THE LATEST IN THE MANAGEMENT OF HYPERTENSION

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October, 2010

(no conflicts to disclose)
Objectives:

1. Emphasize the three fundamental possible causes of hypertension.
2. Place the preventive importance of hypertension control in context.
3. Summarize the entire range of antihypertensive medications.
4. Demonstrate where hypertension fits in the cardiovascular continuum.
5. Consider the importance and problems of some key clinical trials.
HYPERTENSION IN TWO GENERATIONS

- Primary care physician: two patients in same family, different generations, difficult control.
- Father, age 70, has new onset hypertension.
- Daughter, age 35, has new onset hypertension.
  - She is markedly obese.
- Multiple medications used with each patient, with minimal success.
- Family connection finally made.
- Key, but different tests ordered on both patients.
BP Status of U.S. Adults, 1990-2000

BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Researchers for NHANES estimated the prevalence of different BP states in adults (≥18 years of age) based on evaluations conducted between 1999 and 2000. For reference, prevalence is projected onto the absolute population at risk, based on the estimated adult population in 2004.


Hypertension pts. (50 million: 24% of US population): Treatment and Control

% of Hypertensives taking Medications
- Not on Rx
- 53% on Rx

% on Rx Achieving BP Control
- 24% Controlled on Rx
- 29% Not Controlled on Rx

NHANES III, The Centers for Disease Control and Prevention, and the National Center for Health Statistics, Burt et. al., 1995
HYPERTENSION: TO DISCUSS

• GOALS
• MECHANISMS
• CLASSES OF MEDICATIONS
• CLINICAL STUDIES
GOALS: HYPERTENSION Rx

- HYPERTENSION AWARENESS
- 24 HR. BLOOD PRESSURE CONTROL
- MEDICATION TOLERANCE
- ABSENCE OF SIDE EFFECTS
- ABSENCE OF DETRIMENTAL METABOLIC EFFECTS
- AVOID TARGET ORGAN DAMAGE
MECHANISMS OF HYPERTENSION

• INCREASED CARDIAC OUTPUT
• INCREASED INTRAVASCULAR VOL.
• INCREASED PERIPHERAL RESISTANCE
“CURABLE” HYPERTENSION

• COARCTATION OF THE AORTA
• CUSHING’S DISEASE
• HYPERALDOSTERONISM
• PHEOCHROMOCYTOMA
• RENOVASCULAR
RENOVASCULAR HYPERTENSION

- FIBROSIS
- ATHEROSCLEROSIS

Renal Artery Duplex Study is Essential
# JNC 7 Classification of Hypertension

<table>
<thead>
<tr>
<th>Classification</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and &lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>or 80-89</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140-159</td>
<td>or 90-99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>or ≥100</td>
</tr>
</tbody>
</table>

DBP = diastolic blood pressure; SBP = systolic blood pressure.
*BP classification is based on the higher blood pressure, either systolic or diastolic.
Adapted from Chobanian AV et al.²
Progression to Increased Blood Pressure in the Framingham Heart Study (90% of Adults, age 55-65, will develop BP↑ in their lifetime)

Incidence as 0-60 Percent (0-0.6)

BP = blood pressure.

CV Mortality Risk Doubles with Each 20/10 mm Hg Increment in Blood Pressure*

# Classification of HF: Comparison Between ACC/AHA HF Stage and NYHA Functional Class

<table>
<thead>
<tr>
<th>ACC/AHA HF Stage</th>
<th>NYHA Functional Class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong> At high risk for heart failure but without structural heart disease or symptoms of heart failure (eg, patients with hypertension or coronary artery disease)</td>
<td></td>
</tr>
<tr>
<td><strong>B</strong> Structural heart disease but without symptoms of heart failure</td>
<td>I Asymptomatic</td>
</tr>
<tr>
<td><strong>C</strong> Structural heart disease with prior or current symptoms of heart failure</td>
<td>II Symptomatic with moderate exertion</td>
</tr>
<tr>
<td><strong>D</strong> Refractory heart failure requiring specialized interventions</td>
<td>IV Symptomatic at rest</td>
</tr>
</tbody>
</table>

DIETARY APPROACH TO STOP HYPERTENSION (DASH):

DASH Diet*, which is rich in vegetables, fruits and low-fat dairy products, is effective in lowering BP with high, intermediate and low sodium intake.

