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Hypertension

Strategy for Continued Success in Treatment for the 21st Century

November 15, 2005

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Most important public health problem in developed countries

- Dramatic decrease in undiagnosed and untreated patients in the last 20 years
- Treatment likely the most important factor in the decrease in Cardiovascular mortality in the last 20 years
- 90-95% of cases - cause is unknown

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Current problems

- Choice of treatment regimen - "tailored" to the patient on the basis of:
- Genetics?
- Side effects?
- Compliance?
- Cost?

Prevalence

- Framingham Study (white, suburban US residents)
- 15-20% - BP > 160/95
- 40-50% - BP > 140/90
- Higher incidence in nonwhite population

Overall US Statistics

- Most common reason for office visits and use of prescription drugs
- US Census Bureau - 30% incidence in people over 18 years of age
- 60-65 million US citizens
- Present in over 50% of people over 65

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Risk Factors for Hypertension

- Genetics account for 30% of blood pressure variation
- Salt intake - a necessary but not sufficient cause
- Excess alcohol intake
- Obesity
- Personality traits - hostility, time urgency

African-Americans

- Higher mortality, lower life expectancy than white Americans

Secondary Hypertension

- Incidence varies - likely depends upon the extent of diagnostic workup
- 6% of middle aged males
- Understanding of etiology of hypertension may blur the distinction between Essential and Secondary Hypertension

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Etiologies

- Primary renal disease - an increasing epidemic
- Oral contraceptives
- Pheochromocytoma - rare
- Primary aldosteronism
- Renovascular Disease
- Cushing's syndrome
- Sleep apnea - new association
- Coarctation of the aorta - check BP in both arms!

The Importance of the Kidneys

- Long-term regulation of effective blood volume, sodium balance, and extra cellular fluid volume
- The Pressure-Naturesis mechanism - must work exquisitely - any derangement can lead to a "resetting" of blood pressure so as to re-establish sodium balance

Mechanisms?

- Nitric Oxide may be a primary mediator
- "Macula Dense" mechanism - or tubuloglomerular feedback - a response to distal tubule blood flow and solute concentration changes
- "Myogenic Mechanism" - response of interlobular and arcuate arteries, afferent arterioles to changes in wall tension

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Most significant Mechanism?

- Renin - angiotensin most likely
- Increases in intra-renal Angiotensin II cause decreased distal nephron volume delivery and sodium excretion
- This likely suppresses the Pressure-Naturiesis mechanism

Renin-Angiotensin System

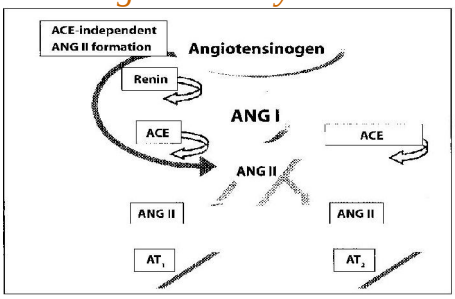

Figure 3. *The RAAS: formation and targets of Angiotensin II.*[10]

Reprinted from *The American Journal of Medicine*, VB9; Unger; The role of the renin-angiotensin system in the development of cardiovascular disease; 6A, 2002, with permission from Excerpta Medica, Inc.

Complications of Chronic Hypertension

- The MOST COMMON risk factor for PREMATURE cardiovascular disease
- Congestive Heart Failure - another epidemic of the 21ast century
- Stroke and intracerebral hemorrhage
- Chronic renal insufficiency

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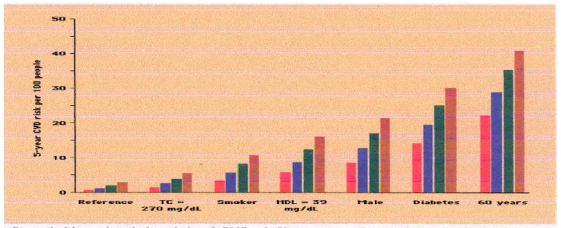
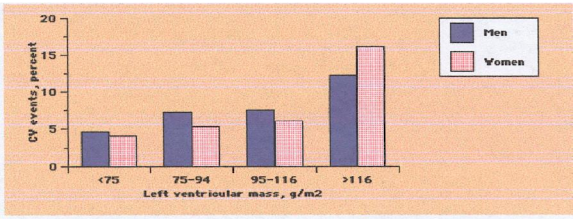


