, -34 to 26%) though combination therapy did have a significant effect reducing absolute incidence rates from 11.7% to 6.9% (RRR = 42%, 95%CI, 19-58%) suggesting that such patients may benefit from additional blood pressure lowering, consistent with the findings noted above.

	Recommendation	Sources	QE	Overall Quality	R
1	In post-stroke patient using ACE I as principal therapy, a thiazide (or similar) diuretic should be used to assure maximal effect	PROGRESS 2001	Ι	Good	А
2	 Diuretics as a principal agent for risk reduction after stroke or TIA Primary prevention Secondary prevention 	ALLHAT, Blood Pressure Lowering Treatment Trialists, Psaty 2003, Collins 1994 PROGRESS 2001, PATS	Ι	Good	А
			III	Poor	С
3	Alternatives to diuretics (in alphabetical order): ACE-I/ARB, beta-blockers, dihydropyridine (long-acting) or diltiazem calcium channel blockers • Secondary prevention *	Yusuf 2000, Staessen (1997), Dhalof 2002, Psaty 2003, ALLHAT 2002, Hansson 1999, Hansson 1999, PROGRESS 2001,	III	Poor	С
4	ACEI may provide additional benefit to existing antihypertensive therapies or for primary stroke prevention In post-stroke patients with pre- hypertension, the addition of an	Yusuf 2000	Ι	Good	А
	ACEI for secondary prevention may be considered but should be with a diuretic	PROGRESS 2001	Ι	Good	А

EVIDENCE

QE = Quality of Evidence; R = Recommendation (see Appendix E)

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C5: High ambient temp and/or extreme conditions

BACKGROUND

There are special situations related to deployment and readiness when it comes to control of HTN and since conditions and physiologic responses may be quite different in extreme deployment conditions, the general recommendations for drug therapy need to be modified. As illustrated in the following table, for example, many drugs including diuretics and beta-blockers might have negative effects on the heat acclimatization process.

Drug or drug class	Proposed mechanism of action
Anticholinergics properties (Atropine)	Impaired sweating
Antihistamines	Impaired sweating
Gluthemide (Doriden [®])	Impaired sweating
Phenothiazines (a class of antipsychotic drugs,	Impaired sweating, (possibly) disturbed
including thorazine [®] , stelazine [®] , and trilafon [®])	hypothalamic temperature regulation
Tricyclic antidepressants, for example imipramine,	Impaired sweating, increased motor activity and
anitriptyline	heat production
Amphetamines, cocaine, "Ecstasy"	Increased psychomotor activity, activated vascular endothelium
Ergogenic stimulants, for example ephedrine/ephedra	Increased heat production
Lithium	Nephrogenic diabetes insipidus and water loss
Diuretics	Salt depletion and dehydration
Beta-blockers, for example propranolol and atenolol	Reduced skin blood flow and reduced blood
	pressure
Ethanol	Diuresis, possible effects on intestinal permeability

Table 4-1.	Drugs	implicated	in	intolerance	to	heat	stress
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It is critical for readiness that soldiers are able to acclimate quickly and safely when they arrive in theater. The process of heat acclimatization causes the following physiologic changes in the body, as noted in the Table below.

TB MED 507/AFPAM 48-152 (I)

Thermal Comfort Improved	Exercise Performance Improved
Core Tomporature Badward	
Core Temperature - Reduced	Cardiovascular Stability – Improved
Sweating – Improved	Heart Rate - Lowered
Earlier Onset	Stroke Volume – Increased
Higher Rate	Blood Pressure – Better Defended
Redistribution (Jungle)	Myocardial Compliance - Improved
Hidromeiosis Resistance	, and a second
(Jungle)	Fluid Balance - Improved
	Thirst - Improved
Skin Blood Flow - Improved	Electrolyte Loss (sweat and urine) -
Earlier Onset	Reduced
Higher Rate (Jungle)	Total Body Water - Increased
	Plasma (Blood) Volume - Increased and
Metabolic Rate - Lowered	Better Defended

For example, treatment with an anti-hypertensive agent, especially a diuretic, may interfere with some changes such as increasing total body water and plasma volume. This might prolong the process of heat acclimatization. It may also make the increased sweating and altered electrolyte loss associated with heat acclimatization more dangerous. The physiologic changes induced by heat acclimatization may also make certain anti-hypertensive agents, such as diuretics, less effective since they work counter the effect(s) of the drug. Unfortunately, there is minimal high quality evidence available on the effects of anti-hypertensive (and other) medications on heat acclimatization.

Our deployed population is increasingly older, with chronic medical conditions and on medication. Although we are thinking about hot and dry climates based on our recent Middle East experience, our military/veteran population also experiences cold, high altitude, high barometric pressure, and extended isolation.

Water/hydration recommendations have been modified during the years because hyponatremia is an important problem in addition to classic dehydration or hypernatremia. In fact, the evidence from the USNS Comfort's most recent deployment to the Persian Gulf in support of Operation Iraqi Freedom is that a high proportion of soldiers, sailors, marines, and Iraqis presented with hyponatremia. Also, the Walter Reed Army Institute of Research (WRAIR) currently is investigating the epidemic of hyponatremia, and updated recommendations for hydration and nutrition will be forthcoming.

