Introduction

This REFERENCE LIST IN CLINICAL HYPERTENSION is produced and published by the American Society of Hypertension, Inc. (ASH). The ASH REFERENCE LIST is designed as a comprehensive outline and reference guide to the clinical hypertension literature.

Due to escalating obesity and population aging in both developed and developing countries, the global burden of hypertension is rising and projected to affect 1.5 billion persons, one-third of the world’s population, by 2025. Thus, hypertension remains the leading cause of death worldwide and one of the world’s great public health problems.

Figure Legend: Global distribution of mortality attributable to 20 leading selected risk factors. Source: WHO, 2002 [http://www.who.int/mdg/publications/04MDGChapter4.pdf](http://www.who.int/mdg/publications/04MDGChapter4.pdf)

This REFERENCE LIST 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.
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BOOKS:

Kaplan, NM and Victor RG  Kaplan’s Clinical Hypertension. 10th Edition. Lippincott,
Williams and Wilkins; 2009.
Association; 2008.
Company; 2005.
Laragh JH. Laragh’s Lessons in renin system pathophysiology for treating hypertension
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
American Heart Association: Heart and Stroke Facts: www.americanheart.org

Section 1: Epidemiology of Hypertension

I. Blood pressure risk as a continuous variable and 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 JNC 7 classification of blood pressure
Benetos A, Thomas F, Bean KE, Guize L. Why cardiovascular mortality is higher in
treated hypertensives versus subjects of the same age in the general population. J. Hypertension. 2003; 21:1635–1640


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


Victor RG, Haley RW, Willett E, Peshock RM, Vaeth PC, Leonard D, Basit M, Cooper...


III. Predominance and importance of systolic hypertension


van Bemmel Gussekloo TJ, Westendorp RG, and Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. J.Hypertens. 2006. 24(2):287-92.


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. Results of Trials
   C. Current Recommendations

II. Pre-natal influences
   A. 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
   I. Hormones: estrogen, adrenal steroids
   J. Sympathomimetic agents: cocaine
   K. Therapeutic agents: NSAIDs, erythropoietin, cyclosporine, tacrolimus
   L. Others: caffeine, licorice, lead, etc.
I. Population versus individual approaches


Wald NJ and Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 326, 2003; 7404:1419.


Skov K, Julius S, Nesbitt S, and Mulvany MJ. Can hypertension be prevented? The Danish Hypertension Prevention Project and the Trial of Prevention of

II. Pre-natal/natal influences
Davies AA, Smith GD, May MT, and Ben-Shlomo Y. Association between birth weight and blood pressure is robust, amplifies with age, and may be underestimated. Hypertension 2006; 48(3):431-36.

III. Environmental exposures and exogenous substances

Section 3: 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 4: Pathophysiologic Mechanisms of Hypertension

I. Hemodynamic Subsets
II. Neural Mechanisms
III. Renal Mechanisms
IV. Vascular Mechanisms
V. Hormonal Mechanisms

A. Renin-Angiotensin-Aldosterone System
   B. Endothelin
   C. Insulin Resistance/Obesity
References

I. Hemodynamic Subtypes


II. Neural Mechanisms


III. Renal Mechanisms


IV. Vascular Mechanisms


V. Hormonal Mechanisms

A. Renin-Angiotensin-Aldosterone System

Blumenfeld JD, Sealey JE, Alderman MH, Cohen H, Lappin R, Catanzaro DF, Laragh JH. Plasma renin activity in the emergency department and its independent


**B. Endothelin**


**C. Insulin Resistance/Obesity**

Section 5: Diagnostic Assessment

I. Accurate and adequate measurement of blood pressure (BP)
   A. Office
   B. Automatic ambulatory monitoring
   C. Home, self-recorded

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

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

V. Overall cardiovascular risk stratification

References

I. Accurate and adequate measurement of blood pressure (BP)
Dabl educational website: www.dableducational.com
Staessen JA, Den Hond E, Celis H, et al. Antihypertensive treatment based on blood
pressure measurement at home or in the physician's office: a randomized controlled trial. JAMA. 2004; 291:955-964.

