The American Society of Hypertension

REVIEW OF CLINICAL HYPERTENSION

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Review of Clinical Hypertension

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# REVIEW OF CLINICAL HYPERTENSION
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Introduction

The AMERICAN SOCIETY OF HYPERTENSION REVIEW OF CLINICAL HYPERTENSION is produced and published by the American Society of Hypertension, Inc. The REVIEW is designed as (a) a comprehensive outline and reference list for current knowledge in the field of clinical hypertension, and (b) an outline of material to be covered in the ASH Clinical Hypertension Review Course. The REVIEW is not designed as a means for improving test scores on the Hypertension Specialist Examination, which is prepared by an entirely separate organization (ASH Specialist Program, Inc.)

Dr. Norman M. Kaplan served as Editor for the ASH CORE CURRICULUM FOR CLINICAL HYPERTENSION, which was the predecessor of the REVIEW. In preparing the present document, Dr. Kaplan’s outline was modified and expanded and the reference list was updated and expanded by the following committee of seven (7) hypertension specialists who served as Section Editors:

Chair
Ronald G. Victor, MD (Cardiology)
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Each section was then reviewed by several additional experts. Before the REVIEW was finalized, the entire content was reviewed by Drs. Norman M. Kaplan and Michael A. Weber with seminal new references provided by Dr. Kaplan. The Committee Members thank all the reviewers for their input and Ms. Melissa Levine and the staff in the ASH office for compiling the new REVIEW.

Probably no other field of clinical medicine enjoys a greater scientific base than hypertension. Increasingly detailed understanding of the basic mechanisms involved in blood pressure regulation and related metabolic disorders has led to the identification of a large list of effective medications as well as lifestyle modifications for hypertension. Randomized controlled trials have provided unequivocal proof that lowering blood pressure with medications dramatically reduces the risk of disability and death from cardiovascular and renal disease. However, high blood pressure remains untreated or inadequately treated in the majority of affected individuals. As a consequence, high blood pressure still is the leading cause of death worldwide.
For these reasons, the REVIEW emphasizes (a) state-of-the-art scientific principles, (b) the application of those principles into daily clinical practice, and (c) evidence from randomized clinical trials that serves as the basis for current practice recommendations by multiple expert panels.

Despite the recent advances in the field, large knowledge gaps about the prevention and treatment of hypertension still exist. Furthermore, opinion leaders in the field differ in their interpretations of major outcome trials and in their approach to central issues in patient management. For these reasons, each Section Editor has (1) starred and annotated the most important references, and (2) included original articles as well as editorials on both sides of controversial and unresolved issues.

In addition to the bibliography provided in each section, the following general sources were utilized:

**BOOKS:**


CURRENT PRACTICE GUIDELINES:


WEBSITES:

American Society of Hypertension: www.ash-us.org

International Society of Hypertension in Blacks: www.ishib.org

National High Blood Pressure Education Program: www.nhlbi.nih.gov/index.htm
National Kidney Foundation: [www.kidney.org](http://www.kidney.org)

American Heart Association: Heart and Stroke Facts: [www.americanheart.org](http://www.americanheart.org)

The references listed in the outlines mainly provide both (a) updated sources for information after publication of the Books and Reports listed above, and (b) seminal references and review articles. Review articles are indicated by an asterisk, seminal original articles are indicated by a double asterisk. Any editorial comments will appear in italics after the reference.
Section 1: Epidemiology of Hypertension

I. Blood pressure risk as a continuous variable and new JNC 7 classification of blood pressure
II. Ethnic and geographic variation in hypertension prevalence and cardiovascular risk
III. Predominance and importance of systolic hypertension
IV. Conundrum of poor hypertension control rates

References

I. Blood pressure risk as a continuous variable and new JNC 7 classification of blood pressure


II. Ethnic and geographic variation in hypertension prevalence and cardiovascular risk


III. Predominance and importance of systolic hypertension


** IV. Population rates of hypertension awareness, treatment, and control


Section 2: Prevention of Hypertension

I. Population versus individual approaches
   A. Impact of small population-wide effects
   B. Identification of high-risk individuals

II. Pre-natal influences
   A. Genetic
   B. Intrauterine growth retardation
      1. Congenital oligonephropathy
      2. Other mechanisms

III. Environmental exposures and exogenous substances
   A. Weight gain: obesity, sleep apnea
   B. Dietary sodium intake
   C. Other minerals: potassium, calcium, magnesium
   D. Other dietary components: carbohydrate, fat, protein, fiber, antioxidants
   E. Physical activity
   F. Alcohol consumption
   G. Smoking
   H. Stress
      1. Hormones: estrogen, adrenal steroids
      J. Sympathomimetic agents: caffeine
   K. Therapeutic agents: NSAIDs, erythropoietin, cyclosporine, tacrolimus
   L. Others: caffeine, licorice, lead, etc.

