MANAGEMENT of HYPERTENSION

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DISCLOSURE

Any Drug or Product Mentioned in this Discussion is Purely Illustrative and not a Commercial Endorsement

All Opinions Expressed Are the Biases of the Speaker (Which are Considerable)
The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8)
JNC 8
JNC 8
The Issues & Expectations

1. Emphasizing evidence from clinical trials

2. Defining hypertension (When to initiate treatment)

3. Defining treatment targets (How low should BP be lowered in particular patients)

4. Emphasizing multi-drug approaches (Which drugs best achieve control to target)

5. Defining important co-morbid conditions
JNC 8 – The Quest for Evidence

Scientific Evidence Underlying ACC/AHA Guidelines
(JAMA. 2009; 301: 831 – 841)

AHA Level of Evidence A in Current Guidelines*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>11.7%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>26.4%</td>
</tr>
<tr>
<td>PAD</td>
<td>15.3%</td>
</tr>
<tr>
<td>STEMI</td>
<td>13.5%</td>
</tr>
<tr>
<td>Perioperative</td>
<td>12.0%</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>22.9%</td>
</tr>
<tr>
<td>Stable angina</td>
<td>6.4%</td>
</tr>
<tr>
<td>SV arrhythmias</td>
<td>6.3%</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td>23.0%</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>0.3%</td>
</tr>
<tr>
<td>VA/SCD</td>
<td>9.7%</td>
</tr>
<tr>
<td>PCI</td>
<td>11.0%</td>
</tr>
<tr>
<td>CABG</td>
<td>9.0%</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>4.9%</td>
</tr>
<tr>
<td>Radionuclide imaging</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

*In guidelines with level of evidence

Evidence-Based Clinical Practice Guidelines for CVD Prevention
WHAT IS HYPERTENSION?

A Blood Pressure
Or
A Disease Process
## Blood Pressure Classification

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</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>80–89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>&gt;160</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
Cumulative CV Risk with “Non-Hypertensive” BP (SBP < 140 mmHg and DBP < 90 mm Hg)
PATTERNS OF AMBULATORY BP

White Coat Hypertension

Hypertensive Dipping

Masked Hypertension

Hypertensive Non-Dipping

J Clin Hypertension 14:836, 2012
MASKED HYPERTENSION

Relative CV Risk in Diabetics

<table>
<thead>
<tr>
<th></th>
<th>Day</th>
<th>Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>120/74</td>
<td>104/60</td>
</tr>
<tr>
<td>Masked</td>
<td>120/73</td>
<td>141/84</td>
</tr>
</tbody>
</table>

Hypertension 61:964, 2013
MASKED HYPERTENSION
CV Events and Mortality

A. Total mortality

B. CV events

Incidence (%)

Years of follow-up

Hypertension 61:278, 2013
HOME BP MONITORING
Correlation to Ambulatory Monitoring
# Classification and Management of BP for adults

<table>
<thead>
<tr>
<th>BP classification</th>
<th>SBP** mmHg</th>
<th>DBP** mmHg</th>
<th>Lifestyle modification</th>
<th>Initial drug therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
<td>Encourage</td>
<td></td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>80–89</td>
<td>Yes</td>
<td>No antihypertensive drug indicated.</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140–159</td>
<td>90–99</td>
<td>Yes</td>
<td>Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥160</td>
<td>≥100</td>
<td>Yes</td>
<td>Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).</td>
</tr>
</tbody>
</table>

*Treatment determined by highest BP category.
†Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.
‡Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mmHg.
NON-DRUG THERAPY

In

NON-HYPERTENSIVE PATIENTS

Dietary Sodium & Potassium
“Americans consume too much salt”

Sodium Facts, United States

Average daily sodium intake age 2 and up

Tolerable Upper Intake Level

Recommended Adequate Intake Level

How much daily sodium our bodies need

Decreasing sodium intake could prevent thousands of deaths annually.^

^Because nearly 400,000 deaths each year are attributed to high blood pressure.

www.cdc.gov/features/dsSodium
Dietary Potassium Intake in U.S.

