Drug Variability in Hypertension

Investigation and Summary of SPYRAL HTN Global Clinical Trial Program

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Lessons Learned from SYMPLICITY HTN-3

HTN-3 Factor Identified

- Procedural
- Medications
- Study Population
SPYRAL HTN Global Clinical Trial Program

Problems in Drug Therapy of Hypertension

Medications
Response Rate to Various Treatments for Hypertension

Philipp et al., Br J Med 1997, 315:154-159
Poor BP Control is Associated with Target Organ Damage

Uso of monotherapy and combination therapy to achieve blood pressure (BP) targets (<140/90 mmHg or <130/80 mmHg in diabetics) in patients under GP care

Number of drugs used

- 1 drug: 36.8%
- 2 drugs: 40.9%
- ≥3 drugs: 22.3%

BP control rate*

- 1 drug: 36.6%
- 2 drugs: 41.0%
- 3 drugs: 22.3%

*<140/90 mm Hg (<130/80 mm Hg in diabetics)
Problem of Polypharmacy
Compliance bei antihypertensiver Therapie

Verringerung der Compliance durch die Anzahl der verordneten Tabletten

Düsing und Vetter, Nieren- und Hochdruckkrankheiten 7 (2000)
Holzgreve, Internist (1996)
Multiple Daily Dosing Reduces Compliance

Systematic review of 76 studies

- Compliance (%)
  - Daily doses (n)
  - Daily Doses (n)

- p=0.001
- p<0.001
- p=0.008

Claxton et al., Clin Ther 23 (2001): 1296-1310
Good Compliance Increases the Likelihood of Achieving Blood Pressure Control

Retrospective, population-based study of medical and pharmacy claims and records in USA, 1999-2002 (n=840)

<table>
<thead>
<tr>
<th>Compliance (medication possession ratio)</th>
<th>Blood pressure control* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (≥ 80%)</td>
<td>43</td>
</tr>
<tr>
<td>Medium (50-79%)</td>
<td>34</td>
</tr>
<tr>
<td>Low (&lt; 50%)</td>
<td>33</td>
</tr>
</tbody>
</table>

* <140/90 mmHg for patients without diabetes; <130/85 mmHg for patients with diabetes
† Odds ratio = 1.45; p=0.026 after controlling for age, gender and comorbidities. Analysis limited to patients receiving monotherapy

Bramley et al., J Manag Care Pharm 12 (2006): 239-245
Antihypertension Medication Nonadherence Is Common and Difficult to Detect

Nearly 50% of patients become non-adherent to antihypertensive therapy within 1 year of initiating therapy.

“Physicians generally tend to overestimate patient’s adherence. Studies have demonstrated that clinicians’ estimates of non-adherence are very poor, with a positive predictive value of only approximately 30%. In fact, detecting non-adherence in clinical practice is almost impossible.”

Time course of office BP change

RDN
△ from Baseline (mmHg)

Control
△ from Baseline (mmHg)

Systolic
Diastolic

† p<0.0001 for between-group comparisons
‡‡ p=0.002 for between-group comparisons
‡‡‡ p=0.005 for between-group comparisons
Two-way repeated measures ANOVA, p=0.001

Reconstruction on a chromatogram of the protonated or deprotonated drugs after liquid chromatography high resolution tandem mass spectrometry (LC–HR–MS/MS) analysis. Arrows indicate retention times, at which drug should appear. Dashed lines represent background noise. In this patient example 3 out of 6 (50%) agents were taken as prescribed.
Blood Pressure Reduction After 6 Months

Ewen et al., Clin Res Cardiol (2015)
Adherence After RDN

A Responder office SBP

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=63</td>
<td>81.7</td>
<td>79.2</td>
</tr>
</tbody>
</table>

p=0.174

B Non-responder office SBP

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=37</td>
<td>90.6</td>
<td>83.4</td>
</tr>
</tbody>
</table>

p=0.006

Ewen et al., Clin Res Cardiol (2015)
Clinical Evidence: Randomized Sham Control Trial

Primary Efficacy End Point.

Secondary Efficacy End Point.

Were there frequent drug changes between baseline and 6 months of follow up?