References

I. Population versus individual approaches


II. Pre-natal/natal influences


III. Environmental exposures and exogenous substances


Section 3: Pathophysiologic Mechanisms of Hypertension

I. Renal and hormonal mechanisms
   A. Renin-dependent mechanisms
   B. Renin-independent mechanisms

II. Neural Mechanisms
   A. Reflex and cortical control of sympathetic nerve activity
   B. Methods for studying the sympathetic control of blood pressure in humans
   C. Adrenergic receptors
   D. Neural mechanisms of hypertension
      1. Brainstem compression
      2. Baroreflex failure
      3. Renal afferents
      4. Insulin, leptin, and obesity-related hypertension
      5. Nitric oxide deficiency

III. Vascular Mechanisms
   A. Hemodynamics in diastolic vs. systolic hypertension
   B. Large vessel stiffness
   C. Endothelial function

References

I. Renal and hormonal mechanisms:

Review of the impact of angiotensin II and other vasoactive hormone-excess states on the pressure natriuresis relationship and the pathogenesis of hypertension.
II. Neural mechanisms:


III. Vascular mechanisms:


Section 4: Genetics of Hypertension

I. Monogenic causes of human hypertension
   A. Glucocorticoid remediable aldosteronism
   B. Liddle’s syndrome
   C. Apparent mineralocorticoid excess
   D. Congenital adrenal hyperplasias
      1. Caused by mutations in 11-β-hydroxylase
      2. Caused by mutations in 17-α-hydroxylase
   E. Pseudohypoaldosteronism Type II
   F. Hypertension + brachydactyly syndrome
   G. Gain of function mutation of the mineralocorticoid receptor

II. Genetics of human primary hypertension
   A. Risk of primary hypertension in population
   B. Risk of primary hypertension in individuals with positive family history
   C. Polygenic nature
   D. Familial clustering of other cardiovascular risk factors
   E. Renal involvement
   F. Pharmacogenetic implications

References

I. Monogenic causes of human hypertension


II. Genetics of human primary hypertension


Section 5: Diagnostic Assessment

I. Accurate and adequate measurement of blood pressure (BP)
   A. Office
      1. Equipment
      2. Technique including identification of postural hypotension
      3. Diagnostic criteria
   B. Automatic ambulatory monitoring
      1. Equipment and technique
      2. Diagnostic criteria and comparison with office readings
   C. Home, self-recorded
      1. Equipment and technique
      2. Diagnostic criteria and comparison with office readings

II. Additional assessment of prognosis
   A. Nocturnal pattern of BP
   B. BP on arising
   C. BP during exercise
   D. Masked hypertension

III. White coat hypertension
   A. Definition and diagnostic criteria
   B. Prevalence: age, gender, psychological factors
   C. Mechanisms and natural history
   D. Associations with target organ damage
   E. Prognostic implications
   F. Management

IV. Initial evaluation
   A. Purposes
      1. Recognize specific identifiable causes of hypertension
      2. Assess target organ damage
      3. Determine overall cardiovascular risk status
   B. Procedures
      1. History
      2. Physical examination, including fundoscopic
      3. Laboratory testing: routine and additional as indicated
      4. Renin profiling

V. Overall cardiovascular risk stratification
   A. Major components of cardiovascular risk
   B. Graduation of risk
   C. Need for special procedures
References

I. **Accurate and adequate measurement of blood pressure (BP)**


Dabl educational website: [www.dableducational.com](http://www.dableducational.com)


II. Additional assessment of prognosis


III. White coat hypertension


IV. Initial evaluation


V. Overall cardiovascular risk stratification


Section 6: Metabolic Abnormalities and Hypertension

I. Obesity related hypertension
   A. Prevalence of the association
   B. Pathophysiology
      1. Metabolic factors: insulin resistance, leptin, etc.
      2. Renal – volume factors
      3. Sympathetic nervous system involvement
      4. Role of the anatomical location of excess body fat
   C. Evaluation
      1. Problems of blood pressure measurement
      2. Assessment of other risk factors
      3. Ascertainment of sleep apnea
   D. Management