<table>
<thead>
<tr>
<th></th>
<th>Sodium (2,300 mg)</th>
<th>Potassium (4,400 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE (30-50 yo)</td>
<td>4,043 mg</td>
<td>3,060 mg</td>
</tr>
<tr>
<td>FEMALE</td>
<td>3,031 mg</td>
<td>2,373 mg</td>
</tr>
<tr>
<td>WHITE (≥20 yo)</td>
<td>3,478 mg</td>
<td>2,720 mg</td>
</tr>
<tr>
<td>BLACK</td>
<td>3,270 mg</td>
<td>*2,219 mg</td>
</tr>
</tbody>
</table>

“PRIMITIVE” Potassium/Sodium Intake  4 - 10

www.ars.usda.gov/services/docs.htm?docid=18349
SALT RESISTANCE IN HYPERTENSION

R = Salt-resistant
S = Salt-sensitive
35-50% White HTN
65-80% Black HTN

N = Normotensive
H = Hypertensive

J Clin Hypertension 7:170, 2013
META-ANALYSIS OF BENEFIT OF SALT REDUCTION

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in systolic blood pressure (95% CI)</th>
<th>Weight (%)</th>
<th>Change in systolic blood pressure (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive people</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parijs 1973</td>
<td>-6.70 (-13.42 to 0.02)</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>MacGregor 1982</td>
<td>-10.00 (-14.70 to -5.30)</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Silman 1983</td>
<td>-8.70 (-28.73 to 11.33)</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Puska 1983 (H)</td>
<td>1.80 (-6.26 to 9.86)</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Watt 1983</td>
<td>-0.50 (-3.44 to 2.44)</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Erwteman 1984</td>
<td>-2.70 (-7.01 to 1.61)</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Richards 1984</td>
<td>-5.20 (-13.24 to 2.84)</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Chalmers 1986</td>
<td>-5.10 (-7.88 to -2.32)</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Grobbee 1987</td>
<td>-0.80 (-4.33 to 2.73)</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>ANHMRC 1989 (P)</td>
<td>-5.50 (-8.40 to -2.60)</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>ANHMRC 1989 (X)</td>
<td>-3.60 (-4.97 to -2.23)</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>MacGregor 1989</td>
<td>-8.00 (-11.92 to -4.08)</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Benetos 1992</td>
<td>-6.50 (-9.77 to -3.23)</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Fotherby 1993</td>
<td>-8.00 (-15.39 to -0.61)</td>
<td>1.4</td>
<td></td>
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<tr>
<td>Cappuccio 1997 (H)</td>
<td>-6.60 (-11.75 to -1.45)</td>
<td>2.2</td>
<td></td>
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<tr>
<td>Meland 1997</td>
<td>-8.70 (-10.64 to -6.76)</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Sacks 2001 (H)</td>
<td>-7.00 (-12.68 to -1.32)</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Gates 2004</td>
<td>-7.70 (-11.86 to -3.54)</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Swift 2005</td>
<td>-8.30 (-11.89 to -4.71)</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Melander 2007 (H)</td>
<td>-4.80 (-6.41 to -3.19)</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>He 2009</td>
<td></td>
<td>57.3</td>
<td>-5.39 (-6.62 to -4.15)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\tau^2=4.06$, $\chi^2=50.67$, df=20, $P<0.001$, $I^2=61\%$

