Evaluating the Pressor Effects of Drugs & Ambulatory Blood Pressure Monitoring Studies

Conference Center at 1777 F Street NW • Washington, DC
February 4th, 2019
9:00 am – 4:30 pm
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William E. Vlahos, MD
Division of Cardiology
University of Medicine
Boston University of Medicine

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William C. Cushman, MD
Co-Chair VA Hypertension-Lipid Field Advisory Committee
Chief, Preventive Medicine Section
VA Medical Center, Memphis, TN

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William D. White, MD
Professor of Medicine
Hypertension and Cardiology, Mayo University of Connecticut School of Medicine

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George H. Reis, MD
Professor of Medicine
Director, American Heart Association Hypertension Center
University of Pittsburgh, Pittsburgh, PA

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Thai K. Balanek
Division of Cardiovascular and Renal Products
CNH/CGER

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Eran Johansson
Division of Cardiovascular and Renal Products
CNH/CGER

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Duchic Shimbo, MD
The Hypertension Center
Columbia University Medical Center

Clinical Pharmacology Considerations for Evaluating Pressor Effects
Raj Madan, MD
Team Lead, CBT and CHERM Team
Office of Clinical Pharmacology
CNH/CGER

Medications, BP and CV Risk
Robert P. Bankhead, MD, MD
Clinical Professor of Internal Medicine
Columbia University, New York School of Medicine
February 3, 2015

ASSESSMENT OF PRESSOR EFFECTS OF DRUGS: GUIDANCE FOR INDUSTRY
COMMENTS
Christie F. Bensman, MD
Pharmacology
Pharmacy, 12th Floor
February 6, 2015
Welcome & Overview

Dr. Mark McClellan, Director, Duke-Margolis Center for Health Policy
9:00 am – 9:05 am

E-mail questions to pressor@duke.edu
Opening Remarks

Dr. Ellis Unger, Director, Office of Drug Evaluation I

9:05 am – 9:15 am
FDA Perspective on the Evaluation of Blood Pressure in Drug Development

Dr. Norman Stockbridge, Director, Division of Cardiovascular and Renal Products

9:15 am – 9:30 am
Part I:
Issues FDA Raised in the Draft Guidance

Sessions 1A, 1B, 1C, & 1D
9:30 am – 1:50 pm
Session 1A: Understanding the Temporal Relationship Between Changes in Blood Pressure and Changes in Risk

9:30 am – 10:20 am

E-mail questions to pressor@duke.edu
Temporal Relationships of Drug-Induced BP Effects and CV Outcomes

Michael A. Weber, MD
Division of Cardiovascular Medicine
Downstate College of Medicine
State University of New York
The Risk of IHD Mortality Doubles With Each 20/10 Increase of BP Above 115/75 mm Hg

BP and Events During Drug Therapy  Looking for a Connection

Drug-induced BP changes and events:

3 temporal categories

1. Obvious connection: Very high BP soon followed by major events

2. Modest but measurable BP changes associated with increased CV events after weeks or months

3. Minor mean changes in BP that might have CV effects when large patients groups receive chronic treatment
Category 1:

BP effects immediate and severe
CV events seen early
Cancer Therapies: Becacizumab (Avastin)

- VEGF inhibitor used in high doses to treat cancer
- Raises BP, but also destroys vascular endothelium, causes tissue ischemia and might even stimulate vasculotoxic proteins analogous to eclampsia