II. Dyslipidemia
   A. Prevalence of the association
   B. Mechanisms
   C. Management
      1. Dietary
      2. Drug: Antihypertensive effects of lipid reductions
      3. Dyslipidemia treatment

III. The metabolic syndrome
   A. The role of upper body obesity
   B. Components of the syndrome
   C. Pathophysiology
      1. Insulin resistance/hyperinsulinemia
      2. Other factors
   D. Management
      1. Insulin sensitizing agents
      2. Associated kidney disease

IV. Diabetes mellitus
   A. Prevalence of the association with types 1 and 2 diabetes
   B. Pathophysiology
      1. Obesity
      2. Endothelial dysfunction
      3. Nephropathy
      4. Role of inflammation
   C. Evaluation
      1. Glucose intolerance, insulin resistance
      2. Micro- and macrovascular diseases
         a. Retinopathy
         b. Nephropathy
         c. Cardiomyopathy
D. Management
   1. Control of hyperglycemia
   2. Control of hypertension
      a. Selection of antihypertensive agents
      b. Goals of therapy

References

I. Obesity related hypertension

http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/


II. Dyslipidemia


III. The metabolic syndrome


IV. Diabetes mellitus


Section 7: Hypertensive Target Organ Damage

I. Cardiac
   A. Manifestations
      1. Left ventricular hypertrophy
      2. Systolic and diastolic dysfunction
      3. Congestive heart failure
      4. Coronary artery disease
   B. Prevalences of each type
   C. Pathogenesis: the role of hypertension
   D. Consequences
   E. Effect of antihypertensive therapies on regression or prevention

II. Cerebrovascular
   A. Manifestations
      1. Intracranial disease: types of strokes
      2. Carotid stenosis
      3. Dementia
   B. Pathogenesis: the role of hypertension
   C. Treatment of hypertension
      1. In acute stroke therapy
      2. For chronic stroke prevention

III. Renal parenchymal disease
   A. Association of hypertension with various renal diseases
      1. Acute renal disease
      2. Chronic renal disease, diabetic and nondiabetic
   B. Role of hypertension in progressive renal insufficiency
      1. Progression of renal damage
   C. Cardiovascular complications

IV. Other vascular diseases
   A. Types
      1. Atherosclerotic: aneurysms, dissection embolization
      2. Fibromuscular dysplasia
      3. Vasospastic and inflammatory
      4. Therapy
   B. Peripheral arterial disease

V. Retinopathy
   A. Association of hypertension with retinopathy

VI. Sexual dysfunction
   A. Prevalence
   B. Management
References

I. **Cardiac**


II. Cerebrovascular


III. Renal


IV. Other vascular disease


V. Retinopathy


VI. Sexual dysfunction


Section 8: Therapy of Hypertension: 
Lifestyle Modifications and Non-Pharmacologic Therapies

I. The place for combined lifestyle modifications
   A. Preventive potential
   B. Therapeutic efficacy

II. Antihypertensive effects and additional benefits of individual modifications
   A. Cessation of smoking
   B. Reduction of excess weight
   C. Increased physical activity
   D. Moderate reduction of sodium intake
   E. Increased intake of potassium
   F. Moderate intake of alcohol
   G. Maintenance of adequate intake of calcium and magnesium
   H. Other dietary constituents
      1. Fiber
      2. Protein
      3. Dietary fat and fish oil; protein; carbohydrates
      4. Caffeine
      5. Anti-oxidants

   I. Other therapies
      1. Relaxation techniques
      2. Acupuncture
      3. Surgical decompression of ventrolateral medulla
      4. Herbal remedies
      5. Breathing-control

References

I. The place for combined lifestyle modifications


**Appel LJ, Champagne CM, Harsha DW, Cooper LS, Obarzanek E, Elmer PJ, et al. Writing Group of the PREMIER Collaborative Research Group. Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. JAMA. 2003 Apr 23-30; 289(16):2083-93. This is the first trial to demonstrate the benefit of a combination of behavioral steph to control and prevent hypertension. 810 participants, 38% with hypertension, most overweight and sedentary, 62% women, and 34% African-American. After six months of established lifestyle modification were noted to have a significant decrease in blood pressure and hypertension control. One of the key findings is a prescription of the application of the DASH diet and weight loss.


Pickering TG. Lifestyle modification and blood pressure control: is the glass half full or half empty? JAMA. 2003 Apr 23-30; 289(16):2131-2.