Cumulative absolute risk of CVD at five years Cumulative absolute risk of cardiovascular disease (CVD) at five years according to systolic blood pressure and specified levels of other risk factors. The reference category is a nondiabetic, nonsmoking 50 year-old woman with a serum total cholesterol (TC) of 154 mg/dL (4.0 mmol/L) and HDL-cholesterol of 62 mg/dL (1.6 mmol/L). The CVD risks are given for systolic blood pressure levels of 110, 130, 150, and 170 mmHg. In the other categories, the additional risk factors are added consecutively. As an example, the diabetes category is a 50-year-old diabetic man who is a smoker and has a total cholesterol (TC) of 270 mg/dL (7 mmol/L) and HDL-cholesterol of 39 mg/dL (1 mmol/L). (Adapted from Jackson, R, Lawes, CM, Bennett, DA, et al, Lancet 2005; 365:434).

The Risk of Left Ventricular Hypertrophy

- Associated with heart failure, ventricular arrhythmias, SUDDEN DEATH, and death following a myocardial infarction



Cardiovascular risk with LVH by echocardiography Four-year, age-adjusted incidence of cardiovascular events in men and women in the Framingham Study according to left ventricular mass determined by echocardiography. Subjects with increased left ventricular mass (far right panel) had a marked increase in cardiovascular risk. (Adapted from Levy, D, Garrison, RJ, Savage, DD, et al, N Engl J Med 1990; 322:1561.)

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Diagnosis

- US Preventive Services Task Force recommends a BP measurement for each office visit for patients over 21 years of age
- Proper diagnosis requires 3-6 office visits over several weeks or months - studies reveal a 10-15 mm Hg drop between visits #1 and #3!

How to take blood pressure!

- After five minutes supine, then 2 minutes after standing
- Arm at heart level
- Cuff size - length of bladder 80%, width of bladder 40% of circumference of the upper
- Check both arms - take higher reading
- Diagnosis - 3 readings at rest at least one week apart

Basic Evaluation of the Hypertensive Patient

- History and Physical Examination
- Laboratory Testing - hematocrit, urinalysis, routine chemistries (glucose, creatinine, electrolytes), lipid profile
- Electrocardiogram
- Possible - echocardiography if LVH suspected or present on ECG

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Renovascular Hypertension

- Most common cause of secondary hypertension

When to suspect ?

- Severe, refractory hypertension
- Onset before puberty, or sudden onset after age 50
- Unexplained creatinine elevation
- Elevated creatinine after ACE or ARB therapy
- Patients with generalized atherosclerosis
- Incidental findings of asymmetry in kidney size
- Abdominal bruit
- “Flash” pulmonary edema with severe hypertension
- Negative family history of hypertension

Therapeutic Options and Goals

- Fundamental Relationship of Pressure, Resistance, and Cardiac Output -
- BP = Cardiac Output x Resistance
- Medications attack these fundamental mechanisms

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Classes of Drugs affecting Cardiac Output

- Diuretics - decrease blood volume
- Beta - Blockers - decrease cardiac contractility
- Central nervous system alpha-agonists (I.e. Clonidine)

Classes of Drugs Affecting Peripheral Resistance

- Vasodilators (I.e. hydralazine, minoxidil)
- ACE Inhibitors
- Angiotensin Receptor Blockers
- Calcium channel blockers (dihydropyridines and non-dihydropyridines)
- Alpha-1 Blockers (I.e. terazosin)

How do you sort out which drug for which patient?

- Side-effects vary
- Costs and insurance coverage vary significantly
- There may be “COMPELLING INDICATIONS” for one class of drugs vs. another
- What do the large-scale epidemiologic studies and “Clinical Guideline” reports tell us?

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Joint National Committee on the Prevention, Detection, and Treatment of High Blood Pressure

- Funded by the National Heart, Lung and Blood Institute
- Last report - May, 2003 in Journal of the American Medical Association
- Six years since JNC 6 report (1997)

JNC 7

SEVEN

KEY

MESSAGES!

JNC 7

- In patients over 50, Systolic BP over 140 mm Hg is a much more important risk factor than diastolic BP
- The risk of CVD, beginning at 115/75, DOUBLES with each increment of 20/10 mm Hg; normotensive people at age 55 have a 90%lifetime chance of having hypertension

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JNC 7

- "Pre-Hypertension" - new category of patients with BP of 120-139/ 80-89 mm Hg should be evaluated and advised re CV risk modification
- Thiazide-type diuretics should be used in most with uncomplicated hypertension, either alone or in combination UNLESS there are "compelling indications" for other medications

JNC 7

- Most patients will require 2 or more medications to reach a goal of 140/90 or less, or 130/80 in patients with diabetes or chronic kidney disease
- Initiation of 2 medications should be considered if BP is more than 20/10 mm Hg above goal BP

JNC 7

- "The most effective therapy prescribed by the most careful clinician will control hypertension only if patients are motivated."