The military medical infrastructure is geared toward acute medical and trauma care. Those with more permanent conditions or treatments that require monitoring or testing may not be deployable on a world-wide basis. When permanent medical conditions that require frequent monitoring arise acutely on a deployment, the patient is generally evacuated out of the theater of operations. For those with HTN on therapy under those conditions, decisions may come down to minimizing medications and letting BP run a little high vs. evacuating the patient out of the area.

Considerations for treatment of hypertension in the deployed environment:

- 1. Medical support Most soldiers are followed in their Battalion aid stations. Most aid stations have limited ability to do laboratory testing. The lowest level facility with the ability to do basic labs, such as blood chemistry, is a combat-support hospital. Depending on the tactical situation, this facility may be over 100 miles from the most forward troops. Moving from place to place usually requires an armed convoy of at least 2 vehicles and up 8 personnel. Every movement exposes the involved personnel to risk of attack. These considerations preclude the use of any medication that requires regular/frequent blood monitoring.
- 2. Environmental conditions It is not unusual for soldiers to be working outdoors (sun and shade) for an extensive time in temperatures over 120° F. Fluid loss due to medications may result in increased rates of dehydration. Soldiers also frequently work at altitudes over 5000 feet. In these cases, acclimatization to the altitude may cause additional diuresis. Soldiers deployed in cold weather conditions will also experience diuresis as part of their acclimatization process. Clinicians who care of Soldiers who face the possibility of deployment should use caution when prescribing medications that have a serious potential for affecting electrolyte balance because of the limited ability to monitor the patient. There is also concern about medications that limit maximum heart rate, as many of the Soldiers are involved in physically demanding work. Limiting their ability to increase cardiovascular output may increase their risk of environmental injury and compromise their capacity to respond to a tactical situation that requires running, jumping, carrying heavy objects, or other types of sustained heavy physical exertion.
- 3. Nuclear, Biological, and Chemical (NBC) operations- Soldiers are likely to be operating in chemical protective equipment, sometimes for several hours at a time. This will dramatically increase the Soldiers' heat load, regardless of environmental conditions. It is also more difficult to drink fluids. Soldiers' will be unable to take oral medications while wearing a protective mask. Depending on the tactical situation, Soldier's may be required to take medications for pretreatment against nerve agent poisoning (pyridostigmine bromide) or biological warfare agents

(usually a fluoroquinolone). If a Soldier is exposed to nerve agent, he or she will be treated with Atropine and 2-PAM Chloride. Clinicians should be cautious about any medication that would either decrease the ability of the Soldier to compensate for heat stress, make a soldier more sensitive to nerve agent poisoning, or make the resuscitation drugs less effective.

- 4. Compliance Medications that require a lot of Soldier compliance should be avoided. Due to the pace of operations, it is frequently difficult for Soldiers to adhere to a strict dosing regimen. Because of this, medications with once a day dosing are preferable. Similarly, meals are often served on an irregular schedule. This makes it preferable to avoid prescribing medications that must be taken with food. There is no real privacy other than a few senior officers everyone is sharing quarters, latrines and meals. Because of this, medications that require multiple daily doses or that need to be added to food or beverages are less likely to be taken. Bulk of items and disposal of waste are also of consideration.
- 5. Temperature sensitivity Gel caps melt and should not be used in hot climates.
- 6. Nutrition Rations provided under deployment conditions are usually high in sodium and fat. The standard dining facility (DFAC) menu is not the same as in base conditions. Soldiers do not get a choice on where they are going, what they are doing, or where they can eat. The alternate food to the DFAC is fast food and all the snack foods that come in Care Packages or are purchased through the PX.

RECOMMENDATIONS

These recommendations are based on consensus opinion that considers the available literature, experience in the field, and physiology.

- Patients who are likely to be deployed should preferably be started on ACEI/ARB or CCB. Diuretics, if needed, should be used in low doses. This stipulation also applies to those who do extreme physical activity and are prone to dehydration. Patients should be stable on their medications prior to deployment. Clinicians should discuss how deployment might effect blood pressure control and describe potential complications of treatment with their patients as part of pre-deployment processing. If possible, the patient should be monitored for signs and symptoms of dehydration and adequate blood pressure control for the first 7-10 days of deployment while they are becoming acclimatized.
- 2. For patients who are diagnosed with and/or started on treatment for hypertension during a deployment, dihydropyridine CCBs are the preferred agents in the desert environment since they are available in once a day formulations, do not limit heart rate, and do not require electrolytes to be checked after initiation.