II. Antihypertensive effects and additional benefits of individual modifications


Acupuncture Research Program (SHARP): clinical trial design and screening results.


**Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001; 344: 3–10. One of the primary papers from the landmark DASH trial which demonstrated that with appropriate application of a diet based on nine or more servings of fruits and vegetables in addition to moderate sodium restriction can significantly benefit lowering blood pressure including the significant African-American cohort.


Section 9: Therapy of Hypertension: Pharmacology of Antihypertensive Drugs

I. Basic principles of clinical pharmacology relevant to treatment of hypertension
   A. Receptors
   B. Drug disposition and pharmacokinetics
      1. Absorption
      2. Bioavailability
      3. Distribution to tissues
      4. Binding to plasma proteins
      5. Volume of distribution
      6. Half-life and clearance
   C. Drug metabolism and pharmacodynamics
      1. Factors affecting drug metabolism
      2. Assessment of extent and duration of action
   D. General principles of drug therapy
      1. Assessment of comparative efficacy
      2. Assessment of adverse effects
      3. Individualization of therapy

II. Single drug classes used in chronic treatment
   A. Diuretics
      1. Thiazides and thiazide-like diuretics Loop
      2. Potassium-sparing
      3. Selective aldosterone antagonists
   B. Adrenergic inhibitors
      1. Peripheral sympathetic inhibitors
      2. Central alpha-agonists
      3. Alpha-blockers
      4. Beta-blockers
      5. Alpha-beta-blockers
   C. Direct vasodilators
      1. Hydralazine
      2. Minoxidil
      3. Nitrates
   D. Calcium-channel blockers
      1. Dihydropyridine
      2. Non-dihydropyridine
   E. Angiotensin converting-enzyme inhibitors
   F. Angiotensin II receptor blockers
   G. Vasopeptidase inhibitors
   H. Endothelin antagonists

III. Combination drugs
   A. Diuretic + adrenergic inhibitor + vasodilator
   B. Diuretic + beta-blocker
   C. Diuretic + central alpha-agonist
   D. Diuretic + alpha-blocker
   E. Diuretic + Angiotensin converting-enzyme inhibitor
IV. Drugs for parenteral use

V. Monitoring adequacy of therapy
   A. Need for 24-hour control
   B. Avoidance of tissue hypoperfusion
   C. Decision to “step-down” therapy

References (Please note that all of the articles in the sections below are either review articles or seminal articles.)

I. Basic principles of clinical pharmacology relevant to treatment of hypertension


II. Single drug classes used in chronic treatment


Eplerenone Post-myocardial infarction Heart Failure Efficacy and Survival Study (EPHESUS) Investigators. JAMA. 2003; 287:1309-1321.


III. Combination drugs


IV. Drugs for parenteral use (see Section 14)

V. Monitoring adequacy of therapy (see Section 9 and 10)

Section 10: How to Evaluate Clinical Trials

I. Performance of clinical trials
   A. Terminology (e.g., randomization, blinding, placebo-controlled, intention-to-treat, etc.)
   B. Design and structure
      1. Observational studies
      2. Clinical Trials
         a. Placebo-controlled
         b. “Equivalence” or non-superiority
   C. Inclusion and exclusion criteria; ethical issues
   D. End-points
      1. Types: surrogate, primary or secondary, hard
      2. Ascertainment of reliability: statistical power of positive and negative results; degree of adherence to protocol, criteria for recognition of end-points
   E. Applicability to different hypertensive

II. Description of results
   A. Relative vs. absolute benefits
   B. Meta-analysis
      1. Primary hypothesis
      2. Inclusion criteria
      3. Outcomes of interest
      4. Analytic methods
   C. Cost-effectiveness

References

I. Performance of clinical trials


II. Description of results

Rothwell Pm. External validity of randomized controlled trials: to whom do the results of this trial apply? Lancet. 2005; 365:82-93.
Section 11: Which Drugs for Which Patients?
Evidence from Randomized Controlled Hypertension Treatment Trials

I. Early (typically placebo-controlled) trials in diastolic hypertension

II. Early trials in systolic hypertension (usually placebo-controlled)

III. Comparison of target blood pressures

IV. Trials of different initial antihypertensive drug therapies: No significant differences in primary endpoint

V. Trials of different initial antihypertensive drug therapies: Significant differences in primary endpoint

VI. Trials of antihypertensive drug therapies for specific uses
     -- table

VII. Results of Meta-analyses

VIII. ALLHAT Editorials

References (in historical rather than alphabetical order):

I. Early (typically placebo-controlled) trials in diastolic hypertension

Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. JAMA. 1967; 202:1028-1034.