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Additional Key Points

- The relationship between BP and CV disease risk is “continuous, consistent, and independent of other risk factors.”
- Ambulatory Monitoring is useful in some circumstances - drug resistance, hypotensive symptoms, episodic hypertension, and autonomic dysfunction

Is there controversy about JNC 7?

Absolutely!

The ALLHAT study vs the rest of the world!

ALLHAT
JAMA December 2002

- Over 33, 000 patients followed for mean 4.9 years (4-8)
- Higher risk group - over 55, at least one OTHER risk factor for CHD

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Treatment Options

- Chlorthalidone - 12.5 - 25 mg/day
- Amlodipine 2.5 - 10 mg/ day
- Lisinopril 10-40 mg/day
- Doxazocin - REMOVED FROM THE STUDY - chlorthalidone found to be superior prior to study termination

Study Goals

- Primary Outcome - fatal Coronary Heart Disease or nonfatal myocardial infarction
- All groups were compared to DIURETIC group - 1.7: 1.0: 1.0 ratio
- Secondary Outcomes - all-cause mortality, stroke, and other cardiovascular disease events

Blood Pressure Goal Achievement Rates

- Chlorthalidone
  - 63.9% (3), 68.2% (5)
- Amlopidine
  - 63.4% (3), 66.3% (5)
- Lisinopril
  - 59.2% (3), 61.2% (5)
  - P < .001 for chlorthalidone vs lisinopril

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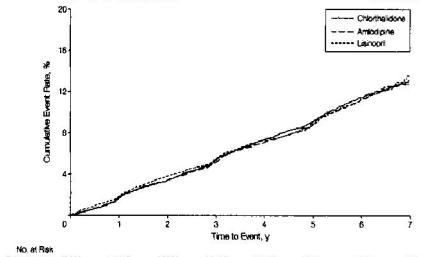
Primary and Secondary Outcomes

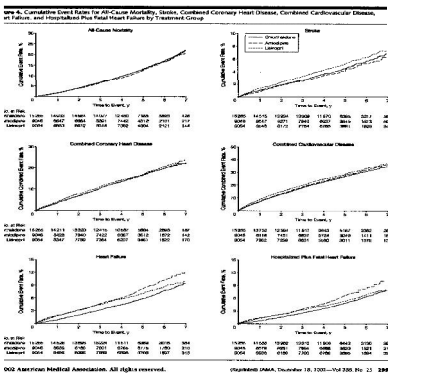
- Amlodipine vs. Chlorthalidone - no difference
- BUT - Heart Failure risk increased 38% with amlodipine (p< .001)
- Absolute difference of 2.5% at 6 years
- 35% higher risk of HF hospitalization

Figure 3. Cumulative Event Rates for the Primary Outcome (Fatal Coronary Heart Disease or Nonfatal Myocardial Infarction) by Treatment Group



No. at Risk							
Chlorthalidone	15255	14477	13820	13102	11362	6340	2966	209
Amlodipine	9048	8576	8218	7843	6824	3870	1878	215
Lisinopril	9054	8535	8123	7711	6662	3632	1770	196

No significant difference was observed for amlodipine (relative risk [RR], 0.98; 95% confidence interval [CI], 0.90-1.07; $P = .65$) or lisinopril (RR, 0.99; 95% CI, 0.91-1.08; $P = .81$) vs chlorthalidone with a mean follow-up of 4.9 years.



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Are these curves different enough to make a clinical difference?

Primary and Secondary Outcomes

- Lisinopril vs. Chlorthalidone - no difference for Primary or Secondary outcomes
- Lisinopril group - 15% higher risk of stroke (p=.02) and 10% higher risk of combined CVD (p < .001)
- 6 year absolute risk difference of 2.4%

Did this study answer key clinical questions?

- "Are newer types of antihypertensive agents, which are more costly, as good or better than diuretics in reducing CHD incidence and progression?"

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Newer Modification?

