Contemporary Management of Uncontrolled and Treatment Resistant Hypertension

Brent M. Egan, MD
Professor of Medicine
USCSOM – Greenville

Disclosures (past 3 years):
Honoraria: BCBSSC, Medtronic
Grant Support: Daiichi-Sankyo, Medtronic, Novartis
Royalties: UpToDate
Contemporary Management of Uncontrolled and Treatment Resistant Hypertension

• Clinical Epidemiology of Hypertension in the U.S.

• Dissecting the categories of uncontrolled and treatment resistant hypertension (TRH)

• Clinical Management of uncontrolled and TRH

• Summary
Clinical Epidemiology of Hypertension in the U.S. 1999–2012

Uncontrolled HTN in the U.S. 1988–2008. Clinical *Factors linked with untreated HTN*

Multivariable Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>2.26–2.73</td>
<td>1.70–3.51</td>
</tr>
<tr>
<td>0–1 Visit/yr</td>
<td>4.30–4.98</td>
<td>3.11–6.95</td>
</tr>
<tr>
<td>BMI &lt;25</td>
<td>1.69–2.04</td>
<td>1.16–3.12</td>
</tr>
<tr>
<td>CKD &lt;St 3</td>
<td>1.95–2.28</td>
<td>1.10–3.66</td>
</tr>
<tr>
<td><strong>FCR &lt;10%</strong></td>
<td>7.65–8.36</td>
<td>4.78–12.3</td>
</tr>
<tr>
<td>FCR 10-20%</td>
<td>1.74–2.37</td>
<td>1.13–3.19</td>
</tr>
</tbody>
</table>

- ~50% of uncontrolled HTN is untreated and disproportionately men with limited healthcare at relatively low risk for CVD
- *Physician message:* It’s difficult to treat & control HTN in patients we don’t see—*population health opportunity*!?
Uncontrolled HTN in the U.S. 1988–2008 Treated with 1–2 BP Meds

- Most Rx, uncontrolled Pts reported taking 1–2 BP meds, a proxy for therapeutic inertia.
- This group was older, had higher FCR than Pts controlled on 1–2 meds & comprised 34.4% of all uncontrolled and 72.0% of Rx uncontrolled Pts
- **Physician message**: Older uncontrolled Pts on 1 – 2 BP meds have good reasons for controlled HTN but many have SBP <150 mmHg

**Multivariable Regression**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, 10 yr</td>
<td>1.23–1.39</td>
<td>1.09–1.55</td>
</tr>
<tr>
<td><strong>FCR &gt;20%</strong></td>
<td><strong>1.88–2.64</strong></td>
<td><strong>1.18–3.91</strong></td>
</tr>
<tr>
<td>Black</td>
<td>1.38–1.58</td>
<td>0.94–2.06</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.08–1.47</td>
<td>0.82–2.15</td>
</tr>
<tr>
<td>Male</td>
<td>1.16–1.57</td>
<td>0.87–2.02</td>
</tr>
<tr>
<td>0–1 visit/yr</td>
<td>1.29–1.76</td>
<td>0.86–2.75</td>
</tr>
</tbody>
</table>


Multivariable Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4 Visits/yr</td>
<td>2.52–5.69</td>
<td>1.37–13.2</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>1.78–2.04</td>
<td>1.17–3.53</td>
</tr>
<tr>
<td>CKD ≥St 3</td>
<td>2.43–3.19</td>
<td>1.67–5.08</td>
</tr>
<tr>
<td>FCR &gt;20%</td>
<td>4.29–5.02</td>
<td>1.95–9.75</td>
</tr>
<tr>
<td>Black</td>
<td>1.14–2.06</td>
<td>0.79–3.23</td>
</tr>
</tbody>
</table>

- Clinical characteristics associated with aTRH included ≥4 visits/yr, obesity, CKD & FCR >20%
- **Physician Message**: This is the fastest growing group of uncontrolled HTN Pts, they’re high risk and give us many opportunities to do better

Categories of Apparent Treatment Resistant Hypertension (aTRH)

- Measurement artifacts (30% – 70%)
- Inadequate regimens (≥50%)
- Suboptimal adherence (10%–60%)
- True treatment resistant hypertension (~30%?), i.e., BP above goal on ≥3 different or controlled on ≥4 classes of BP meds at ‘optimal’ doses preferably including a diuretic
Automated BP & Office Hypertension: Accurate and Representative BP

Data on 50 HTN Pts. The 1\textsuperscript{st} BP reading was taken by the physician using the BpTRU. The 2\textsuperscript{nd} through 6\textsuperscript{th} BP readings were taken using the BpTRU with only the Pt in the exam room.