II. Early trials in systolic hypertension (usually placebo-controlled)


III. Comparison of target blood pressures


IV. Trials of different initial antihypertensive drug therapies: No significant differences in primary endpoint


The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid

V. Trials of different initial antihypertensive drug therapies: Significant differences in primary endpoint


VI. Results of meta-analyses

VII. Trials of antihypertensive drug therapies for “compelling indications”


Eplerenone Post-myocardial infarction Heart Failure Efficacy and Survival Study (EPHESUS) Investigators. JAMA. 2003; 287:1309-1313.

Table: Specific Uses for Antihypertensive Drugs

<table>
<thead>
<tr>
<th>“Condition”</th>
<th>Treatment Prevents/Delays</th>
<th>Recommended in 1997</th>
<th>Recommended in 2004</th>
</tr>
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<tbody>
<tr>
<td>Heart Failure (of the systolic type)</td>
<td>CV Events</td>
<td>ACE-I (CONSENSUS, SAVE, etc.)</td>
<td>β-Blockers (MERIT-HF, etc.); spironolactone (RALES); ARB (Val-HeFT, CHARM)</td>
</tr>
<tr>
<td>After Recent Myocardial Infarction (MI)</td>
<td>Recurrent Infarction or Death</td>
<td>β-Blocker (ISIS, etc.)</td>
<td></td>
</tr>
<tr>
<td>Diminished LV function after recent MI</td>
<td>Recurrent Infarction, CHF Hospitalization</td>
<td>ACE-I (SAVE, TRACE)</td>
<td>Eplerenone (EPHESUS)</td>
</tr>
<tr>
<td>Known CV Disease</td>
<td>CV Events</td>
<td></td>
<td>ACE-I (HOPE, EUROPA)</td>
</tr>
<tr>
<td>Type 1 Diabetes Mellitus</td>
<td>Deterioration in Renal Function</td>
<td>ACE-I (CCSG)</td>
<td></td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>CV Events</td>
<td></td>
<td>ACE-I (MICRO-HOPE)</td>
</tr>
<tr>
<td>Type 2 Diabetic Nephropathy</td>
<td>Deterioration in Renal Function</td>
<td></td>
<td>ARBs (IDNT, RENAAL)</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>Progression of Microalbuminuria</td>
<td></td>
<td>ACE-I (MICRO-HOPE); ARB (IRMA-2)</td>
</tr>
<tr>
<td>Older Hypertensive Persons</td>
<td>CV Events</td>
<td>Diuretic (SHEP); DHP-CA (Syst-Eur)</td>
<td>ACE-I or DHP-CA (STOP-2); DHP-CA (Syst-China); ARB (SCOPE, second-line); ARB (LIFE)</td>
</tr>
<tr>
<td>Non-diabetic Renal Impairment</td>
<td>Deterioration in Renal Function</td>
<td>“loop” diuretic</td>
<td>ACE-I (REIN, AIPRI, AASK); ARB + ACE-I (COOPERATE)</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>Stroke and CV Events</td>
<td></td>
<td>ACE-I±diuretic (PROGRESS)</td>
</tr>
<tr>
<td>LVH (using strict criteria)</td>
<td>CV Events (really only stroke?)</td>
<td></td>
<td>ARB (LIFE)</td>
</tr>
</tbody>
</table>

CONSENSUS = COoperative North Scandinavian ENalapril SSurvival Study (N Engl J Med. 1987; 316:1429-1435)
SHEP = Systolic Hypertension in the Elderly Program (JAMA, 1991; 265:3255-3264)
Syst-Eur = Systolic Hypertension in Europe trial (Lancet. 1997; 360:757-764)
MERIT-HF = MEtoprolol Randomized Intervention Trial in congestive Heart Failure (JAMA, 2000; 283:1295-1302)
CHARM = Candesartan in Heart failure: Assessment of Reduction in Morbidity and mortality
(Lancet. 2003;362:759-766)
EPHESUS = Eplerenone Post-myocardial infarction Heart Failure Efficacy and Survival Study
EUROPA = EUropean Reduction Of cardiac events with Perindopril in stable coronary Artery
disease (Lancet. 2003; 362:782-788)
MICRO-HOPE = MIcroalbuminuria, Cardiovascular and Renal Outcomes substudy of the Heart
RENAAL = Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the
STOP-2 = Swedish Trial in Old Patients with hypertension #2 (Lancet. 1999; 354:1751-1756)
Syst-China = Systolic Hypertension in China trial (J Hypertens. 1998; 16:1823-1829)
SCOPE = Study on COgnition and Prognosis in the Elderly (J Hypertension. 2003; 21:875-886)
LIFE = Losartan Intervention for Endpoint Reduction (Lancet. 2002; 359:995-1003)
REIN = Ramipril Evaluation In Nephropathy trial (Lancet. 1998; 352:1252-1256)
AIPRI = Angiotensin-converting-enzyme Inhibition in Progressive Renal Insufficiency (Kidney
Int. 1997; Suppl. 63:S63-S67)
AASK = African American Study of Kidney disease and hypertension (JAMA. 2002; 288:2421-2431)
COOPERATE = Combination treatment of angiotensin-II receptor blocker and angiotensin-