### A CNS ischemia events

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegra, 2009</td>
<td>5</td>
<td>1326</td>
<td>5</td>
<td>1321</td>
<td>39.7%</td>
<td>1.00 [0.29, 3.43]</td>
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<tr>
<td>Giantonio, 2007</td>
<td>1</td>
<td>287</td>
<td>0</td>
<td>285</td>
<td>4.0%</td>
<td>2.98 [0.12, 72.83]</td>
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<tr>
<td>Kabbinavar, 2003</td>
<td>2</td>
<td>32</td>
<td>0</td>
<td>35</td>
<td>3.8%</td>
<td>5.45 [0.27, 109.49]</td>
</tr>
<tr>
<td>Kelly, 2012</td>
<td>7</td>
<td>504</td>
<td>1</td>
<td>505</td>
<td>7.9%</td>
<td>7.01 [0.87, 56.80]</td>
</tr>
<tr>
<td>Kindler, 2007</td>
<td>2</td>
<td>53</td>
<td>0</td>
<td>55</td>
<td>3.9%</td>
<td>5.19 [0.25, 105.54]</td>
</tr>
<tr>
<td>Kindler, 2010</td>
<td>2</td>
<td>277</td>
<td>2</td>
<td>263</td>
<td>16.3%</td>
<td>0.95 [0.13, 6.69]</td>
</tr>
<tr>
<td>Miller, 2007</td>
<td>7</td>
<td>365</td>
<td>0</td>
<td>346</td>
<td>4.1%</td>
<td>14.22 [0.82, 248.06]</td>
</tr>
<tr>
<td>Okines, 2013</td>
<td>1</td>
<td>99</td>
<td>0</td>
<td>101</td>
<td>3.9%</td>
<td>3.06 [0.13, 74.23]</td>
</tr>
<tr>
<td>Price, 2012</td>
<td>4</td>
<td>315</td>
<td>0</td>
<td>236</td>
<td>4.5%</td>
<td>6.75 [0.37, 124.76]</td>
</tr>
<tr>
<td>Rini, 2010</td>
<td>5</td>
<td>362</td>
<td>1</td>
<td>347</td>
<td>8.1%</td>
<td>4.79 [0.56, 40.82]</td>
</tr>
<tr>
<td>Sandler, 2006</td>
<td>2</td>
<td>427</td>
<td>0</td>
<td>440</td>
<td>3.9%</td>
<td>5.15 [0.25, 107.00]</td>
</tr>
</tbody>
</table>

Total (95% CI): 4047 / 3934 = 100.0%  Risk Ratio: 3.22 [1.71, 6.07]

Total events: 38 / 9 = 88.9%

Heterogeneity: Chi² = 7.22, df = 10 (P = 0.70); I² = 0%

Test for overall effect: Z = 3.62 (P = 0.0003)

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![Graph showing risk ratio with 95% confidence intervals for experimental and control groups.](image)
Avastin: Is stroke totally dependent on BP effects?

Mayo Clinic experience: Avastin data: 10 strokes, all within 3 weeks of starting therapy; 7 of 10 had hypertension history; 9 of 10 had severe hypertension following Avastin; 6 of 10 died within 3 months (Seet et al. Neurocrit Care 2011;15:421-427)
Category 2:

BP Effects sufficient to be measurable and noted
Timing of CV events: Occur within weeks or months
VALUE: Hypertension Outcomes Trial Comparing Valsartan and Amlodipine

• Randomized 15,313 high risk hypertensive patients to valsartan or amlodipine-based regimens

• Unintended early BP difference favored amlodipine

• Early CV event rates significantly higher with valsartan

VALUE: Unintended Early Difference In BP

**Sitting SBP by Time and Treatment Group**

Baseline | 1 | 2 | 3 | 4 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 | 66
---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----
Valsartan (N= 7649) | 155 | 150 | 145 | 140 | 135 | 130 | 125 | 120 | 115 | 110 | 105 | 100 | 95 | 90 | 85
Amlodipine (N = 7596) | 160 | 155 | 150 | 145 | 140 | 135 | 130 | 125 | 120 | 115 | 110 | 105 | 100 | 95 | 90

**Difference in SBP Between Valsartan and Amlodipine**

Baseline | 1 | 2 | 3 | 4 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 | 66
---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----
Amlodipine (N = 7596) | -0.5 | -1.5 | -2.5 | -3.5 | -4.5 | -5.5 | -6.5 | -7.5 | -8.5 | -9.5 | -10.5 | -11.5 | -12.5 | -13.5 | -14.5

### Outcome and SBP Differences at Specific Time Periods: Primary Composite Endpoint

<table>
<thead>
<tr>
<th>Time Interval (months)</th>
<th>Δ SBP mmHg</th>
<th>PRIMARY ENDPOINT Odds Ratios and 95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall study</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>3–6</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>6–12</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>12–24</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>24–36</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>36–48</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Study end</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