DEVICE MANAGEMENT OF HYPERTENSION BY SLOWING AND REGULARIZING BREATHING:

BIM (Breathe with Interactive Music)+. RESPeRATE®, InterCure Ltd., Lod, Israel#. Such devices can decrease hypertension.

DIURETICS

- THIAZIDES
- LOOP (eg Furosemide)
- POTASSIUM SPARING
  - AMILORIDE
  - TRIAMTERENE
  - SPIRONOLACTONE
BETA BLOCKERS

• WITHOUT ISA:
  - ATENOLOL (TENORMIN)
  - BETAXOLOL (KERLONE)
  - BISOPROLOL (ZEBETA)
  - CARVEDILOL (COREG)
  - METOPROLOL (LOPRESSOR, TOPROL XL)
  - NADOLOL (CORGARD)
  - NEBIVOLOL (BYSTOLIC)
  - PROPRANOLOL (INDERAL)
  - TIMOLOL (BLOCADREN)

• WITH ISA:
  - ACEBUTOLOL (SECTRAL)
  - CARTEOLOL (CARTROL)
  - PENBUTOLOL (LEVATOL)
  - PINDOLOL (VISKEN)
TOPROL-XL
(Metoprolol Succinate)

AN EXCELLENT BETA BLOCKER
FOR TREATING HYPERTENSION
AND CONGESTIVE HEART FAILURE
Death From Heart Failure (Merit HF*)

Risk reduction: 49%
P = 0.0023

Percent of patients

Placebo n=2001

Metoprolol XL n=1990

Carvedilol or Metoprolol European Trial (COMET) for CHF*

58 Months Follow-up:

• Metoprolol tartrate 50 mg bid to 1,518 patients:
  – All-cause Mortality: 40%
  – All-cause Mortality+All-cause Adm: 76%

• Carvedilol 25 mg bid to 1,511 patients:
  – All-cause Mortality: 34%
  – All-cause Mortality+All-cause Adm: 74%

• (MERIT-HF: Average Toprol-XL (Metoprolol succinate) was 159 mg/day)

Possible Carvedilol Benefits

Blockade of all 3 Adren. Receptors ($\beta_1,\beta_2,\alpha_1$), may Maximize Hemodynamic Benefit

Blockade of $\alpha_1$ Recept. Causes ↓ Peripheral Resistance and may help Rx BP↑

Antioxidant Effects may ↓ Cardiac Cell Death (Apoptosis)

Antioxidant Effects may ↓ Development of Nitrate Tolerance

Increased Insulin Sensitivity
CARVEDILOL DOSING

• GENERAL HYPERTENSION DOSE:
  25 mg qAM after 2 days at 12.5 mg qAM

• MAXIMUM DOSE, HYPERTENSION, OR CHF:
  25 mg bid if < 85 kg
  50 mg bid if > 85 kg
Left Ventricular Remodeling
Effect of Carvedilol on Ejection Fraction

Pharmacology: Bystolic is a Beta-adrenergic blocking agent with high $\beta$-$1$ selectivity, no ISA or alpha-adrenergic blocking effects, and it has nitric oxide mediated vasodilatory effects.
Bystolic™ - Nebivolol
Prescription Information

Dosing:

– Hypertension: Initial- 5mg daily.
  • May increase at 2 week intervals to maximum dose of 40mg daily.

– Heart Failure: Initial- 1.25mg daily – Off label.
  • Increase by 2.5mg every 1-2 wks as tolerated to maximum dose of 10mg daily.
Bystolic™ - Nebivolol

Summary

• Bystolic, nebivolol, is a highly cardioselective beta blocker with nitric oxide mediated vasodilating activity. This unique hemodynamic profile may provide benefit to a broader patient population. Unfortunately, limited head to head outcomes trials have not been published.

• Convenient once daily dosing and few drug interactions.