II. Additional assessment of prognosis

III. White coat hypertension
Verdecchia P, Palatini, Schillaci G, et al. Independent predictors of isolate clinic (‘white-
IV. Initial evaluation


V. Overall cardiovascular risk stratification

Donnelly R, Hanwood D, Londeon NJM. ABC of arterial and venous disease. Non-


Section 6: Metabolic Abnormalities and Hypertension

I. Obesity related hypertension
   A. Prevalence of the association
   B. Pathophysiology
   C. Evaluation
   D. Management

II. Dyslipidemia
   A. Prevalence of the association
   B. Mechanisms
   C. Management

III. The metabolic syndrome
   A. Components of the syndrome
B. Pathophysiology
C. Management

IV. Diabetes mellitus
A. Prevalence of the association with types 1 and 2 diabetes
B. Pathophysiology
C. Evaluation
D. Management

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I. Obesity related hypertension
http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
Davy KP, Hall JE. Obesity and hypertension: two epidemics or one? Am J Physiol Regul
Després JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk
Field AE, Coakley EH, Must A, et al. Impact of overweight on the risk of developing
common chronic diseases during a 10- year period. Arch Intern Med. 2001; 161:1581-
1586.
Hall JE, Hildebrandt DA, Kuo J. Obesity hypertension: role of leptin and sympathetic
Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep
apnea, and hypertension in a large community-based study. Sleep Heart Health Study.
Stevens VJ, Obarzanek E, Cook NR, et al. Long-term weight loss and changes in blood
pressure: results of the Trials of Hypertension Prevention, phase II. Ann Intern Med.
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SY, Davis SN, Biaggioni I. Autonomic contribution to blood pressure and metabolism in
Esler M, Straznicky N, Eikelis N, Masuo K, Lambert G, Lambert E. Mechanisms of
sympathetic activation in obesity-related hypertension. Hypertension. 2006; 48(5):787-
96.

II. Dyslipidemia
Executive Summary of The Third Report of The National Cholesterol Education
Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood
Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on
coronary atherosclerosis in patients with acute coronary syndromes: a randomized
atorvastatin in hypertensive patients who have average or lower-than-average
cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-- Lipid


**III. The metabolic syndrome**


**IV. Diabetes mellitus**


Section 7: 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. Pathogenesis: the role of hypertension
C. Consequences
D. Effect of antihypertensive therapies on regression or prevention

II. Cerebrovascular
A. Manifestations
B. Pathogenesis: the role of hypertension
C. Treatment of hypertension
1. Acute stroke
2. Chronic stroke

III. Renal parenchymal disease
A. Association of hypertension with various renal diseases
B. Role of hypertension in progressive renal insufficiency
C. Cardiovascular complications

IV. Other vascular diseases
A. Types
1. Atherosclerotic: aneurysms, dissections embolization
2. Vasospastic and inflammatory
3. Peripheral arterial disease

V. Retinopathy

VI. Sexual dysfunction
A. Prevalence
B. Management

References

I. Cardiac
Verdecchia P, Angeli F, Borgioni C, Gattobigio R de Simone G, Devereux RB, Porcellati
Bhatia RS, Tu JV, Lee BS, Austin PC. Outcome of heart failure with preserved ejection fraction in a population-based study. NEJM. 2006; 355:260-269.

II. Cerebrovascular
Goldstein IB, Bartzokis G, Guthrie D, Shapiro D. Ambulatory blood pressure and brain a

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
   6. Cessation of substance abuse

References
I. The place for combined lifestyle modifications


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


Griffith LE, Guyatt GH, Cook RJ, et al. The influence of dietary and nondietary calcium
Britton A. How much and how often should we drink? BMJ. 2006;332(7552):1224-5.
Section 9: Treatment of Hypertension: Overcoming Barriers to Control

I. Current Status

II. Physician barriers

III. Therapy barriers

IV. Patient barriers

V. Structural barriers

References

I. Current Status


II. Physician barriers


### III. Therapy Barriers


**IV. Patient barriers**


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.


**V. Structural barriers**


Section 10: Therapy of Hypertension: Features of Antihypertensive Drugs

I. General principles of drug therapy
II. Individual drug classes used in chronic treatment
   A. Diuretics
   B. Adrenergic inhibitors
   C. Direct vasodilators
   D. Calcium-channel blockers
   E. Angiotensin converting-enzyme inhibitors
   F. Angiotensin II receptor blockers
   G. Other Agents
III. Combination drugs
IV. Current patterns of use
V. Monitoring adequacy of therapy
   A. Need for 24-hour control
   B. Avoidance of tissue hypoperfusion
   C. Decision to “step-down” therapy

References

I. General principals of drug therapy
Morgan TO, Anderson A. Different drug classes have variable effects on blood pressure depending on the time of day. Am J Hypertens. 2003;16(1):46-50.


