THE LATEST IN THE MANAGEMENT OF HYPERTENSION

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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.

HYPERTENSION: TO DISCUSS

- GOALS
- MECHANISMS
- CLASSES OF MEDICATIONS
- CLINICAL STUDIES

GOALS: HYPERTENSION Rx

- HYPERTENSION AWARENESS
- 24 HR. BLOOD PRESS. 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 PERIPH. 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>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>or 90-99</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>≥100</td>
</tr>
</tbody>
</table>

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

DBP classification is based on the higher SBP. Adapted from Chobanian AV, et al.

Progression to Increased Blood Pressure in the Framingham Heart Study (90% of Adults, ages 55-65, will develop BP⩾ in their lifetime)

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 Stage¹</th>
<th>NYHA Functional Class²</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>C</td>
<td>Symptomatic with moderate exertion</td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic with minimal exertion</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)*. RESPReRATE®, InterCure Ltd., Lod, Israel#. Such devices can decrease hypertension.


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### DIURETICS

- **THIАЗИDEs**
- **LOOP** (eg Furosemide)
- **POTASSIUM SPARING**
  - AMILORIDE
  - TRIAMTERENE
  - SPIRONOLACTONE

### BETA BLOCKERS

- **WITHOUT ISA:**
  - ATENOLOL (TENORMIN)
  - BETAXOLOL (KERLONE)
  - BISOPROLOL (ZEBETA)
  - CARVEDILOL (COREG)
  - METOPROLOL (LORPRESSOR, TOPROL XL)
  - NADOLOL (CORDARAN)
  - NEBIVOLOL (BISTOLIC)
  - PROPRANOLOL (INDERAL)
  - TIMOLOL (BLOCADREN)

- **WITH ISA:**
  - ACEBUTOLOL (SECTORAL)
  - CARTEOLOL (CARTROL)
  - PENBUTOLOL (LEVATOL)
  - PINDOLOL (VISKEN)

### TOPROL-XL (Metoprolol Succinate)

**AN EXCELLENT BETA BLOCKER FOR TREATING HYPERTENSION AND CONGESTIVE HEART FAILURE**

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**Death From Heart Failure (Merit HF*)**

- **Metoprolol XL**
- **Placebo**

- **Risk reduction:** 49%
- **P-value:** 0.0023

**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 Adr. 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

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**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

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**Left Ventricular Remodeling**

Effect of Carvedilol on Ejection Fraction

![Graph showing the effect of Carvedilol on Ejection Fraction with Placebo](image)


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**Bystolic™ - Nebivolol**

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.

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**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.

BETA BLOCKERS, HYPERTENSION AND HEART RATE (Oct. 2008)†

- 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

- 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: Mortality

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, 89% 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=532

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

p = 0.01

ISDN-hydralazine
Placaebo

ALPHA-1 BLOCKERS

• DOXAZOSIN (CARDURA)
• PRAZOSIN (MINIPRESS)
• TERAZOSIN (HYTRIN)

PERIPHERAL ANTIADRENERGICS

Guanadrel (Hylorel)
Guanethidine (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: TEKTURNA® (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*

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

![Graph showing primary endpoint results]

Primary End Point and Selected Secondary End Points

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


Activity ecNOS - PERTINENT

Effects of incubation of HUVECs with serum of:

<table>
<thead>
<tr>
<th>Controls</th>
<th>PERTINENT Patients with CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity ecNOS</td>
<td>2.4</td>
</tr>
</tbody>
</table>

p < 0.01†

p = controls vs baseline

‡ p = perindopril vs placebo

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

Bradykinin - PERTINENT

<table>
<thead>
<tr>
<th>Controls</th>
<th>PERTINENT Patients with CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinin (pg/mL)</td>
<td>12.4</td>
</tr>
</tbody>
</table>

p < 0.05‡

p = controls vs baseline

‡ p = perindopril vs placebo

From PERTINENT (EUROPA substudy) presentation at ESC. Aug 2004.
CHARM-Added Trial*

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

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

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


DIABETES RISK AND BP Rx

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

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.

ALLHAT*: 10,702 AFRICAN AMERICANS

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 = 301)</th>
<th>Placebo (n = 301)</th>
<th>p Value</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts (%) 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 (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>0.64 (0.57-0.72)</td>
</tr>
</tbody>
</table>

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

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*

Result: 27 subjects (17 European, 10 US, 105/69 mmHg BP 129 ± 20 mmHg, BMI 32 ± 5 kg/m², 53 ± 2 years).

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.

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