APPENDIX D: PHARMACOTHERAPY EVIDENCE

Table D1. Outcome Trials of Antihypertensive Agents

Study	Drug Regimen	Ν		Primary Outcomes	Remarks
Antihynerten	sive Therapy vs Placebo		n		
SHEP 1991 R,DB,PC	chlorthalidone vs placebo	4,736 SBP 160- 219, DBP<90	4.5yrs	Nonfatal and fatal stroke RR 0.64 (P=.0003) ARR 2.4%; NNT=43	Nonfatal MI and + coronary death: RR .73 Major CV events: RR .68 All-cause mortality: RR .87
EWPHE 1985 R,DB,PC	HCTZ/triamterene vs placebo	840 SBP 160- 239 DBP 90- 119	4.7 yrs	Total mortality: RR 0.91 (P=.41) ARR 2.7%; NNT=37 CV mortality: RR 0.73 (P=.037) ARR 5.8%; NNT=17	Cardiac mortality RR 0.62 (P=.036) Cerebrovascular mortality RR 0.68 (P=.16)
TOMHS 1993 R,DB,PC	chlorthalidone, acebutolol, enalapril, doxazosin, or amlodipine vs placebo	902 DBP < 100	4.4 yrs	Major CHD event: RR 0.76 ARR 1.2%; NNT=81 Major clinical event RR 0.69 ARR 2.2%; NNT=46	Treatment vs placebo: Major and other clinical events RR 0.66 (P=.03)
MRC-old 1992 R,SB,PC	HCTZ or atenolol, vs placebo	4396 65-74 yrs SBP 160- 209 DBP < 115	5.8 yrs	Stroke: RR 0.75 (P=.04) ARR 1.4%; NNT=70 Coronary events: RR 0.81 (P=.08) ARR 1.3%; NNT=76 All CV events: RR 0.83 (P=.03) ARR 2.1%; NNT=47	Diuretic vs placebo: Stroke: RR 0.69 (P=.04) Coronary events: RR 0.56 (P=.0009) All CV events: RR 0.65 (P=.0005) Beta-blocker vs placebo: not statistically significant
STOP-HTN 1991 R,DB,PC	HCTZ/amiloride, atenolol, metoprolol or pindolol vs placebo	1627 70-84 yrs SBP 180- 230 and DBP ≥ 90 or DBP 105-120	5.4 yrs (mean 2.1)	Combined MI, stroke, and other CV death: RR 0.60 (P=.0031) ARR 4.4%; NNT=23	Stroke morbidity and mortality: RR 0.53 (P=.0081) Total mortality: RR 0.57 (P=.0079)

Study	Drug Regimen	Ν	Duratio n	Primary Outcomes	Remarks
MRC 1985 R,SB,PC	bendrofluazide propranolol vs placebo		5 yrs	Stroke: RR 0.55 (P<.01) ARR 0.6%; NNT=176 All CV events: RR 0.81 (P<.05) ARR 0.8%; NNT=128 Coronary events: RR 0.94 ARR 0.2%; NNT=657 All cause death: RR 0.98 ARR 0.7%; NNT=1371	Diueretic vs beta-blocker: ↓ stroke (P=.002)
Syst_Eur 1997 R,DB,PC		4695 HTN (SBP160 -219, DBP < 95)	2 yrs	Fatal and nonfatal stroke: RR 0.58 (P=.003) ARR 1.4%; NNT=72	
PROGRESS 2001 R,DB,PC	perindopril +/- indapamide vs placebo	6105 HTN or non- HTN with hx of stroke or TIA	4 yrs	Total stroke (fatal and non-fatal) -combo of perindopril + indapamide ↓ BP by 12/5 mm Hg and stroke risk by 43% regardless of HTN status -perindopril alone ↓ BP by 5/3 mm Hg but did not affc t stroke recurrence (RRR -19% to 23%) -combo (perindopril + indapamide) CV mortality OR 0.72 (0.55-0.95) CV events OR 0.60 (0.51-0.71) Stroke OR 0.57 (0.46-0.70) MI OR 0.65 (0.48-0.88) -peridopril alone CV mortality OR 0.96 (0.80-1.15) stroke OR 0.95 (0.77-1.19)	

Study	Drug Regimen	Ν	Duratio n	Primary Outcomes	Remarks
Thiazide diur	etics (with or without beta	a-blockers)	vs Other A	Antihypertensive Classes	
ALLHAT 2002 R,DB,AC	chlorthalidone vs amlodpine vs lisinopril	33,357 HTN + > 1 CHD RF	4.9 years	Composite fatal CHD, nonfatal MI amlodipine vs chlorthalidone RR .98 (P=.65) ARR .11% NNT=921 lisinopril vs chlorthalidone RR .99 (P=.81) ARR .14% NNT=733	amlodipine vs chlorthalidone: HF RR 1.38 (P<.001) lisinopril vs chlorthalidone: combined CVD events RR 1.10 (P<.001); stroke RR 1.15 (P=.02) HF RR 1.19 (P<.001)
STOP-HTN2 1999 PROBE	HCTZ/ Amiloride or atenolol/metoprolol/ pindolol vs enalapril/lisinopril or felodipine/isradipine	6614 70-84 yrs SBP ≥ 180 DBP ≥ 105	5 yrs	· · · · ·	ACEI vs CCB: HF RR 0.76 (P=.025) MI RR 0.77 (P=.016)
HAPPHY 1987 R	Thiazide vs beta-blocker	6569 DBP 100- 130	3.8 yrs	CHD events: no difference Total mortality: no difference	Fatal stroke BB < D 0.81
ANBP-2 2003 PROBE,	ACE (enalapril) vs diuretic (HCTZ)	6083 age 65-84 yrs	4.1 yrs	CV events or death from any cause ACE: 695 events (56.1/100 pt yrs) Diuretic: 736 events (59.8/100 pt yrs) ACE HR 0.89(0.79-1.00; p=0.05) NNT 32 (Male or Female) NNT 23 (Male)	Open label study; endpoint assessments were blinded Males had 2x as many events as female ACE had more fatal strokes ACE: 11%↓ in CVD events or death from any cause
CAPPP 1999 PROBE	captopril vs HCTZ/bendrofluazide or atenolol/metoprolol	10985 DBP ≥ 100	6.1 yrs	Composite fatal and nonfatal MI, stroke, and other CV death: RR 1.05 (P=.52) ARR (w/diuretic or beta-blocker) 0.5%; NNT=196	Captopril vs conventional: CV mortality: RR 0.77 (P=.092) Fatal and nonfatal stroke: RR 1.25 (P=.044)
ALLHAT 2000 R,DB,AC	chlorthalidone vs. doxazosin arm	24335 HTN + > 1 CHD RF	3.3 yrs	Composite fatal CHD, nonfatal MI:RR 1.03 (P=.71) ARR .04%; NNT=2304	Doxazosin arm DC'd: stroke RR 1.19 (P=.04); combined CVD events RR 1.25 (P<.001); CHF RR 2.04 (P<.001)