• Common adverse effects seen with beta blockers (fatigue, ED, bradycardia, depression) appear to be less common with nebivolol.
Meta-analysis of nine trials with beta blockers, 34,096 patients, 78% received Atenolol.

Heart rate slowing associated with ↓life expectancy and more MI’s, CHF and strokes.

Is this Atenolol effect or bradycardia?

†Bangalore S et al. J Am Coll Cardiol 2008;52:1482-1489.
GEMINI TRIAL (2004): Diabetics with Hypertension*

- Carvedilol reported to have some metabolic advantages over Metoprolol tartrate in hypertensive diabetic patients.
- Average Carvedilol dose 17.5 mg bid
- Average Metoprolol tartrate dose 128 mg bid
- Metoprolol succinate would have been preferred

*Bakris GL et al. JAMA. 2004;292:2227-2236
Calcium Blockers: Role In Hypertension

• Relaxation of Vascular Smooth Muscle Results in Decreased Peripheral Vascular Resistance

• All Calcium Channel blockers cause cardiac muscle depression
PRAISE Trial*: CHF

All-cause mortality and cardiac morbidity events %

Placebo (n = 583) Amlodipine (n = 571)

Central Alpha-2 Agonists

- **Clonidine (Catapres).**
  - Still used frequently.
- **Guanabenz (Wytensin).**
- **Guamfacine (Tenex).**
- **Methyldopa (Aldomet).**
  - Of interest is the safety of Aldomet for the fetus.
DIRECT VASODILATOR

HYDRAZINE (APRESOLINE®)
A-Heft Trial

1,050 African-American patients with advanced heart failure
NYHA III-IV for ≥ 3 months
LV function ≤ 35% (≤ 40% if LV dilated per echo)
90% receiving diuretics, 69% ACE-I, 17% ARBs, 74% beta-blocker

Isosorbide dinitrate (ISDN) plus hydralazine (BiDil®)
20 mg ISDN and 37.5 mg hydralazine 3X daily. Dosage could be doubled by enrolling physician.
n=518

Placebo
n=532
36.1% female
37.0% diabetic

Primary Endpoint:
Weighted composite of all-cause death, first hospitalization for heart failure, and change in quality of life at a mean follow-up of 10 months

NEJM, Nov 11, 2004, Vol 351, No. 20, 2049-2057
A-Heft Trial: Mortality

Presented at AHA 2004

\[ p = 0.01 \]
ALPHA-1 BLOCKERS

- DOXAZOSIN (CARDURA)
- PRAZOSIN (MINIPRESS)
- TERAZOSIN (HYTRIN)
PERIPHERAL ANTIADRENERGICS

Guanadrel (Hylorel)
Guanethididine (Ismelin)
Reserpine (Serpasil)

POTASSIUM CHANNEL OPENER

Minoxidil
COMBINED ALPHA-BETA BLOCKERS

- **BUCINDOLOL** (Thailand only)
- **CARVEDILOL**
- **LABETALOL**
ALDOSTERONE

• ↑ Ventricular Hypertrophy.
• ↑ Interstitial Cardiac Fibrosis.
• ↑ Perivascular Fibrosis.
• ↑ PAI-1 activity (possible).
• Probably plays important role in the pathophysiology of CHF.
• Released by Angiotensin II.
SELECTIVE ALDOSTERONE BLOCKER:

EPLERENONE (INSPIRA®): Of value in hypertension and CHF

25-50 mg once daily
50 mg bid max. in BP↑
Must watch for hyperkalemia

In EPHESUS*, there was ↑ survival post acute MI with EF < 40 % and clinical evidence for CHF

RENIN INHIBITOR (NEW CLASS)

GENERIC NAME: ALISKERIN.
TRADE NAME: TEKTURNIA® (NOVARTIS).
Dose: 150 to 300 mg once a day.