**Favours valsartan**  **Favours amlodipine**

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ALLHAT Study Design

Randomized, double-blind, multicenter trial
33,357 subjects, aged ≥ 55 y, with stage 1 or stage 2 hypertension
and ≥ 1 CHD risk factor*

Primary outcome: Fatal CHD or non-fatal MI
Secondary outcomes: All-cause mortality; Stroke;
Combined CHD†; Combined CVD‡
Mean follow-up: 4.9 years

Chlorthalidone 12.5-25 mg/d (n=15,255)
Amlodipine besylate 2.5-10 mg/d (n=9048)
Lisinopril 10-40 mg/d (n=9054)

CHD, coronary heart disease; MI, myocardial infarction; CVD, cardiovascular disease.
* Previous (>6 mos) MI or stroke, LVH, type 2 diabetes, current smoker, HDL-C <35 mg/dL, other documented CVD.
† Primary outcome, coronary revascularization, hospitalized angina.
‡ Combined CHD, stroke, treated angina, heart failure, peripheral vascular disease.

ALLHAT: Stroke (Lisinopril vs Chlorthalidone)

**RR (95% CI)**

- Total: 1.15 (1.02-1.30)
- Age <65: 1.21 (0.97-1.52)
- Age ≥65: 1.13 (0.98-1.30)
- Men: 1.10 (0.94-1.29)
- Women: 1.22 (1.01-1.46)
- Black*: 1.40 (1.17-1.68)
- Nonblack: 1.00 (0.85-1.17)

*Systolic BP 4 mmHg difference favoring chlorthalidone

ALLHAT. JAMA 2002; 288:2981-2997
Empagliflozin: CV Outcomes Trial in Compliance with FDA’s CV Safety Requirements for Diabetes Drugs

This SGLT2 agent compared with placebo when added to patients with type 2 diabetes
Systolic Blood Pressures During Empagliflozin Trial
Cardiovascular Outcomes During Empagliflozin Trial
Did BP Changes Explain Results of Empagliflozin Trial?

• Effects on primary CV endpoint and CV mortality seen by 6 months

• Consistent fall in SBP 3-4 mmHg (vs. P) during trial

• But changes in glucose/HbA1c/lipids/uric acid/BMI also found – did they contribute to the CV result?
Category 3

Minor changes in BP, rarely obvious in clinical practice

But, chronic treatment in large numbers of patients:

-------- Can ABPM identify BP effects?
## Summary of Risk for Cardiovascular Events With Various COX-2 Inhibitors and NSAIDs*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Summary Relative Risk for Cardiovascular Event (95% CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib, ≤25 mg</td>
<td>1.33 (1.00-1.79)</td>
</tr>
<tr>
<td>Rofecoxib, &gt;25 mg</td>
<td>2.19 (1.64-2.91)</td>
</tr>
<tr>
<td>Celocoxib</td>
<td>1.06 (0.91-1.23)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.40 (1.16-1.70)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>0.97 (0.87-1.07)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>1.06 (0.70-1.59)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.07 (0.97-1.18)</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>1.25 (1.00-1.55)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>1.30 (1.07-1.60)</td>
</tr>
</tbody>
</table>

*CI=confidence interval; bold typeface - statistically significant

Mirabegron

- Mirabegron is a beta-3 agonist to treat overactive bladder
- It can increase BP, possibly through minor beta-1 effects
- In young volunteers, it increased SBP by 3 mmHg
- But in older, real patients it increased mean SBP by approx 0.5 mmHg

How do we deal with this?
BP Effects of Mirabegron: 24h Ambulatory Mean SBP
Mean Hourly Changes in Ambulatory SBP from Baseline: Mirabegron and Placebo
24h Ambulatory BP Monitoring
Mirabegron and Placebo