The white coat response associated with office BP can be virtually eliminated with the BpTRU device.

Prognostic Significance of Home BP

- Patients: 4939 treated hypertensives age 70±6 yr
- Data: Baseline office and 4-day (2 readings / day) home BP taken with Omron 705 CP
- Follow-up: mean 3.2 yrs  
  (O=office; H=home; (-) = normal; (+) = high).
  \[
  \begin{array}{cccc}
  O-/H- & O+/H+ & O-/H+ & O+/H- \\
  RR & 1.00 & 1.96 & 2.06 & 1.18 \\
  \end{array}
  \]
- Home BP is more strongly related to target organ damage and CV outcomes than office

2013 Cholesterol Guidelines Would Treat ~ 7 Million More HTN Pts with Statins than ATP–3

Pt >21 yrs without CHD or ESRD
- Screen for CVD risk factors
- Measure LDL-C

Clinical ASCVD
- High-Intensity Statin

DM Type 1 or 2, age 40–75, LDL 70–189
- Moderate-Intensity Statin
- If ≥7.5%, high intensity statin

NO DM, age 40–75, LDL 70–189
- Calculate 10-yr risk of ASCVD
- If risk ≥7.5%, mod-high intensity statin
- If risk 5–<7.5%, moderate-intensity statin

LDL ≥190
- High-Intensity Statin

Legend:
- should be done
- reasonable to do
ASCVD=atherosclerotic cardiovascular disease

http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.citation
AFCAPS/TexCAPS: Effect of Lovastatin 20–40 mg Daily on Major Cardiac Events in Various Patient Subgroups

Lovastatin Reduced the Risk of Major Cardiac Events

High- and Moderate-Intensity Statin Therapy

High-intensity statins lower LDL ~50%
  • Atorvastatin 40–80 mg
  • Rosuvastatin 20–40 mg

Moderate-intensity statins lower LDL 30 – 35%
  • Atorvastatin 10–20 mg
  • Rosuvastatin 5–10 mg
  • Simvastatin 20–40
  • Pravastatin 40–80 mg
  • Lovastatin 40 mg

Statins and Hypertension Control

In NHANES and CCI, hypertensive patients on statins are more likely to attain BP control.

“In a meta-analysis of 40 RCTs, patients on statins had a 2.6 mmHg lower SBP than patients on placebo.”

In ASCOT, hypertensives on atorvastatin had less treatment resistant hypertension (TRH) than patients on placebo.”

Caveat: “These studies were not designed to assess statin effects on BP or TRH. . . ”

Practical application: “If statins lower BP and reduce TRH, then implementing the 2013 Cholesterol Guideline, which increases hypertensives eligible for statin therapy by a net of ≈7 million, could improve BP control.”

CCI: Control of BP and LDL in Hyperlipidemic Hypertensives (2000-2011)

In one decade, SC OQUIN practices had a relative improvement of:
• 56% in BP Control to <140/<90 mm Hg
• 78% in LDL Control to <100 mg/dL
• 167% in both BP and LDL Control, which reduces CHD ≥50%