Study	Drug Regimen	Ν	Duratio n	Primary Outcomes	Remarks
CONVINCE 2003 R,DB	verapamil ER vs. atenolol or HCTZ	16,602 HTN + 1 CVD RF	3 yrs	CV related events (1st stroke, MI, CVD death): HR 1.02 (P=.77) ARR .05%; NNT=1944	Sponsor closed study for 'business considerations'; not able to demonstrate equivalence
INSIGHT 2000 R,DB	nifedipine GITS vs. HCTZ/amiloride	6,321 HTN + 1 CVD RF	4.25 years	CV death, MI, HF, stroke OR 1.11 (P=.34) ARR .58%; NNT=172	Nifedipine found to be equally effective to HCTZ/amiloride
NORDIL 2000 PROBE,MC	diltiazem (IR initially; SR after 1997) vs. thiazide diuretic or beta-blocker or both	10,881 DBP>100	4.5 yrs	Fatal and nonfatal stroke, MI, other CV death RR 1.00 (P=.97) ARR .14% NNT=752	Diltiazem found to be as effective as thiazide diuretic, beta-blocker, or both
Other Antihyp	pertensive Class Compar		1		
LIFE 2002 R, DB	losartan vs atenolol	9193 HTN and LVH 92% white	4.8 yrs	 -composite of stroke, MI, CV death -losartan sig ↓ endpoint by 13% (RRR) (p=0.021) compared to atenolol -ARR 1.8%; adjusted HR 0.87 (0.77- 0.98) -results were driven purely by a ↓ in stroke ARR 1.7%; RRR 25%; Adjusted HR 0.75 (0.63-0.89; p=0.001) 	-HCTZ 12.5 mg added on open label -BP lowering was similar b/w the 2 drugs -only ~50% achieved BP goal<140/90 with 1 drug
INVEST 2003 PROBE	verapamil SR vs. atenolol	22,576 HTN + CAD	2.7 yrs	1st death, nonfatal stroke, nonfatal MI RR 0.98 (P=.57) ARR .24% NNT=422	63% on trandolapril in verapamil group 44% on HCTZ in atenolol group Verapamil-trandolapril found to be as effective as atenolol-HCTZ

Study	Drug Regimen	N	Duratio	Primary Outcomes	Remarks
AASK R, 3x2 factorial design	Metoprolol vs ramipril vs amlodipine	1094 African Am. with renal disease; no DM	n 4 yrs	 1°: Rate of change in GFR (GFR slope) -2°: Combined >50% ↓ GFR, ESRD, all-cause death (clinical outcome) 2° outcome results: -NSD in clinical outcome b/w usual and lower BP groups (2% RR; -22 to 21; p=0.85) -ramipril vs metoprolol (22% RR; CI 1 to 38; p=0.04) -ramipril vs amlodipine (38% RR; CI 14 to 56; p=0.004) -metoprolol vs amlodipine (20% RR; CI -10 to 41; p=0.17) 	 -other HTN drugs could be added open label (most commonly a diuretic) -patients split into two BP goals: "usual" MAP 102-107 (N=554) (achieved BP 140/85) "lower" MAP <92 (M=540) (achieved BP 127/77) -not powered to detect differences in ESRD or in morbidity or mortality -amlodipine arm was stopped early due to clear advantage of metoprolol for ↓ ESRD or death -amlodipine group had sig. lower SBP than in metoprolol or ramipril groups
Other Compar	risons				
HDFP 1979 R,C	Stepped care (SC) chlorthalidone, triamterene or spironolactone (add reserpine then hydralazine) vs. Referred Care (RC)	10940 DBP 90- 104, 105- 114, ≥ 115	5 yrs	All cause mortality SC vs RC: RR 0.83 (P<.01) ARR 1.3%; NNT=76	Cerebrovascular death: RR 0.55 AMI death: RR 0.74
HOT 1998 PROBE	felodipine (added therapy to target DBP: < 90, < 85, < 80)	18790	3.8 yrs	Nonfatal MI, nonfatal stroke, CV death Lowest incidence at DBP 82.6	RR 1.07 < 90 vs < 80 RR 0.99 < 90 vs < 5 RR 1.08 < 85 vs < 80 P=.5 for trend