VIII. ALLHAT Editorials:

Laragh JH, Sealey JE. Relevance of the plasma renin hormonal control system that regulates
blood pressure and sodium balance for correctly treating hypertension and for evaluating
Moser M. Results of ALLHAT: is this the final answer regarding initial antihypertensive drug
Messerli F. ALLHAT, or the soft science of the secondary endpoint. Ann Intern Med. 2003;
139:777-780.

Section 12: Which Drugs for Which Patients? Antihypertensive Drug Selection Based on Renin System Pathophysiology

I. Renin (R) versus Volume (V) Hypertension: The Laragh Method
   A. Pathophysiological Stratification of Patients (also see Section 3)
   B. Selection of “R” and “V” drugs
      1. Patient with newly diagnosed or untreated hypertension
      2. Patient with persistent hypertension despite drug treatment
      3. Patient with a hypertensive crisis
   C. Renin and Assessment of Cardiovascular Risk

II. Age/Ethnicity: The Veterans Administration and British AB/CD Method
   A. Trial Results
   B. British Hypertension Society Guidelines

References

I. Renin (R) versus Volume (V) Hypertension: The Laragh Method


**Alderman MH, Madhavan S, Ooi WL, Cohen H, Sealey JE, Laragh JH. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension [see comments]. N Engl J Med 1991;324(16):1098-104. This prospective work-site study of more than 1700 patients with essential hypertension demonstrated that risk of heart attack was increased in patients with high plasma renin activity prior to antihypertensive drug treatment. Plasma renin activity was an independent risk factor for heart attack in this study.


**II. Age/Ethnicity: The Veterans Administration and British AB/CD Method**


**Dickerson JEC, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ. Optimization of antihypertensive treatment by crossover rotation of four major drug classes. Lancet 1999;353:2008-2013. A prospective, crossover-design study demonstrating that most patients with essential hypertension can have their blood pressure controlled with single drug therapy when a systematic, pathophysiologic-based approach is used. Blood pressure control with an ACE inhibitor was related to the pretreatment plasma renin activity level.

Section 13: Barriers to Hypertension Treatment and Control

I. Physician barriers: translating research into practice
II. Patient barriers: methods to improve adherence
III. Structural barriers

References

I. Physician barriers: translating research into practice

II. Patient barriers: methods to improve adherence


Benson J et al. Keep taking the tablets; balancing the pros and cons when deciding to take blood pressure treatment. Br Med J. 2003; 326;1314-5.


III. Structural barriers: changes in health care delivery systems

Section 14: Approach to Resistant Hypertension (also see Section 12)

I. Definition
II. Prevalence
III. Causes
   A. Pseudo-resistance
   B. Non-adherence to therapy
   C. Non-compliance (by physician) with treatment guidelines
   D. Drug-related adverse effects
   E. Associated conditions
   F. Identifiable causes of hypertension
   G. Volume overload
IV. Evaluation and Therapy
   A. Ambulatory blood pressure monitoring
   B. Hemodynamic assessment
   C. Assessment of adherence to prescribed therapy
   D. Institution and maintenance of lifestyle modifications
   E. Maintenance of slight contraction of intravascular volume
   F. Appropriate additions of drug therapy
   G. Referral to a Hypertension Specialist

References:

I. Definition


II. Prevalence

III. Causes


Vidt DG. Contributing factors in resistant hypertension: Truly refractory disease is rarely found in a properly conducted workup. Postgrad Med. 2000 (May 1); 107:57-70.