### SC Improvement in CV Mortality Rank vs. Other ‘Stroke Belt’ States: 1995 to 2009.

**50\(^{th}\) in US 1995** | **34\(^{th}\) in US 2011**

<table>
<thead>
<tr>
<th>1995 Rank</th>
<th>2009 Rank</th>
<th>Δ rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>31—Virginia</td>
<td>27—Virginia</td>
<td>+4</td>
</tr>
<tr>
<td>34—North Carolina</td>
<td>32—N. Carolina</td>
<td>+2</td>
</tr>
<tr>
<td>35—Indiana</td>
<td>34—S. Carolina</td>
<td>+16</td>
</tr>
<tr>
<td>41—Arkansas</td>
<td>40—Georgia</td>
<td>+4</td>
</tr>
<tr>
<td>43—Alabama</td>
<td>39—Indiana</td>
<td>-4</td>
</tr>
<tr>
<td>44—Georgia</td>
<td>44—Kentucky</td>
<td>+2</td>
</tr>
<tr>
<td>46—Kentucky</td>
<td>45—Tennessee</td>
<td>+4</td>
</tr>
<tr>
<td>47—Louisiana</td>
<td>48—Louisiana</td>
<td>-1</td>
</tr>
<tr>
<td>49—Tennessee</td>
<td>46—Arkansas</td>
<td>-5</td>
</tr>
<tr>
<td>50—South Carolina</td>
<td>50—Alabama</td>
<td>-7</td>
</tr>
<tr>
<td>51—Mississippi</td>
<td>51—Mississippi</td>
<td>0</td>
</tr>
</tbody>
</table>

**Source:** CDC WONDER
Overview of ‘JNC 8’ Guidelines for Managing High BP in Adults

Adults ≥18 Years with Hypertension
   - Implement & Continue Lifestyle Intervention(s)
   - Set BP Goal and Begin BP Lowering

Medication based on age (race), diabetes, CKD

No DM, CKD
   - Age ≥60
     - BP Goal <150/<90
       - Non-Black
         - Thiazide-type diuretic, ACEI, ARB, CCB alone or combo
     - Age <60
       - BP Goal <140/<90

DM or CKD
   - Age <60
     - BP Goal <140/<90
       - Black
         - TTD, CCB alone or combo
   - All Ages–DM
     - BP Goal <140/<90
       - ACEI or ARB alone or combo w/ CCB, TTD
   - All Ages–CKD
     - BP Goal <140/<90

Benazepril plus Amlodipine or HCTZ for Hypertension in High-Risk Patients

Methods 11,506 high-risk HTN patients were randomized to benazepril + amlodipine or benazepril + HCTZ.

Results BPs were 131.6/73.3 with ACEI–CCB and 132.5/74.4 with ACEI–HCTZ.

• There were 552 primary events with ACEI-CCB (9.6%) and 679 with ACEI–HCTZ (11.8%), HR, 0.80, p<0.001.

• For the secondary end point (death from CV causes, nonfatal MI, nonfatal stroke), the HR was 0.79, p=0.002).

Conclusions Benazepril and amlodipine was better than benazepril and HCTZ in reducing CV events in high risk hypertensive patients.

‘Predictors’ of BP Control in the 1\textsuperscript{st} Rx Year among Hypertensive Patients in CCI

In >100,000 hypertensive patients:

• Initial therapy with single-pill combinations (HR, 1.53 [95% CI, 1.47-1.58]) provided better hypertension control in the first year than free combinations (HR, 1.34; [95% CI, 1.31-1.37]) or monotherapy (reference).

• Greater use of single-pill combinations as initial therapy may improve hypertension control and cardiovascular outcomes in the first treatment year.
Categories of Apparent Treatment Resistant Hypertension (aTRH)

- Measurement artifacts (30% – 70%)
- Inadequate regimens (≥50%)
- Suboptimal adherence (10%–60%)
- True treatment resistant hypertension (~30%?), i.e., BP above goal on ≥3 different or controlled on ≥4 classes of BP meds at ‘optimal’ doses preferably including a diuretic

*Curr Opin Cardiol*. 2011;26:356–361
BP Measurement Artifacts

Office hypertension (~20–25%)\(^1,2\)
Pseudohypertension (~10%)\(^3\)
Cuff-inflation hypertension (<5%?)\(^4\)

**Clues to measurement artifacts:**
Less target organ damage than expected\(^4\)
Hypotensive symptoms with lowering or control of office BP control

\(^1\)JAMA 1988;259:225–228.
\(^3\)Hypertension 1983;5:122–127.
Prevalence of Optimal Treatment in Apparent TRH in a Community-Based Practice Network

• Among 468,877 hypertensives in CCI, their clinicians more often prescribed optimal therapy for aTRH when CVD risk was greater (black, CVD, CKD)

• ~1 in 7 of all uncontrolled hypertensives and 1 in 2 with aTRH are prescribed ≥3 BP meds in optimal regimens.