Study	Drug Regimen	Ν	Duratio n	Primary Outcomes	Remarks
Meta-Analyses	5			<u> </u>	
Psaty et al., 2003	1st line diuretics, beta- blockers, ACEIs, CCBs, alpha-blockers, ARBs	192,478 (42 trials)	> 1 year	Major CV endpoints or all-cause mortality	Low-dose diuretic superior to placebo for: CHD RR .79; CHF RR .51; stroke RR .71; CVD events RR .76 Diuretic vs. CCB CVD events RR .94; CHF RR .74 Diuretic vs ACEI CHF RR .88; CVD events RR .94; stroke RR .86 Diuretic vs beta-blocker CVD events RR .89 Diuretic vs alpha-blocker CHF RR .51; CVD events RR .84
BPLTTC 2003	ACEI, CCB, ARB, beta- blockers or diuretics, or BP target	162,341 (29 trials)	(mean range 2-8.4 years)	Major CV disease or death	Total mortality: ACE vs placebo RR .88; CCB vs placebo RR .89; ARB vs control RR .94; ACEI vs diuretic/beta-blocker RR 1.00; CCB vs diuretic/beta-blocker RR .99; ACEI vs CCB RR 1.04; Treatment favorable vs placebo for all CV events except: HF for CCB vs placebo RR 1.21 Stroke ACEI vs diuretic/beta-blocker RR 1.09; ACEI vs CCB RR 1.12 HF CCB vs diuretic/beta-blocker RR 1.33
Staessen et al., 2003	Diuretic or beta-blocker, CCB, ACEI, alpha- blocker, ARB	120,574 (15 trials)	≥2 yrs	Difference in SBP and total and CV mortality, CV events, stroke, MI, HF	Newer agents not found to have an effect on CV events independent of BP effect: total mortality new vs old OR 0.98 (P=.38) HF new vs old OR 1.23 (P=.02)

Study	Drug Regimen	N	Duratio n	Primary Outcomes	Remarks
Opie et al., 2002	CCBs vs diuretics or beta-blockers, ACEI	24322 (6 trials)	≥2 yrs	Total and CV mortality, major CV events	CCB vs diuretic or beta-blocker: Nonfatal stroke: RR 0.75 (P=.001) Total MI: RR 1.18 (P=.013) Total mortality: RR 1.005 CV mortality: RR 1.049 (P=.486) Major CV events: RR 1.011 (P=.767) CCB vs ACEI in DM: Nonfatal MI: 2.26 (P=.001) Total MI: 2.2 (P=.004)
Pahor et al., 2000	CCB (IR or SR) vsdiuretic, beta- blocker, ACEI, clonidine	27743 (9trials)	≥2 yrs	CV events	CCB vs other: AMI: RR 1.26 (P=.0003) HF: RR 1.25 (P=.005) Major CV events: RR 1.1 (P=.018) Stroke: RR 0.9 (P=.1) All-cause mortality: RR 1.03 (P=.54) CV mortality: RR 1.06 (P=.36) nonCV mortality: RR .99 (P=.83)
BPLTTC 2000	ACEI vs placebo , CCB CCB vs placebo, ACEI or CCB vs other therapies; treatment of differing intensities		1000 pt yrs	Stroke, CHD, HF, CV death, major CV events, total mortality	ACEI vs placebo: Stroke: RR 0.7 CHD: RR 0.8 Major CV events: RR 0.79 CV death: RR 0.74 Total mortality: RR 0.84 CCB vs placebo: Stroke: RR 0.61 Major CV events: RR 0.72 CV death: RR 0.72 No difference ACEI vs diuretic or beta-blocker (except ↑ stroke RR 1.05) No difference CCB vs diuretic or beta-blocker (except ↓ stroke RR 0.87, ↑ CHD RR 1.12)

APPENDIX E: Guideline Development Process

Development of the 1999 Hypertension Guideline (Versions 1.0)

The initial Veterans Health Administration (VHA) Hypertension guideline development process was undertaken from August 1996 through March 1997. The guideline was developed by and for clinicians from the Department of Veterans Affairs (VA) and the Department of Defense (DoD). The list of contributors included nurses, nephrologists, cardiologists, pharmacists, internal medicine and primary care physicians, and experts in the field of guideline and algorithm development.

The 1999 guideline drew heavily from the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI), 1997. It also integrated the recommendations developed by VHA's Medical Advisory Panel (MAP) to the Pharmacy Benefits Management Strategic Health Group examining the pharmacological management of persons with hypertension. The original guideline objectives were: to describe the critical decision points in the management of hypertension ; to provide a clear and comprehensive guideline incorporating current information and practices for practitioners throughout the DoD and Veterans Health Administration system and to improve local management of patients with hypertension and improve patient outcomes.

Development of the 2003 Hypertension Guideline Update (Version 2.0)

The development of the 2003 Hypertension Guideline Update (version 2.0) was initiated in March 2002 and continued through January 2004. The development process followed the steps described in "Guideline for Guideline," an internal working document of VHA's National Clinical Practice Guideline Council, which requires an ongoing review of the work in progress.