II. Individual drug classes used in chronic treatment

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


Leenen FH, Nwachuku CE, Black HR, Cushman WC, Davis BR, Simpson LM, Alderman MH, Atlas SA, Basile JN, Cuyjet AB, Dart R, Felicetta JV, Grimm RH,


Tsuyuki RT, McDonald MA. Angiotensin receptor blockers do not increase risk of myocardial infarction. Circulation. 2006;114(8):855-60.


III. Combination drugs


IV. Current patterns of drug use

V. Monitoring adequacy of therapy

Section 11: Clinical Trials: Methods, Results and Consequences

I. Methodology

II. Results of comparative trials

III. Meta analyses

IV. Goals of Therapy

References:

I. Methodology

Rothwell Pm. External validity of randomized controlled trials: to whom do the results of this trial apply? Lancet. 2005; 365:82-93.
Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" Lancet. 2005;365(9453):82-93.
Pocock SJ. The simplest statistical test: how to check for a difference between treatments. BMJ. 2006;332(7552):1256-8.

II. Results of comparative trials


PROGRESS Collaborative Group. Randomized trial of a perindopril-based blood-pressure lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001; 358:1033-1041.


### III. Meta Analyses


Mancia G. Role of outcome trials in providing information on antihypertensive treatment:
IV. Goals of Therapy


Townsend RR. Can we justify goal blood pressure of <140/90 mm Hg in most hypertensives? Curr Hypertens Rep. 2005;7(4):257-64.


Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003;326(7404):1419.


Section 12: Hypertension in Special Populations

I. Infants and children
II. Women
III. Pregnancy related
IV. Older persons with systolic hypertension
V. African-Americans
VI. Other ethnic minorities
VII. The diabetic hypertensive (also see Section 6)
VIII. Perioperative hypertension

References:


I. Infants and children


II. Women

III. Pregnancy related hypertension


IV. Older persons with systolic hypertension


Mar;16(3):249-58.

V. African-Americans
VI. Other ethnic minorities


VII. The diabetic hypertensive (see Section 6)

VIII. Perioperative hypertension


Section 13: Approach to Resistant Hypertension (also see Section 12)

I. Definition
II. Prevalence
III. Causes
IV. Evaluation and Therapy

References:

I. Definition


II. Prevalence

III. Causes

IV: Evaluation and Therapy

Section 14: Hypertensive Crises
I. Definition and Epidemiology


II. Mechanisms


III. Clinical features and evaluation


IV. Therapy


Vidt DG. Emergency room management of hypertensive urgencies and emergencies. J
Section 15: Identifiable (Secondary) Causes of Hypertension

I. Renal parenchymal diseases (see Section 7)
   A. Classification
   B. Management

II. Renovascular hypertension and ischemic nephropathy
   A. Prevalence in different populations
   B. Mechanisms
   C. Clinical features
   D. Diagnosis
   E. Therapy

III. Mineralocorticoid hypertension
   A. Aldosterone excess
      1. Clinical features
      2. Differential diagnosis
      3. Diagnosis
      4. Therapy of primary aldosteronism
   B. Deoxycorticosterone (DOC) excess
   C. Cortisol excess

IV. Pheochromocytoma and catecholamine-secreting paraganglioma
   A. Pathophysiology
   B. Clinical features
   C. Diagnosis
   D. Therapy

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


II. Renovascular hypertension and ischemic nephropathy

III. Mineralocorticoid hypertension
Charmandari E, Kino T, Souvatzoglou E, Vottero A, Bhattacharyya N, Chrousos GP. Natural glucocorticoid receptor mutants causing generalized glucocorticoid resistance:


Giacchetti G, Ronconi V, Lucarelli G, Boscaro M, Mantero F. Analysis of screening and confirmatory tests in the diagnosis of primary aldosteronism: need for a


IV. Pheochromocytoma and catecholamine-secreting paraganglioma


V. Adrenal incidentaloma

Kohane IS, Masys DR, Altman RB. The incidentalome: a threat to genomic medicine. JAMA. 2006;296(2):212-5.

VI. Other hormonal causes

VII. Other