Protocol mandated:
- **Maximum** doses and
- **No** medication changes

~40% of patients underwent medication changes*

69% of first medication changes were medically necessary

*Changes included class or dose

unpublished
SYMPPLICITY HTN-Japan
– First Randomized Controlled Trial of Catheter-Based Renal Denervation in Asian Patients –
Kazuomi Kario, MD; Hisao Ogawa, MD; Ken Okumura, MD; Takafumi Okura, MD; Shigeru Saito, MD; Takafumi Ueno, MD; Russel Haskin; Manuela Negoita, MD; Kazuyuki Shimada, MD on behalf of the SYMPPLICITY HTN-Japan Investigators
Change in Office Blood Pressure through 12-Months Post-Procedure

Baseline SBP (mm Hg) | 180 | 179 | 184*  \\
Baseline DBP (mm Hg) | 96  | 95  | 102*  \\

P<0.001 at all time points

Error Bars= 1.96 SE

*Baseline = time of RDN procedure

Bakris et al., ESC CTU, 2014
Change in Office Blood Pressure through 12-Months Post-Procedure

Sham vs non Sham not different

P<0.001 at all time points
Error Bars= 1.96 SE

Baseline SBP (mm Hg) | 180 | 179 | 184*
Baseline DBP (mm Hg) | 96  | 95  | 102*

*Baseline = time of RDN procedure

Bakris et al., ESC CTU, 2014
Change in Mean 24-hour Ambulatory Blood Pressure through 12 Months

**Results:**

**RDN 6 Months**

- Baseline SBP: 159 mm Hg
- Baseline DBP: 87 mm Hg

**RDN 12 Months**

- Baseline SBP: 158 mm Hg
- Baseline DBP: 86 mm Hg

**Crossover 6 Months**

- Baseline SBP: 163 mm Hg
- Baseline DBP: 94 mm Hg

*Baseline = time of RDN procedure

- **P<0.001 for all**
- **Error Bars=1.96 SE**

**Sham vs non Sham not different**

_Bakris et al., ESC CTU, 2014_
Change in Office Blood Pressure through 12-Months Post-Procedure

Subjects unblinded

Non-Crossover 6 Months

Non-Crossover 12 Months

Baseline SBP (mm Hg) | 176 | 176
Baseline DBP (mm Hg) | 94 | 94

Δ 6 to 12 months = +11.5/+5 mmHg

P<0.001 at all time points
Error Bars=1.96 SE

Baseline SBP (mm Hg) | 176 | 176
Baseline DBP (mm Hg) | 94 | 94

Bakris et al., ESC CTU, 2014
Change in Office Blood Pressure through 12-Months Post-Procedure

Subjects unblinded

Non-Crossover 6 Months

Non-Crossover 12 Months

Baseline SBP (mm Hg) 176 |
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Δ 6 to 12 months = +11.5/+5 mmHg

P<0.001 at all time points
Error Bars=1.96 SE

Bakris et al., ESC CTU, 2014
Discuss. Böhm
Change in Mean 24-hour Ambulatory Blood Pressure through 12 Months

Subjects unblinded

Non-Crossover 6 Months

Non-Crossover 12 Months

Δ 6 to 12 months = +4.9/+3.7 mmHg

Baseline SBP (mm Hg) | 151 | 151
Baseline DBP (mm Hg) | 86 | 86

Error Bars=1.96SE

Bakris et al., ESC CTU, 2014
Discuss. Böhm
## Antihypertensive Treatment - Compliance

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>No of Users</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Month</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Month</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Month</th>
<th>4&lt;sup&gt;th&lt;/sup&gt; Month</th>
<th>5&lt;sup&gt;th&lt;/sup&gt; Month</th>
<th>6&lt;sup&gt;th&lt;/sup&gt; Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>5 171</td>
<td>81%</td>
<td>62%</td>
<td>52%</td>
<td>46%</td>
<td>43%</td>
<td>41%</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>3 615</td>
<td>85%</td>
<td>70%</td>
<td>61%</td>
<td>55%</td>
<td>51%</td>
<td>49%</td>
</tr>
<tr>
<td>Ca&lt;sup&gt;2+&lt;/sup&gt;-Ch. Blocker</td>
<td>3 244</td>
<td>78%</td>
<td>58%</td>
<td>49%</td>
<td>45%</td>
<td>42%</td>
<td>41%</td>
</tr>
<tr>
<td>ACE-Inhibitors</td>
<td>2 710</td>
<td>82%</td>
<td>65%</td>
<td>55%</td>
<td>50%</td>
<td>47%</td>
<td>45%</td>
</tr>
</tbody>
</table>