The 1999 VHA Hypertension Guideline represented a "seed document" that was updated and adapted by the joint VHA/DoD Hypertension Guideline Development Group over a six-month period from January to June 2003. As with the original Working Group, the charge of the VHA/DoD group was to provide evidence-based action recommendations whenever possible; hence, major clinical randomized controlled trials (RCTs) and observational studies published from August 1999 through January 2004 in the areas of diagnosis and treatment of chronic hypertension.

Target Audience

This guideline is designed for primary care providers. While each module is designed for use by primary care providers in an ambulatory care setting, the modules can also be used to coordinate and standardize care within subspecialty teams and as a teaching tool for students and house staff.

Guideline Development Process

The Offices of Quality and Performance and Patient Care Service, in collaboration with the network Clinical Managers, the Deputy Assistant Under Secretary for Health, and the Medical Center Command of the DoD identified clinical leaders to champion the guideline development process. During a preplanning conference call, the clinical leaders defined the scope of the guideline and identified a group of clinical experts from the VA and DoD that formed the Guideline Development Working Group.

At the start of the update process, the clinical leaders, guideline panel members, outside experts, and experts in the field of guideline and algorithm development were consulted to determine which aspects of the 1999 guideline required updating. These consultations resulted in the following recommendations that guided the update efforts: (1) update any recommendations from the original guideline likely to be effected by new research findings; (2) provide information and recommendations on health systems changes relevant to hypertension care; (3) address content areas and models of treatment for which little data existed during the development of the original guideline; and (4) review the performance and lessons learned since the implementation of the original guideline.

The Working Group participated in a face-to-face session to reach a consensus about the guideline recommendations and to prepare a draft document. The draft was revised by the experts through numerous conference calls and individual contributions to the document.

Experts from the VA and DoD internal medicine, cardiology and primary care reviewed the final draft. Their feedback was integrated into the final draft. Nonetheless, this document is a work in progress. It will be updated every two years, or when significant new evidence is published.

This 2003 Guideline Update is the product of many months of diligent effort and consensus building among knowledgeable individuals from the Department of Veterans Affairs (VA), Department of Defense (DoD), academia, and guideline facilitators from the private sector. An experienced moderator facilitated the multidisciplinary Working Group. The list of participants is included in the introduction to the guideline update.

Formulating of Questions

The Working Group developed researchable questions and associated key terms after orientation to the seed guidelines and to goals that had been identified by the Working Group. The questions specified: (adapted from the Evidence-Based Medicine (EBM) toolbox, Centre for Evidence-Based Medicine, (http://minerva.minervation.com/cebm/)

- Population characteristics of the target patient population
- Intervention exposure, diagnostic, or prognosis
- Comparison intervention, exposure, or control used for comparison
- Outcome -outcomes of interest

These specifications served as the preliminary criteria for selecting studies.

Selection of Evidence

Published, peer-reviewed, RCTs were considered to constitute the strongest level of evidence in support of guideline recommendations. This decision was based on the judgment that RCTs provide the clearest, scientifically sound basis for judging comparative efficacy. The Working Group made this decision recognizing the limitations of RCTs, particularly considerations of generalizability with respect to patient selection and treatment quality. Meta-analyses that included random controlled studies were also considered to be the strongest level of evidence, as well as reports of evidence-based systematic reviews.

A systematic search of the literature was conducted. It focused on the best available evidence to address each key question and ensured maximum coverage of studies at the top of the hierarchy of study types: evidence-based guidelines, meta analyses, and systematic reviews. When available, the search sought out critical appraisals

already performed by others that described explicit criteria for deciding what evidence was selected and how it was determined to be valid. The sources that have already undergone rigorous critical appraisal include Cochrane Reviews, Best Evidence, Technology Assessment, and EPC reports.

The search continued using well-known and widely available databases that were appropriate for the clinical subject. In addition to Medline/PubMed, the following databases were searched: Database of Abstracts of Reviews of Effectiveness (DARE) and Cochrane Central Register of Controlled Trials (CCTR). For Medline/PubMed, limits were set for language (English), date of publication (1999 through May 2002) and type of research (RCT and meta-analysis). For the CCTR, limits were set for date of publication (1990 through 2002). Once definitive reviews or clinical studies that provided valid relevant answers to the question were identified, the search ended. The search was extended to studies/reports of lower quality (observational studies) only if there were no high quality studies.

Exclusion criteria included reviews that omitted clinical course or treatment. Some retrieved studies were rejected on the basis of published abstracts, and a few were rejected after the researchers scanned the retrieved citation for inclusion criteria. Typical exclusions included studies with physiological endpoints or studies of populations that were not comparable to the population of interest (e.g., studies of hypertension in children or pregnancy).

The results of the search were organized and reported using reference manager software. At this point, additional exclusion criteria were applied. The bibliographies of the retrieved articles were hand-searched for articles that may have been missed by the computer search. Additional experts were consulted for articles that may also have been missed.

Literature Review and Inclusion Criteria

As a result of the original and updated literature reviews, articles were identified for possible inclusion. These articles formed the basis for formulating the guideline recommendations. The literature search for the guideline update was validated by: (1) comparing the results to a search conducted by the independent research and appraisal team; (2) a review of the database by the expert panel; and (3) requesting articles pertaining to special topics from the experts in the working group.