• Prescribing more optimal Rx for uncontrolled hypertensives could improve BP control.

Overnight Rostral Fluid Shift & Obstructive Sleep Apnea (OSA) in Treatment Resistant HTN (TRH)

OSA was greater in TRH than controlled HTN (apnea-hypopnea index [AHI]: 43 vs 18/hr, \( P=0.02 \)). In both groups, AHI correlated strongly with leg fluid volume displaced overnight (\( R^2=0.56, P<0.0001 \)) with greater changes in TRH than controlled HTN (347 vs 176 mL, \( P=0.01 \)).

Our findings support the concept that fluid redistribution centrally during sleep accounts for the high prevalence of OSA in TRH.

BP Effects of Low-Dose Spironolactone in 1411 ASCOT Hypertensives Uncontrolled on 3 Meds

4% serum K+ >5.5
and 2% >6.0 mmol/L

Concerns of Patients with Resistant Hypertension: Global Survey 2011.

*Patients with TRH want more options.* 75% of TRH patients are concerned about the number of medications they are taking and say their quality of life would greatly improve if they could control their BP with fewer medications; 84% wish it were easier to get their BP under control, and 79% of TRH patients would like more options to help them manage their BP.

Symplicity-3 U.S.Trial: Main Study Finding

SBP reduced 2.4 mmHg denervation vs. sham, p=0.26.

Effect of Baroreflex Activation on BP in Resistant Hypertension—265 Pts BP ~170/100 on 5.2 BP Meds

British NICE Hypertension Treatment Guideline
Adapted by Clinical Leaders in the CCI Network

<table>
<thead>
<tr>
<th>Age &lt;55 Years</th>
<th>Age ≥55 Years or Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>A</td>
</tr>
<tr>
<td>Step 2</td>
<td>A + C</td>
</tr>
<tr>
<td>Step 3</td>
<td>A + C + D</td>
</tr>
<tr>
<td>Step 4</td>
<td>Intensify diuretic or add α- and/or β-blocker</td>
</tr>
</tbody>
</table>

Intensify diuretic =

i. add 12.5–25 spironolactone if eGFR >45, K⁺ <4.8
ii. change HCTZ to chlorthalidone if eGFR>45, K⁺ >4.7 or eGFR 30 - >45
iii. Use or add loop diuretic if eGFR <30

A=ACEI or ARB; C=calcium antagonist; D=thiazide-type diuretic

http://www.nice.org.uk/guidance/CG127
Resistant Hypertension: Diagnostic & Therapeutic Recommendations: Will resolve ≥80% of TRH.

1. **Confirm Treatment Resistance.** Office BP >140/90 on ≥3 BP meds optimal doses, preferably including a diuretic

2. **Exclude Pseudoresistance.** Is patient adherent with regimen? Obtain automated office BP, out-of-office BP to exclude office effect

3. **Identify & Reverse Contributing Lifestyle Factors,** e.g., Obesity, physical inactivity, excess alcohol, high salt

4. **Discontinue, minimize interfering substances,** e.g., NSAIDs, sympathomimetics, oral contraceptives

5. **Screen for 2^o Causes of Hypertension,** e.g., OSA, 1^o aldo, CKD, renal artery stenosis, pheo, Cushing’s dz

6. **Pharmacologic Treatment.** Maximize diuretic Rx, incl possible aldo antagonist, use agents with complementary mechanisms

7. **Refer to Specialist** for known or suspected 2^o cause(s) of hypertension or if BP remains uncontrolled after 6 months Rx

Contemporary Management of Uncontrolled and Treatment Resistant Hypertension

• Clinical Epidemiology of Hypertension in the U.S.

• Dissecting the categories of uncontrolled and treatment resistant hypertension (TRH)

• Clinical Management of uncontrolled and TRH

• Summary