Pharmacist-Physician Collaboration for Uncontrolled Treatment-Resistant Hypertension

Steven M. Smith, PharmD, MPH, BCPS
Assistant Professor of Pharmacy & Medicine
Treatment- Resistant Hypertension (TRH)

- “BP that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes” (AHA, 2008)
  - Ideally, one of the agents should be a diuretic
  - All 3[+] agents should be prescribed at an “optimal dose”

- More simply… hypertension requiring ≥4 drugs to control BP

TRH Prevalence is Increasing

NHANES, 1988-2008

Percent with RHTN among U.S. Adults with Hypertension

- 1988-94: 2.3% Controlled, 6.5% Uncontrolled
- 1999-2004: 5.2% Controlled, 9.3% Uncontrolled
- 2005-08: 7.3% Controlled, 13.4% Uncontrolled

Smith SM. Pharmacotherapy 2013;33:1071-86
TRH-associated MACE

First occurrence of all-cause mortality, nonfatal MI, nonfatal stroke, or hospitalization for HF or angina

TRH-associated Mortality

Survival (%)

Time to Event (years)

Normotensive
Controlled HTN
Uncontrolled HTN
Apparent Resistant HTN

logrank p<0.0001

Physician-Pharmacist Collaboration

- Team-based care, including Physician-Pharmacist Collaboration (PPC) is effective in HTN management

- Unknown efficacy vs. usual care in patients with uncontrolled TRH
Physician-PharmD Collaboration in TRH

32 Clinics Randomized

9-month PPCM Intervention
n=11 clinics
n=330 consented subjects

136 excluded:
-129 controlled BP
-7 other exclusions

194 Qualifying Subjects

TRH at Baseline
(n=111; 27.7%)

24-month PPCM Intervention
n=9 clinics
n=349 consented subjects

142 excluded:
-135 controlled BP
-7 other exclusions

207 Qualifying Subjects

Usual Care Control Group
n=12 clinics
n=374 consented subjects

150 excluded:
-138 controlled BP
-12 other exclusions

224 Qualifying Subjects

TRH at Baseline
(n=58; 25.9%)

Physician-PharmD Collaboration in TRH

Adjusted* Difference (95% CI):
SBP: -6.7 mm Hg (-12.8, -0.44)
DBP: -0.4 mm Hg (-4.0, 3.3)

*Adjustment for office, baseline BP, age, CKD/DM, med adherence

Physician-PharmD Collaboration in TRH

Adjusted* Odds Ratio: **1.92** (95% CI 0.33, 11.2; p=0.47)

*Adjustment for office, baseline BP, age, CKD/DM, med adherence
Adherence

Self-reported High Adherence

- Baseline: 80% (PPC Intervention), 80% (Usual Care)
- 9-month: 100% (PPC Intervention), 100% (Usual Care)

Improvement from Low to High Adherence

- Overall: 6.3% (p=0.36), 1.7% (p=0.016)
- Minorities: 8.1% (p=0.016), 0%

Collaborative care seems to work well in the most difficult-to-treat HTN cases

- Improved adherence
- Greater follow-up frequency
  - 8.9 vs. 4.2 total clinic visits or clinically-related phone calls
  - 6.2 vs. 1.0 HTN-related clinic visits
- More optimal medication regimens?
  - \( \uparrow \) spironolactone use [18\% vs. 6\% at 9-mo]
  - \( \downarrow \) \( \alpha_1 \) antagonist use [2\% vs. 12\% at 9-mo]
  - Reduction in class duplication [11.7\% vs 8.6\% at baseline \( \rightarrow \) 2\% vs. 8\% at 9-mo]

Implications

Conclusions

- RH is common, challenging, and associated with adverse outcomes, including:
  - ↑ death, MI, stroke, decrements in HrQoL, substantially increased healthcare utilization & costs
- Medication optimization may be the most effective approach to ↓ BP (? effect on hard outcomes), but is not being done
- Pharmacists can play an important role in team-based care for HTN and TRH more specifically
Questions?
EXTRA SLIDES
Antihypertensive Use is Increasing

Smith SM. Pharmacotherapy 2013;33:1071-86

NHANES Dataset

Percent of U.S. Adults Taking Drug

Diuretics
ACE-Is
β-blockers
Thiazides
ARBs
CCBs

*p≤0.02
Therapeutic Inertia is Decreasing

RH-associated MACE

First occurrence of all-cause mortality, non-fatal MI, or non-fatal stroke

RH-associated MACE

RH-associated Mortality: Impact of BP

Hazard Ratio (95% CI)