It is important to note that due to application of article screening criteria in the updated guideline, some of the studies that were included in the original guideline were not included in the updated analyses.

Preparation of Evidence Tables (reports)

A group of clinician reviewers and other researchers in health care, with experience in evidence-based appraisal, independently read and coded each article that met inclusion criteria. Each article was turned into a one-page summary of the critical appraisal by the research team and added to a central electronic database. Clinicians from the Center for Evidence-Based Practice at the State University of New York, Upstate Medical University, Department of Family Medicine [SUNY] contributed several of the appraisal reports. Each of the evidence reports covered:

- Summary of findings
- Methodology
- Search terms
- Resources searched
- Summary table of findings
- Critical appraisal of each study

Quality ratings were made for each evidence using the grading scale presented in Table 4 [USTFP, 2001). The quality rating procedure used in this update was different from the rating scale used in the development of the original guideline in 1999. Where adjustments to the update process were made, articles from the original process were re-graded to reflect the changed rating scale (e.g., the level of recommendation [R] was assigned for each evidence, based on study design and significance of the quality of the evidence)

Recommendation and Overall Quality Rating

Evidence Grading System used in 1999 (version 1.0)

	1a. Strength of Recommendation
Level I	Usually indicated, always acceptable and considered useful and effective.
Level IIa	Acceptable, of uncertain efficacy and may be controversial. Weight of evidence in favor of usefulness/efficacy.
Level IIb	Acceptable, of uncertain efficacy and may be controversial. May be helpful, not likely to be harmful.
Level III	Not acceptable, of uncertain efficacy and may be harmful. Does not appear in guidelines.

1b. Level of Evidence			
	Α	В	С
Primary Evidence	Randomized	Well designed clinical studies	Panel consensus
Secondary Evidence	Other Clinical studies	Clinical studies related to topic but not in a population with hypertension	Clinical studies Unrelated to topic

Evidence-based practice involves integrating clinical expertise with the best available clinical evidence derived from systematic research. The Working Group reviewed the evidence and graded it using the rating scheme developed by the USPSTF (2001). The experts themselves, after an orientation and tutorial on the evidence grading process, formulated Quality of Evidence ratings (see Table 1), a rating of Overall Quality (see Table 2), a rating of the Net Effect of the Intervention (see Table 3), and an overall Recommendation (see Table 4).

Evidence Grading System used in 2003 (version 3.0)

TABLE 1: Quality of Evidence (QE)		
Ι	At least one properly done RCT	
II-1	Well designed controlled trial without randomization	
II-2	Well designed cohort or case-control analytic study	
II-3	Multiple time series, dramatic results of uncontrolled experiment	
III	Opinion of respected authorities, case reports, and expert committees	

	TABLE 2: Overall Quality
Good	High grade evidence (I or II-1) directly linked to health outcome
Fair	High grade evidence (I or II-1) linked to intermediate outcome; <i>or</i> Moderate grade evidence (II-2 or II-3) directly linked to health outcome

Poor Level III evidence or no linkage of evidence to health outcome

TABLE 3: Net Effect of the Intervention		
Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering; <i>or</i> A large impact on an infrequent condition with a significant impact on the individual patient level.	
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering; <i>or</i> A moderate impact on an infrequent condition with a significant impact on the individual patient level.	
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering; <i>or</i> A small impact on an infrequent condition with a significant impact on the individual patient level.	
Zero or Negative	Negative impact on patients; <i>or</i> No relative impact on either a frequent condition with a substantial burden of suffering; or An infrequent condition with a significant impact on the individual patient level.	

TABLE 4: Final Grade of Recommendation				
	The net benefit of the intervention			
Quality of Evidence	Substantial	Moderate	Small	Zero or Negative
Good	Α	В	С	D
Fair	В	В	С	D
Poor	Ι	Ι	Ι	Ι

Abstract of the USPSTF:

- Once assembled, admissible evidence is reviewed at three strata: (1) the individual study, (2) the body of evidence concerning a single linkage in the analytic framework, and (3) the body of evidence concerning the entire preventive service. For each stratum, the Task Force uses explicit criteria as general guidelines to assign one of three grades of evidence: good, fair, or poor.
- Good or fair quality evidence for the entire preventive service must include studies of sufficient design and quality to provide an unbroken chain of evidence-supported linkages that generalize to the general primary care population and connect the preventive service with health outcomes. Poor evidence contains a formidable break in the evidence chain, such that the connection between the preventive service and health outcomes is uncertain.
- For services supported by overall good or fair evidence, the Task Force uses outcomes tables to help categorize the magnitude of benefits, harms, and net benefit from implementation of the preventive service into one of four categories: substantial, moderate, small, or zero/negative.

The Task Force uses its assessment of the evidence and magnitude of net benefit to make a recommendation, coded as a letter: from A (strongly recommended) to D (recommend against). It gives an "I" recommendation in situations in which the evidence is insufficient to determine net benefit (Harris et al., 2001).