Isolated Systolic Hypertension

- Systolic BP > 140 mm Hg
- Diastolic BP < 90 mm Hg
- SHEP* (Thiaz. ± β Blocker)
  - 36% Stroke ↓
  - Other CV events ↓
- Syst-EUR+ (Nitrendipine ± Enalapril/HCTZ)
  - Stroke ↓ 42%
  - Other CV events ↓

Sites of Action of ACEIs and AT₁-Receptor Blockade*

Angiotensinogen → Renin → Angiotensin I → ACEI → Bradykinin → Inactive degradation products

Chymase → Trypsin Peptidase

Angiotensin II → AT₁-receptor blocker

AT₁-receptor

Vasoconstriction
Salt/water retention
Remodeling

Anti-proliferation
Cell differentiation
Tissue repair

AT₂-receptor

Vasodilation
Natriu-/diuresis
Anti-remodeling

NO

Statins: ↓ reg.

ACE Inhibitors In Diabetic Patients

• May decrease Proteinuria.

• May decrease deterioration of renal function.
Racial Differences

African Americans:

• African American study of Kidney Disease (AASK*) (AHA 2001) Showed Advantage for ACE Inhibitor (Ramipril) in Conserving Renal Function (composite of GFR, ESRD & death)

• Better BP Response to Diuretics

HOPE STUDY*

GENERAL USE OF RAMIPRIL IN HIGH RISK CV PATIENTS ≥ 55 YR. WITH INTACT LV FUNCTION RESULTED IN FEWER CARDIOVASCULAR EVENTS

Primary Endpoint (EUROPA): Patients with proven stable CHD

% CV death, MI or cardiac arrest

Placebo annual event rate: 2.4%

Perindopril: RRR: 20%, p = 0.0003

n = 12,218

Primary End Point and Selected Secondary End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Perindopril better</th>
<th>Placebo better</th>
<th>RRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Mortality, MI, Cardiac Arrest</td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>CV Mortality</td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Non fatal MI</td>
<td></td>
<td></td>
<td>22</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td></td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>Total mortality, MI, Unstable angina, and Cardiac Arrest</td>
<td></td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>

**Activity ecNOS - PERTINENT**

Effects of incubation of HUVECs with serum of:

<table>
<thead>
<tr>
<th>Group</th>
<th>Basal: 1 mo.</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>3.5</td>
<td>p &lt; 0.01#</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2.4</td>
<td>3.3</td>
</tr>
</tbody>
</table>

*#* p=controls vs baseline

*‡* p = Δ perindopril vs Δ placebo

*From PERTINENT (EUROPA substudy) presentation at ESC. Aug 2004.*
Bradykinin - PERTINENT

Controls

PERTINENT Patients with CAD

From PERTINENT (EUROPA substudy) presentation at ESC. Aug 2004.
**TNFα - PERTINENT**

**Controls**

- Controls: 18.0

**PERTINENT Patients with CAD**

- Basal: 1 mo.
  - Placebo: 27.7
  - Perindopril: 27.1
- 1 year
  - Placebo: 28.9
  - Perindopril: 24.6

- **p < 0.01** #
- **p < 0.05** ‡

# p=controls vs basal
‡ p = Δ perindopril vs Δ placebo

From PERTINENT (EUROPA substudy) presentation at ESC. Aug 2004.
IN CONTRAST TO VALHEFT, CHARM-Added SHOWED Candesartan benefit for CHF in the presence of an ACE-inhibitor and/or a β-blocker

*Lancet 2003;362:767-771
DIABETES RISK AND BP Rx

- Probably ↑ by HCTZ and β-blockers.
- Probably neutral with Ca channel blockers.
- Probably ↓ by ACEI or ARB.

ASCOT-BPLA*

- Primary end point not significant due to early termination.
- Secondary end points (nonfatal MI, fatal CHD, total CV event/procedures, fatal/nonfatal stroke and fatal/nonfatal CHF) favored: Amlodipine Perindopril vs Atenolol Thiazide
- 30% reduction in new onset diabetes: Amlodipine Perindopril vs Atenolol Thiazide

ALLHAT

High Incidence of Cardiovascular Disease Including CHF in Association with Doxazosin (Cardura®) use.
ALLHAT*

Total of 33,357 Participants Randomized to Receive Chlorthalidone 12.5-25 mg, Amlodipine 2.5-10 mg or Lisinopril 10-40 mg

ALLHAT Study Conclusions

- Thiazide-Type Diuretics are Superior in Preventing One or More Major Forms or CV Disease and are Less Expensive for the Treatment or Hypertension than Rx such as Amlodipine or Lisinopril.
- Thiazides Should be Preferred for First-Step Antihypertensive Therapy.
ACE inhibition (lisinopril) is much less effective at preventing stroke compared with chlorthalidone, probably due to poorer BP control with ACE inhibition in African Americans.