- Controlled HTN
- Uncontrolled HTN
- Controlled Resistant HTN
- Uncontrolled Resistant HTN

Primary Outcome
- All-cause Mortality
- CV Mortality

Controlled Resistant HTN
Uncontrolled Resistant HTN
Uncontrolled HTN
Controlled HTN
RH-associated Mortality in Women

Unpublished Data; presented at AHA Scientific Sessions 2014
Impact on HrQoL

Impact on HrQoL

Impact on HrQoL

Impact on HrQoL

## RH Impact on Healthcare Utilization

<table>
<thead>
<tr>
<th>Medical Resource</th>
<th>Non-rHTN (n=41,552)</th>
<th>RHTN (n=1,924)</th>
<th>P-value</th>
<th>IRR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td># office visits</td>
<td>9.56 ± 0.11</td>
<td>15.2 ± 0.65</td>
<td>&lt;0.001</td>
<td>1.17 (1.09–1.26)</td>
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<tr>
<td># outpatient visits</td>
<td>1.07 ± 0.03</td>
<td>2.06 ± 0.19</td>
<td>&lt;0.001</td>
<td>1.30 (1.07–1.57)</td>
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<td># ER visits</td>
<td>0.28 ± 0.01</td>
<td>0.49 ± 0.03</td>
<td>&lt;0.001</td>
<td>1.36 (1.19–1.55)</td>
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<tr>
<td># inpatient visits</td>
<td>1.27 ± 0.04</td>
<td>3.42 ± 0.32</td>
<td>&lt;0.001</td>
<td>1.57 (1.37–1.80)</td>
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<td>LOS, days</td>
<td>0.22 ± 0.004</td>
<td>0.54 ± 0.04</td>
<td>&lt;0.001</td>
<td>1.96 (1.62–2.38)</td>
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<td># Rx fills</td>
<td>30.0 ± 0.28</td>
<td>69.0 ± 1.46</td>
<td>&lt;0.001</td>
<td>1.74 (1.67–1.82)</td>
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<tr>
<td>HTN meds</td>
<td>9.5 ± 0.08</td>
<td>30.7 ± 0.49</td>
<td>&lt;0.001</td>
<td>-</td>
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<tr>
<td>Non-HTN meds</td>
<td>20.5 ± 0.22</td>
<td>38.3 ± 1.17</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Data represent mean ± SE, unless otherwise noted. *Controlling for age, sex, race, ethnicity, BMI, income level, educational attainment, smoking status, physical activity, number of chronic comorbidities, and insurance status; non-resistant HTN group is reference.

Unpublished Data; presented at AHA Scientific Sessions 2014
Economic Considerations

Marginal Effect (vs. no HTN):
- RH: $3,016
- Treated non-RHTN: $1813
- Untreated HTN: $986
Spironolactone: PATHWAY-2

Screening
~350 patients; BP not controlled despite treatment with recommended and/or maximum tolerated doses of triple therapy with ACEI/ARB/direct renin inhibitor (A)+ CCB (C) + Diuretic (any except spironolactone) (D)

Single blind placebo run-in (4 weeks)

Randomisation

SPIRONOLACTONE
25mg → 50mg
Wk 1 → 6 → 12
Part 1 → Part 2

BISOPROLOL
5mg → 10mg
Wk 1 → 6 → 12
Part 1 → Part 2

DOXAZOSIN
4mg → 8mg
Wk 1 → 6 → 12
Part 1 → Part 2

PLACEBO
Wk 1 → 6 → 12
Part 1 → Part 2

Open Label Amiloride
10mg o.d. (increasing to 20mg o.d. as required)
Observational follow-up until study is completed for all patients and unblinding reveals the best treatment for individual patients

Spironolactone: PATHWAY-2

Antihypertensive Use in RH in U.S.

N=261,854 patients
N=411,652 episodes of RH
Antihypertensive Use in RH in U.S.

- β-Blockers
- Thiazide diuretics
- DHP CCBs
- ARBs
- ACE inhibitors
- Aldosterone Antags
U.S. Aldosterone Antagonist use in RH

* June 2008: AHA Scientific Statement published, recommending use of AAs (or amiloride as alternative)

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Percent of All Antihypertensives</th>
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<tbody>
<tr>
<td>2008 Q3</td>
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<tr>
<td>2009 Q1</td>
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<td>2014 Q1</td>
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<td>2014 Q3</td>
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</tbody>
</table>

- Amiloride (alternative to AAs)
- Eplerenone
- Spironolactone
U.S. Thiazide use in RH

* June 2008: AHA Scientific Statement published, recommending use of chlorthalidone over HCTZ