Lack of Evidence - Consensus of Experts

The majority of the literature supporting the science for these guidelines is referenced throughout the document and is based upon key RCTs and longitudinal studies published from 1999 through 2003. Following the independent review of the evidence, a consensus meeting was held to discuss discrepancies in ratings and formulate recommendations. Where existing literature was ambiguous or conflicting, or where scientific data was lacking on an issue, recommendations were based on the clinical experience of the Working Group. These recommendations are indicated in the evidence tables as based on "Working Group Consensus".

Algorithm Format

The goal in developing the guideline for hypertension was not to repeat the guideline development process, but rather, to incorporate the information from several existing, national consensus, evidence-based guidelines into a format which would maximally facilitate clinical decision making. The use of the algorithm format was chosen because of the evidence that such a format improves data collection, diagnostic and therapeutic decision-making and changes patterns of resource use. However, few guidelines are published in such a format. To enhance continuity of care, the Hypertension Guidelines (version 1.0 and 2.0) were designed to encompass a broad spectrum of outpatient care of persons with hypertension. This required incorporating multiple published guidelines into a single, unified document.

The algorithmic format allows the provider to follow a linear approach to critical information needed at the major decision points in the clinical process, and includes:

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

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm (SMDMC, 1992). Arrows connect the numbered boxes indicating the order in which the steps should be followed.

	Rounded rectangles represent a clinical state or condition.
\bigcirc	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No. A horizontal arrow points to the next step if the answer is YES. A vertical arrow continues to the next step for a negative answer.
	Rectangles represent an action in the process of care.
\bigcirc	Ovals represent a link to another section within the guideline.

A letter within a box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. Included in the annotations are brief discussions that provide the underlying rationale and specific evidence tables. Annotations indicate whether each recommendation is based on scientific data or expert opinion. A complete bibliography is included in the guideline.

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APPENDIX F: PARTICIPANTS LIST

Peter Glassman, MBBS, MSc VA Medical Center 11301 Wilshire Blvd. Bldg. 500, Rm. 3224

Los Angeles, CA 90073 310-478-3711, ext. 48337 310-268-4933 (fax) Email: Peter.Glassman@med.va.gov

William Cushman, MD

Chief, Preventive Medicine Section Veterans Affairs Medical Center 1030 Jefferson Avenue Memphis, TN 38104-2193 Phone: 901-523-8990, Ext. 6605 FAX: 901 577-7457 Email: William.Cushman@med.va.gov

Paul R. Conlin, MD

Chief, Endocrinology Section VA Boston Healthcare System 150 South Huntington Avenue Jamaica Plain MA 02130 Phone: 617 232-9500 x 6252 Fax: 617 264-6561 Email: paul.conlin@med.va.gov

Elaine Furmaga, PharmD

Clinical Pharmacy Specialist Department of Veterans Affairs Pharmacy Benefits Management-Strategic Healthcare Group (119D) 1st Ave – 1 Block North Cermak Rd Building 37 Room 139 Hines IL 60141 Phone: 616-956-5957 Fax: 616-956-1575 Email: Elaine.Furmaga@med.va.gov

Thakor G. Patel, MD

Program Chief, Renal Disease, Diabetes and Cancer Department of Veterans Affairs (11A) 810 Vermont Avenue, NW Washington, D.C. 20420 202-273-8490 202-273-9142 (fax)Email: tgpatel@mail.va.gov

Douglas, Kevin, MD, MAJ, USA

Walter Reed Medical Center 6900 Georgia Avenue Washington, DC Phone: 202-782-5560 Email:Kevin.Douglas@NA.AMEDD.ARMY.MIL

Angela Allerman, PharmD, BCPS

Clinical Pharmacy Specialist DoD Pharmacoeconomic Center Bldg 1001 2421 Dickman Rd Fort Sam Houston, TX 78234-5081 Phone: 210-295-1271 Fax: 210-295-2789 Email: www.pec.ha.osd.mil

Vincent P Fonseca, Lt Col, MD, MPH

AFMSA/SGOZ 2509 Kennedy Circle BrooksCity-Base, TX 78235-5116 vincent.fonseca@brooks.af.mil Phone: 210.536.6661 Fax: 210.536.2863 DSN: 240

Michael R. Bell, MD, MPH

MAJ, MC, USA Program Manager, Occupational Medicine USACHPPM ATTN: MCHB-TS-MOM 5158 Black Hawk Road APG, MD 21010-5403 Phone: 410-436-2714/7975 Fax: 410-436-4117

Paul Welch, COL, MC, USA

Nephrology Walter Reed Medical Center 6900 Georgia Avenue Washington, DC paul.welch@na.amedd.army.mil

Leonard Pogach, MD

National Program Director, Diabetes VA New Jersey Health Care System Room 9-160 (111) 385 Tremont Avenue East Orange, NJ 07018 Ph: 973-676-1000 ext. 1693 Fax: 973-677-4408 Email: leonard.pogach@med.va.gov

Oded Susskind, MPH

Medical Education Consultant PO Box 112 Brookline, MA 02446 Phone: 617-232-3558 Fax: 617-713-4431 E-mail: oded@tiac.net

Angela V. Klar, MSN, RN, ANP-CS

PEC Solutions Clinical Practice Guideline Coordinator US Army Medical Command Quality Management 2050 Worth Road, Bldg 2792, Suite 26 FT. Sam Houston, TX 78234 Phone: 210-221-8740(DSN 471) Fax: 210-221-8478

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