Test for overall effect: $z=8.52$, $P<0.001$

BMJ 346:f1378, 2013
Risk of Stroke
Relation to Urinary Sodium Excretion

JAMA 306:2229, 2011
EFFECT OF HIGHER POTASSIUM INTAKE
INCIDENT CARDIOVASCULAR EVENTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Log risk ratio (SE)</th>
<th>Risk ratio (inverse variance, random) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cook 2009</td>
<td>-0.44 (0.25)</td>
<td></td>
</tr>
<tr>
<td>Geleijnse 2007</td>
<td>0.21 (0.15)</td>
<td></td>
</tr>
<tr>
<td>O'Donnel 2011</td>
<td>-0.08 (0.07)</td>
<td></td>
</tr>
<tr>
<td>Umesawa 2008</td>
<td>-0.31 (0.11)</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\tau^2=0.03$, $\chi^2=9.78$, df=3, $P=0.02$, $I^2=69%$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z=1.11$, $P=0.27$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascherio 1998</td>
<td>-0.37 (0.22)</td>
<td></td>
</tr>
<tr>
<td>Bazzano 2001</td>
<td>-0.27 (0.12)</td>
<td></td>
</tr>
<tr>
<td>Geleijnse 2007</td>
<td>0.16 (0.16)</td>
<td></td>
</tr>
<tr>
<td>Iso 1999</td>
<td>-0.13 (0.21)</td>
<td></td>
</tr>
<tr>
<td>Khaw CCDS1987</td>
<td>-0.51 (0.16)</td>
<td></td>
</tr>
<tr>
<td>Larsson 2008</td>
<td>-0.14 (0.06)</td>
<td></td>
</tr>
<tr>
<td>O'Donnel 2011</td>
<td>-0.56 (0.14)</td>
<td></td>
</tr>
<tr>
<td>Umesawa 2008</td>
<td>-0.19 (0.16)</td>
<td></td>
</tr>
<tr>
<td>Weng 2008</td>
<td>-0.52 (0.21)</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\tau^2=0.03$, $\chi^2=19.49$, df=8, $P=0.01$, $I^2=59%$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z=3.57$, $P&lt;0.001$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bazzano 2001</td>
<td>-0.03 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Geleijnse 2007</td>
<td>0.1 (0.13)</td>
<td></td>
</tr>
<tr>
<td>Umesawa 2008</td>
<td>-0.43 (0.26)</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: $\tau^2=0.01$, $\chi^2=3.35$, df=2, $P=0.19$, $I^2=40%$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $z=0.35$, $P=0.72$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risk of Stroke
Relation to Urinary Potassium Excretion

JAMA 306:2229, 2011
WHAT IS APPROPRIATE TARGET FOR BP TREATMENT?
# TARGET BLOOD PRESSURE

**Anti-Hypertensive Care**

| Uncomplicated Hypertension (1º CAD Prevention) | < 140/90 mm Hg |
| CAD / Stable Angina | < 130/80 mm Hg |
| High CAD Risk (DM, CKD, CAD-Equiv) | < 130/80 mm Hg |
| LV Dysfunction | < 120/80 mm Hg |
| Diabetic or Proteinuric CKD | < 130/80 mm Hg |
| African-American | < 130/80 mm Hg |

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BENEFIT OF LOWER BP TARGET?
European Society of Hypertension Task Force

J Hypertension 27:2121, 2009
TIGHT vs USUAL BP TARGETS
DM with CAD – CV Outcomes
INVEST Trial

6400 patients
Age > 50 yr
Diabetic
Hx CAD
75+% on ACE I
+ Non-DHP CCB
B-Blocker
HCTZ

Overall log-rank P < .001
Tight control vs usual control log-rank P = .19

Systolic BP
- Uncontrolled (SBP > 140)
  (146 mmHg)
- Usual (SPB 130-139)
  (131 mmHg)
- Tight (SPB < 130)
  (122 mmHg)

JAMA 304:61, 2010
INTENSIVE BP CONTROL IN DM
The ACCORD-BP Trial

4733 pts Type 2 DM:
> 40 yo + CV disease  OR
> 55 yo + ASHD, LVH, albuminuria

Primary Outcome: Non-Fatal MI or CVA; CV Death

Intensive Rx:  
↑ Hypotension
↑ Creatinine
↓ Macroalbuminuria

N Eng J Med 362:1575, 2010
SUB-TYPE of HYPERTENSION as FUNCTION of AGE in US

Hypertension:37869, 2011
TARGET BP IN THE ELDERLY
THE HYVET TRIAL

3845 pts  83.6 yo  173/91 mmHg Baseline BP

Death-Any Cause

Heart Failure

≈ reach target BP 150/80 mmHg

NEJM 358:1887, 2008
ANTI-HYPERTENSIVE

DRUG CHOICES

Is There a Difference in Drugs?
TIME TO BLOOD PRESSURE CONTROL
BENEFIT OF EARLY LOWERING OF BP
Lessons from VALUE Trial

Lancet 363:2022, 2004
SYSTOLIC BLOOD PRESSURE AND STROKE

Absolute SBP or Variability in Value
BENEFIT OF LOWERING SYSTOLIC BP For REDUCTION IN STROKE