IV: Evaluation and Therapy


Section 15: Hypertensive Crises (also see Section 12)

I. Epidemiology
II. Definition: crisis vs. emergency and urgency
III. Mechanisms
   A. Rise in blood pressure (BP) beyond critical level
      1. Vascular necrosis
      2. Breakthrough hyperperfusion
   B. Critical level on background of normotension or hypertension
   C. Role of humoral factors: renin-angiotensin, catecholamines
IV. Clinical features and course
   A. Accelerated – malignant hypertension
   B. Hypertensive encephalopathy, neurologic features, brain imaging
   C. Retinal findings
   D. Cardiac findings
   E. Hematologic: microangiopathic features
   F. Renal: azotemia, proteinuria
   G. Conditions that mimic hypertensive crises
V. Evaluation
   A. History and risk factors
   B. Physical examination
   C. Laboratory tests
      1. Routine
      2. Evaluation for renovascular disease, pheochromocytoma
VI. Therapy
   A. Parenteral drugs
      1. Vasodilators
      2. Adrenergic inhibitors
      3. Diuretics
   B. Goal of therapy: short-term vs. prolonged
   C. Specific situations
      1. Acute stroke
      2. Acute myocardial infarction
      3. Congestive heart failure
      4. Aortic dissection
      5. Pheochromocytoma
      6. Substance abuse
      7. Postoperative
      8. Preeclampsia/eclampsia
References (Please note that all of the articles in the sections below are either review articles or seminal articles.)

I. **Epidemiology**


II. **Definition: crisis vs. emergency and urgency**


III. **Mechanisms**


IV. **Clinical features and course**


V. **Evaluation**


VI. Therapy


Section 16: Identifiable (Secondary) Causes of Hypertension

I. Renal parenchymal diseases (see Section 7)
   A. Classification
      1. Rapidly progressive renal disease
      2. Chronic renal diseases
         a. Diabetic
         b. Non-diabetic
         c. Autosomal dominant polycystic kidney disease
      3. End-stage renal disease
         a. During dialysis
         b. Post-transplantation
      4. Renin-secreting tumors
   B. Management
      1. Antihypertensive drug therapy
         a. Influence of renal insufficiency on choices and doses
         b. Goal of therapy
      2. Other therapies: dietary, drug

II. Renovascular hypertension and ischemic nephropathy
   A. Prevalence in different populations
   B. Mechanisms
   C. Lesions associated with renovascular hypertension
      1. Intrinsic
         c. Atherosclerotic
         d. Fibromuscular
         e. Other
      2. Extrinsic
   D. Clinical features
      1. History
      2. Physical exam
      3. Laboratory findings
   E. Diagnosis
      1. Peripheral and renal vein renin assay
      2. Imaging: nuclear, ultrasonographic, angiographic
      3. Functional: captopril-enhanced renography
   F. Therapy: choices and results
      1. Medical
      2. Angioplasty and stents
      3. Surgical
III. Renin-independent mineralocorticoid hypertension
   A. Mineralocorticoid receptor activating hormones
      1. Aldosterone
         a. Aldosterone-producing adenoma
         b. Bilateral idiopathic zona glomerulosa hyperplasia
         c. Glucocorticoid-remediable aldosteronism
         d. Adrenal carcinoma
         e. Primary (unilateral) adrenal hyperplasia
      2. Deoxycorticosterone (DOC)
         a. Congenital adrenal hyperplasia
            1) 11β-hydroxylase deficiency
            2) 17α-hydroxylase deficiency
         b. DOC-secreting tumor
         c. Glucocorticoid resistance syndrome
      3. Cortisol
         a. Cushing’s syndrome
         b. 11β-hydroxysteroid dehydrogenase deficiency
            1) Congenital: apparent mineralocorticoid excess
            2) Acquired: Glycyrrhetinic acid

   B. Clinical features
      1. Hypokalemia and inappropriate kaliuresis
      2. Normokalemia
      3. Other biochemical changes

   C. Differential diagnosis
      1. Non-mineralocorticoid causes of renal potassium wastage, e.g. Liddle’s syndrome
      2. Renin-dependent (secondary) aldosteronism

   D. Diagnosis of primary aldosteronism
      1. Screening: Plasma aldosterone concentration : plasma renin activity ratio
      2. Confirmatory testing
      3. Subtype diagnosis
      4. Therapy of primary aldosteronism
         A. Medical
         B. Surgical

IV. Adrenal pheochromocytoma and catecholamine-secreting paraganglioma
   A. Pathophysiology
      1. Sporadic
      2. Syndromic
      3. Malignant