Table 1. Hypertension Writing Group Definition and Classification of Hypertension*

Classification	Normal	Stage 1 Hypertension	Stage 2 Hypertension	Stage 3 Hypertension
Descriptive category (BP pattern and CVD status)	Normal BP or rare BP elevations AND No identifiable CVD**	Occasional or intermittent BP elevations OR Risk factors or markers suggesting early CVD**	Sustained BP elevations OR Evidence of progressive CVD**	Marked and sustained BP elevations OR Evidence of advanced CVD**
Cardiovascular risk factors (see Table II)	None	≥1 risk factor present	Multiple risk factors present	Multiple risk factors present
Early disease markers (see Table III)	None	0–1	≥2	≥2 present with evidence of CVD
Target organ disease (see Table IV)	None	None	Early signs present	Overtly present with or without CVD events

*This paradigm expands on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) definition and classification of hypertension by classifying individuals by blood pressure (BP) level or cardiovascular status; however, priority is given to cardiovascular status; **cardiovascular disease (CVD) designation is determined by the constellation of risk factors, early disease markers, and target organ disease as listed in Tables II–IV. BP categories are shown in the Figure.

Cost and prescribing data

- Diuretic use for hypertension decreased from 56% in 1982 to 27% in 1992
- Cost savings would have been $3,100,000,000 had rate not changed!

Limitations

- ARBs not studied
- Beta-blockers not studied because previous studies had indicated equivalence or inferiority compared to chlorthalidone
- When was the last time you used chlorthalidone? Can you generalize about drug classes?

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Conclusions

- "Thiazide-type diuretics should be considered first for pharmacologic therapy in hypertension. They are unsurpassed in lowering BP, reducing clinical events, and are less costly."

The controversy continues…

- "ALLHAT - or the soft science of the secondary end-point" - Franz Messerli, MD in Annals of Internal Medicine
- Endpoints were not validated - Doxazosin was stopped on the basis of a very small reduction in ejection fraction - was this really "Heart Failure" ?
- Was the "Heart Failure" seen in the amlodipine group just peripheral edema?

Conflicts of Interest?

- "ALLHAT has cast a long shadow on JNC 7" - Messerli
- More than one-half of the JNC 7 authors were also ALLHAT investigators

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Are "superiority" studies missing the big picture?

- The ABSOLUTE differences between treatment groups is very small; is P value of crucial clinical significance?
- Is single risk factor reduction paramount, or isn't the real target overall CV disease risk?
- Most patients now require at least 2 medications to achieve goal
- "Compelling Indication" patients continue to increase, esp. patients with Diabetes

Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes

Compelling Indication*	Recommended Drugs†						Clinical Trial Basis‡
	Diuretic	BB	ACEI	ARB	CCB	Ald Ant	
Heart failure	•	•	•	•		•	ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, Val-HeFT, RALES
Postmyocardial infarction		•	•			•	ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS
High coronary disease risk	•	•	•		•		ALLHAT, HOPE, ANBP2, LIFE, CONVINCE
Diabetes	•	•	•	•	•		NKF-ADA Guideline, UKPDS, ALLHAT
Chronic kidney disease			•	•			NKF Guideline, Captopril Trial, RENAAL, IDNT, PRIN, AASK
Recurrent stroke prevention	•		•				PROGRESS

*Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed or provided with the blood pressure.
†Drug abbreviations: BB=beta-blocker, ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, CCB=calcium channel blocker, Ald= ANT=aldosterone antagonist.
‡Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs. Adapted from JNC-7

Citation:
Reproduced with permission from Chobanian AV, Bakris GL, Black HR, et al. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.

ASCOT STUDY

- Anglo-Scandinavian Cardiac Outcomes Study - results presented at ACC session, March, 2005
- Rationale - insufficient outcome data on newer types of BP agents, esp. in combination regimens
- There has been LESS THAN EXPECTTED CHD prevention using standard therapy

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Objectives

- To compare the effect on NON-FATAL MI and TOTAL CHD of a standard regimen of Beta-blocker/diuretic with Calcium-channel blocker/ Ace inhibitor regimen
- Over 19,000 patients followed for a mean of 5.4 years

OCTOBER, 2004

- Data Safety Monitoring Board recommended terminating the study - patients receiving atenolol/hydrochlorthiazide regimen were “disadvantaged”

Preliminary Results

- Primary outcome: 10% risk reduction
- All-cause mortality: 14% reduction
- Total coronary events: 23% reduction
- Fatal and non-fatal stroke: 18% reduction
- CV death: 24% reduction
- NEW ONSET DIABETES: 32% REDUCTION!

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Practical Management Points

- Diagnosis of hypertension should be used to make an OVERALL assessment of CV risk - diabetes, lipid profile, obesity, diet, exercise
- Decide on treatment with the patient's input re possible side-effects and cost
- Encourage home blood pressure cuff use

The doctor still has the power!

- Use what lowers the pressure, and the drug or drugs the patient will comply with!