Frequency of blood pressure and heart rate outliers in mean 24 h values

<table>
<thead>
<tr>
<th></th>
<th>Placebo [n (%)]</th>
<th>Mirabegron (25 mg) [n (%)]</th>
<th>Mirabegron (50 mg) [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP ≥ 15 mmHg</td>
<td>9/80 (11.3)</td>
<td>1/73 (1.4)</td>
<td>11/76 (14.5)</td>
</tr>
<tr>
<td>DBP ≥ 10 mmHg</td>
<td>4/80 (5.0)</td>
<td>0/73 (0)</td>
<td>4/76 (5.3)</td>
</tr>
<tr>
<td>Heart rate ≥ 10 bpm</td>
<td>8/80 (10.0)</td>
<td>6/73 (8.2)</td>
<td>6/76 (7.9)</td>
</tr>
</tbody>
</table>
A

Renal denervation

24-h SBP

Sham control

BP increase (n=10)

BP increase (n=19)

BP increase (n=7)

BP increase (n=18)

BP decrease (n=25)

BP decrease (n=17)

BP decrease (n=28)

BP decrease (n=18)
Conclusions: Off-Target Effects of Drugs on BP and CV Events

1. Severe BP increases causing CV events are usually predictable and occur early in treatment.
2. CV events associated with moderate BP increases (3-4 mmHg) can be demonstrated within weeks/months of starting treatment.
3. Minor BP effects that could cause CV events in large cohorts on chronic treatment are difficult to identify. Is ABPM the answer?

Confounding factors
1. Patients at high CV risk
2. Drugs that have non-BP adverse CV effects
Session 1A: Understanding the Temporal Relationship Between Changes in Blood Pressure and Changes in Risk

9:30 am – 10:20 am

E-mail questions to pressor@duke.edu
Understanding the Temporal Relationship Between Changes in Blood Pressure and Changes in Risk

William C. Cushman, MD
Co-Chair VA Hypertension-Lipid Field Advisory Committee
Chief, Preventive Medicine Section
VA Medical Center, Memphis, TN
Principles

- Any drug that chronically lowers or raises BP and is intended to be taken long-term, may be expected to decrease or increase CV risk.

- Participants in trials whose BP is not reduced or controlled as well as other participants presumably administered the same drugs/doses are usually observed to be at higher risk: this may be from unmeasured differences, e.g., lower medication or lifestyle adherence, longer duration of HTN, more vascular or other end-organ damage, etc.

- In most randomized controlled trials of BP lowering, event differences often begin to appear after 1-2 years, but may not become significant until 3-5 years. HF is an exception and may begin to appear different after 6 months.
VA Cooperative HTN Trial: DBP 90-114 mm Hg

1. Men with DBP 90-114 mm Hg
2. RZ to triple therapy (HCTZ/reserpine/hydralazine) vs PBOs
3. BP:
   • Mean BL: 162-165/104-105 mm Hg
   • Mean change at 4 mos:
     ➢ SBP: -27.2 vs + 4.2 (Δ 31.4)
     ➢ DBP: -17.4 vs +1.2 (Δ 18.6)
4. Mean follow up: 3.3 yrs (stopped early)
5. Risk reduction: 67%
6. NNT: 2.7 over 5 years

Veterans Administration Cooperative Study Group on Antihypertensive Agents. JAMA 1970;213:1143-52
HDFP Mortality Rates
Entire Cohort (n=10,940)

5-yr Mortality reduced by 17% (6.4 vs. 7.7%; P<0.01)
NNT 77

Referred Care
(n=5,456)

Stepped Care
(n=5,485)

Cumulative mortality (%) vs. Year of follow-up

HDFP=Hypertension Detection and Follow-up Program
Stroke rate reduced by 37%, P=0.0003
Ave follow-up 4.5 yrs
Ave SBP Δ: 12 mm Hg
(155 vs 143 mm Hg)

SHEP=Systolic Hypertension in the Elderly Program
At 2 years, mean sitting Δ BP was 15.0/6.1 mm Hg
Hypertension in the Very Elderly Trial
HYVET: HF

Heart Failure

No. of Events per 100 Patients

Follow-up (yr)

No. at Risk
Placebo group 1912 1480 794 367 188
Active-treatment group 1933 1559 872 416 228

P<0.001


SPRINT Primary Outcome (CVD) Cumulative Hazard

25% reduction P<0.001

During Trial (median follow-up = 3.26 years)
Number Needed to Treat (NNT) to prevent a primary outcome = 61

Ave SBP Δ: 13.5 mm Hg
Ave 1 yr Δ: 14.8 mm Hg
SPRINT: All-cause Mortality
Cumulative Hazard

27% reduction
P=0.003

Ave SBP Δ: 13.5 mm Hg
Ave 1 yr Δ: 14.8 mm Hg

During Trial (median follow-up = 3.26 years)
Number Needed to Treat (NNT) to Prevent a death = 90

Kaplan-Meyer curves for the SPRINT Acute Decompensated Heart Failure Outcome by Treatment Group

Vertical bars indicate 95% confidence intervals. P value is from a Cox proportional hazards model stratified by clinical site. Number at risk and number of events is shown every 6 months.