CMR 11-19
• 4-week run-in period with administration of standardized triple combination therapy (Diuretic + ACE inhibitor + CCB)

Optimal and stepped-care antihypertensive treatment + RDN versus
Optimal and stepped-care antihypertensive treatment

Azizi et al., Lancet, 2015
# DENER HTN: Drug Titration Algorithm

<table>
<thead>
<tr>
<th>4 WEEKS</th>
<th>MONTHLY VISITS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standardized triple therapy:</strong></td>
<td><strong>Adjustment of AHT medication done according to HBP goal &lt;135/85 mm Hg</strong></td>
</tr>
<tr>
<td>Indapamid 1.5 mg + Ramipril 10 mg/Irbesartan 300 mg + Amlodipine 10 mg/5 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Randomization</strong></td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>Month 2</td>
</tr>
<tr>
<td>Spiro. 25 mg</td>
<td>Spiro. 25 mg + Biso. 10 mg</td>
</tr>
</tbody>
</table>

**ABPM**
- Month 1
- Month 6

**eGFR**
- Month 1
- Month 2
- Month 3
- Month 4
- Month 5
- Month 6

**MMAS-8**
- Month 1
- Month 2
- Month 3
- Month 4
- Month 5
- Month 6

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Changes in daytime and nighttime ambulatory BP at 6-month follow up

Δ-5.9 mmHg
(95% CI -12.3 to 0.5)
p=0.03

Δ-6.3 mmHg
(95% CI -12.0 to 0.6)
p=0.03

Azizi et al., Lancet, 2015
Changes in daytime and nighttime ambulatory BP at 6-month follow up

Primary efficacy endpoint was met

Azizi et al., Lancet, 2015
Changes in daytime and nighttime ambulatory BP at 6-month follow up

Azizi et al., Lancet, 2015
**SPYRAL HTN–OFF MED Study**

1. **Patients with HTN**
   - Office SBP
   - Taken off medications

2. **1st screening**
   - SBP >180
   - Screen failure

3. **2-week safety check**

4. **3-week washout**
   - ABPM ≥140 to 170
   - Office ≥150 to <180
   - DBP ≥ 90

5. **2nd screening**
   - Baseline ABPM
   - Office SBP

6. **4-week washout**

7. **Randomization/procedure**
   - Renal denervation
   - Sham procedure

8. **Follow-up every 2 weeks (through 3 mo)**
   - Med titration every 2 weeks if uncontrolled

9. **Follow-up every 3–6 weeks (through 3 mo)**

10. **Unblinding**
    - 3 Mo 6 Mo 12 Mo

**Drug testing to confirm washout at 2nd screening visit and 3 mo; drug testing at 6 mo and 12 mo**

**Represents study safety measures**

**N≤60**
SPYRAL HTN–ON MED Study

1st screening
- Office SBP

2nd screening
- Urinalysis
- Observed drug intake
- Office SBP
- ABPM

Confirmed on meds
- Thiazide diuretic
- Calcium channel blocker
- ACE/ARB
- Stable meds

ABPM ≥140 to 170
Office ≥150 and <180
DBP ≥ 90

Renal denervation + meds

Randomization/Procedure

Sham procedure + meds

Drug testing

Unblinding

1 Mo
3 Mo
6 Mo
12–36 Mo

N<50

Office BP

Office BP
ABPM
Problems in Drug Therapy of Hypertension

Take Home Messages

- Medication changes and variable adherence confounders in SYMPLICITY HTN-3

- Many patients changed medications during SYMPLICITY HTN-3

- Drug adherence not measured, but likely a key uncontrolled variable

- Obtain off drug data

- Drug Screening in urine with consenting
Thank you!

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