SBP VARIANCE BY DRUG CLASS

Meta-analysis of 7 Trials  140,866 Patient/Drug Events

Lancet 375:906, 2010
RISK OF CV EVENT BY SBP VARIABILITY
Relationship to Drug Class

Amlodipine

Atenolol

≈ 5500 pts  Dutch TIA  UK-TIA  ASCOT-BPLA

Lancet 375:895,2010
RISK OF STROKE (y axis) vs VARIANCE RATIO OF DRUG “A” to DRUG “B”
DIURETICS

Is There a Difference?
HCTZ vs Chlorthalidone
CV Relative Risk Reduction by BP Decrement

Hypertension 59:110, 2012
HCTZ vs Chlorthalidone
Network Analysis from Clinical Trials

Type of Analysis

- Drug-Adjusted Pooled Network
- Drug-Adjusted Amlodipine Network
- Drug-Adjusted ACE inhibitor Network
- OSBP-Adjusted Network
- MRFIT Observational Retrospective Cohort Study

\[ \text{RR}_{\text{CTDN/HCTZ}} \]
(95% CI)

Hypertension 59:110, 2012
DOSING ANTI-HYPERTENSIVES

Is Time of Day a Factor?
CHRONO-THERAPY OF RAAS INHIBITION
Implications for ACE I / ARB Dosing

VALSARTAN

TELMISARTAN

Chronobiol Int 22:755, 2005

Hypertension 50: 755, 2007
Non-Dippers: < 10% fall in nocturnal BP from daytime average
RESISTANT HYPERTENSION

Uncontrolled BP on 3 drugs of different classes, one of which is a Diuretic

Controlled BP requiring 4 or more drugs of different classes
RESISTANT HYPERTENSION
Aldosterone Antagonism

Canadian J Cardiol, 2012
RESISTANT HYPERTENSION
Renal Sympathetic Nerve Ablation
RENAL SYMPATHETIC NERVE ABLATION

Blood Pressure Outcomes

Eur Heart J, 2011
TREATMENT INITIATION
Stage I – drug therapy after suitable lifestyle modification
Hi Normal – No evidence for drug therapy benefit
Diabetic – Treat for organ damage (albuminuria)
Prior CV Event – No evidence of benefit if normotensive

BLOOD PRESSURE GOALS
All patients – goal < 140/90 mmHg appropriate (especially elderly)
Diabetic – no evidence of benefit of goal < 130 mmHg SBP
CV Disease – goal of 120/75 mmHg has soft support

ELDERLY
Proportional benefit at age > 65 yr same as younger pts
No demonstrated benefit in SBP lowering < 140 mmHg
All drug classes beneficial
Choice of Drug

- Major drug classes – no difference in ability to lower BP
- No undisputable evidence that drugs differ in regard to ability of protect from cardio-vascular events
- Ranking of drugs as 1st, 2nd, 3rd line agents has little merit but particular patients may be more responsive to certain drug classes

Combination Therapy

- 2-drug Regimen – required in vast majority of patients
- Single pill combination advised for adherence to therapy
  - ACE I / ARB / CCB + Thiazide diuretic of proven benefit
  - β-blocker + diuretic and ACE I + ARB not recommended
- 3-drug Regimen – ACEI/ARB + CCB + Diuretic beneficial
JNC 8

? Possible Recommendations?

1. No BP goals < 140/90 mm Hg
2. BP goal for patients 65+ year old, < 150/90 mm Hg
3. 1st Line therapy: ACE I, ARB, CCB, Thiazide
   Chlorthalidone favored over HCTZ
4. β-blocker not a 1st line choice for HTN
   Vaso-dilating β-blockers drugs of choice
5. Preferred combinations
   ACE I / CCB
   ACE I / Thiazide
6. Spironolactone addition in resistant HTN
7. Home BP or ambulatory BP encouraged
El fin
Das
Ende
OUR PROBLEM

Hypertension in the Southeast US is higher than other regions

?GOOD? NEWS

Anti-hypertension drug treatment is higher in the Southeast US than other regions
The Stroke Belt

Rates of Stroke Mortality in White Males Age 70

Age-specific rate per 100,000 population

- >187.8 - 208.6
- >174.5 - 187.8
- >164.6 - 174.5
- >153.0 - 164.6
- 123.6 - 153.0