   B. Clinical features
      1. Symptoms and signs
      2. Conditions that mimic pheochromocytoma

   C. Diagnosis
      1. Biochemical
      2. Localization
3. Genetic testing
   D. Therapy
      1. Benign neoplasm
      2. Malignant neoplasm

V. Adrenal incidentaloma
   A. Prevalence and differential diagnosis
   B. Evaluation and management

VI. Other hormonal causes
   A. Thyroid: Hypo- and hyper-thyroidism
   B. Hyperparathyroidism and other hypercalcemic states
   C. Acromegaly

VII. Other
   A. Drug-induced
   B. Psychogenic
   C. Sleep apnea
   D. Coarctation
   E. Neurovascular compression

References

I. Renal parenchymal diseases


Renovascular hypertension and ischemic nephropathy


III. Renin-independent mineralocorticoid hypertension


IV. Adrenal pheochromocytoma and catecholamine-secreting paraganglioma


V. Adrenal incidentaloma


VI. Other hormonal causes


VII. Other

Section 17: Hypertension in Special Populations

I. Infants and children
   A. Measurement of blood pressure
   B. Definition of hypertension
   C. Etiology
      1. Prepubertal: secondary causes usual
      2. Postpubertal: often the onset of primary (essential) hypertension
   D. Evaluation
   E. Therapy
      1. Lifestyle modifications
      2. Antihypertensive drugs

II. Women
   A. Course
   B. Therapy
   C. Oral contraceptives and estrogen replacement

III. Pregnancy related
   A. Classification
      1. Gestational/transient
      2. Preeclampsia/eclampsia
      3. Chronic hypertension ± superimposed preeclampsia
   B. Epidemiology
      1. Risk factors
      2. Morbidity: fetal and maternal
      3. Prognostic implications post-pregnancy
   C. Pathophysiology of preeclampsia
      1. Genetic contribution
      2. Uteroplacental abnormalities
      3. Hormonal alterations
      4. Complications: renal, hematological, hepatic,
   D. Prevention and treatment of preeclampsia
      1. Aspirin, calcium supplements
      2. Role of antihypertensive drug therapy
      3. Indications for delivery
      4. Postpartum evaluation and management
   E. Chronic hypertension in pregnancy
      1. Prepregnancy counseling and adjustment of medications
      2. Indications for antihypertensive drug therapy
      3. Recognition of identifiable (secondary) causes

IV. Older persons with systolic hypertension
   A. Definition
   B. Prevalence
   C. Pathophysiology (also see Section 3)
      1. Arterial stiffness
      2. Consequences
D. Evaluation beyond routine
   1. Supine and upright blood pressures
   2. Exclusion of identifiable causes
   3. Recognition of co-morbid conditions, e.g. prostatism
E. Therapy
   1. Lifestyle modifications
   2. Management of postural/postprandial hypotension if present
   3. Antihypertensive drug
      a. Choices for initial therapy
      b. Goal of therapy

V. African-Americans
   A. Prevalence
   B. Disease Mechanisms (Also see Sections 3 and 4)
      1. Genetic contribution
      2. Socioeconomic factors
      3. Biochemical/hormonal: sodium sensitivity, plasma renin activity, etc.
      4. Target organ susceptibility: coronary, cerebral, renal
   C. Therapeutic considerations
      1. Differences in response to monotherapy
      2. Appropriate goals to reduce target organ

VI. Other ethnic minorities
VII. The diabetic hypertensive (also see Section 6)
VIII. Perioperative hypertension
IX. Transplant hypertension
X. Hypertension and Erectile Dysfunction

General Reviews


I. Infants and children

**Bao W. Threefoot SA, Srinivasan SR, Berenson GS. Essential hypertension predicted by tracking of elevated blood pressure from childhood to adulthood: the Bogalusa Heart Study. Am J Hypertens. 1995; 8:657-665. One of the essential papers from the landmark Bogalusa Heart Study which identifies in a bi-racial population the early onset
of hypertension and cardiovascular risk factors. Other early reports documented the need for early recognition of hypertension in children and adolescents.


II. Women


III. Pregnancy related hypertension


approaching high blood pressure in pregnancy. From the National High Blood Pressure Education Program.

Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. Lancet. 2001; 357:53-56.


IV. Older persons with systolic hypertension


V. African-Americans


VI. Other ethnic minorities


VII. The diabetic hypertensive (see Section 6)

VIII. Perioperative hypertension


IX. Transplant hypertension