CRITIQUES* OF ALLHAT

• Not comparative—did not control BP equally with each individual medication.
• Did not recognize the heterogeneity of BP.
• Not a monotherapy trial (74% needed more than 1 medication) —therefore cannot recommend first line therapy.
• ACE-I and ARB offer cardioprotection and nephroprotection whereas thiazides can increase Angiotensin II.

*Standidge JB. Current Atheroscler Reports. 2005;7:132-139.
EVALUATION OF ALLHAT

• Diuretics are Probably not Sufficiently Utilized
• Must Consider the Individual Patient, eg.:
  – ACE or ARB for Diabetic
  – ACE and β-Blocker for Associated CHF
  – β-Blocker for Associated Angina and Post MI
• Most patients will need More than One Medication to Control their Hypertension
• The Interpretation by the News Media is that Physicians are not Using the Best and Least Expensive Medicine
ACCOMPLISH STUDY*

Combination single tablet to ↓BP:
Benazepril/Amlodipine vs. Benazepril/hydrochlorothiazide. Benazepril/Amlodipine reported to reduce CV morbidity and mortality 20% in comparison.

Note contrast to ALLHAT results.
Is such a combination just marketing?

New-Onset Hypertension Reduced by Candesartan in TROPHY* [randomized untreated prehypertension patients (BP 120-139/80-89), age 30-65]

<table>
<thead>
<tr>
<th>New-Onset HTN</th>
<th>Candesartan (n = 391)</th>
<th>Placebo (n = 381)</th>
<th>P Value</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts (n) who developed HTN</td>
<td>208</td>
<td>240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts (%) with HTN at year 2 visit</td>
<td>13.6</td>
<td>40.4</td>
<td>&lt;.001*</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.25-0.44)</td>
</tr>
<tr>
<td>Pts (%) with HTN at year 4 visit</td>
<td>53.2</td>
<td>63.0</td>
<td>.007*</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.75-0.95)</td>
</tr>
</tbody>
</table>

RR = relative risk.
*Calculated by Fisher’s exact test.
Adapted from Julius S et al.23


Carotid Blood Pressure Sensors
The CVRx Rheos™ System

- Implantable Pulse Generator
- Baroreflex Activation Leads
- Programming System
Demonstration of Long Term Efficacy

ACC 2007:
Chronic Treatment of Resistant Hypertension
With an Implantable Device: Preliminary Results of European and United States Trials of Rheos™ Baroreflex Activation System*

Results: 27 subjects (17 Europe/10 US, 14m/13f, age 52 ± 10 yrs, BMI 32 ± 6 kg/m², 5.7 ± 2 medications) were implanted at 10 centers. One subject developed an infection before 3 months and is excluded from paired analyses.

Mean Change in Paired Office Cuff Blood Pressure and Heart Rate

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Δ 3 Months (N=26)</th>
<th>Δ 6 Months (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic (mmHg)</td>
<td>187 ± 30</td>
<td>-26 (± 20, p&lt;0.00001)</td>
<td>-21 (± 32, p=0.007)</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>112 ± 21</td>
<td>-17 (± 14, p&lt;0.00001)</td>
<td>-16 (± 17, p=0.0004)</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>81 ± 11</td>
<td>-12 (± 11, p=0.0005)</td>
<td>-9 (± 10, p=0.013)</td>
</tr>
</tbody>
</table>

*P. de Leeuw, J. Bisognano, R. Cody
CONCLUSION

• There is Much Established Benefit from the Treatment of Hypertension.

• Selection of the Optimal Regimen Requires Experience, Judgement, Trial/Error.

• There is diminishing support for starting with diuretic/β-blocker.