Cumulative Incidence of CVD in intensive and standard SBP groups of SPRINT and ACCORD BP

Standard Glycemia Arm

HR (95% CI) = 0.75 (0.65-0.89)

HR (95% CI) = 0.77 (0.63-0.95)

Beddhu, et al. J Am Heart Assoc. 2018 Sep 18;7:e009326
Primary Outcome
Nonfatal MI, Nonfatal Stroke or CVD Death

HR = 0.88
95% CI (0.73-1.06)

Total Stroke

HR = 0.59
95% CI (0.39-0.89)
NNT for 5 years = 89
HOPE-3

n = 12,705, intermediate risk
- Men 55+ yrs
- Women 65+ yrs

Candesartan 16 mg + HCTZ 12.5 mg vs PBO

BP Δ: 6/3 mm Hg

Median FU: 5.6 yrs

Session 1A: Understanding the Temporal Relationship Between Changes in Blood Pressure and Changes in Risk

9:30 am – 10:20 am

E-mail questions to pressor@duke.edu
Break

10:20 am – 10:30 am
Session 1B: Interpreting Results of the PRECISION Study

10:30 am – 11:20 am

E-mail questions to pressor@duke.edu
Nested Blood Pressure Study to Assess Pressor Effects and Consequent Risks of Drugs Not Aiming at BP therapy: What does PRECISION tell us about Relevance of Such a Study for FDA Pressor Draft Guidance?

JEFFREY S. BORER, M.D.
Professor of Medicine, Cell Biology, Radiology, Surgery and Public Health
Director, The Howard Gilman Institute for Heart Valve Disease and The Schiavone Cardiovascular Translational Research Institute
Formerly Chairman of Medicine and Chief, Cardiovascular Medicine
SUNY Downstate, New York City
Adjunct Professor of Cardiovascular Medicine in Cardiothoracic Surgery,
Weill Medical College of Cornell University/ New York-Presbyterian Hospital

Duke Margolis Center
Washington, DC, Feb 4, 2019
PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or Naproxen): Background

- 2000-2004: accumulating data (e.g., VIGOR, meta-analysis) suggest rofecoxib poses dose-related CV risk; celecoxib data are ambiguous (CLASS, APC, ADAPT, etc.)
- FitzGerald suggests that an unbalanced thromboxane activity of all COX2 selective NSAIDs accounts for the adversities.
- 2005: FDA mandates trial to compare CV risk of COX-2 selective vs non-selective NSAIDs. Therefore, PRECISION is developed. Begins in 2006, all data collected by 2016.
- To test hypothesis that different NSAIDs affect BP differently and that any CV risk difference among NSAIDs relates to BP effects rather than FitzGerald Hypothesis Ruschitzka, Borer and Krumm design and chair the prespecified nested PRECISION substudy.
PRECISION – Treatments

OA or RA patients with established CV disease or at increased CV risk who required NSAIDs for ≥ 6 months for symptom relief

- Celecoxib 100 mg BID
- Ibuprofen 600 mg TID
- Naproxen 375 mg BID
- Esomeprazole 20-40 mg

+ optimal preventive care for CV disease risk per local standards (including aspirin)

Option to increase dosage for unrelieved symptoms to the maximum approved by local regulatory authorities

Event driven trial with a minimum follow up of 18 months

Nissen S et al. NEJM 2016
All NSAIDs can increase blood pressure or interfere with blood pressure control
Even small differences in blood pressure can impact cardiovascular morbidity and mortality

* A priori sub-study (n=444 subjects) to delineate differential blood pressure effects and the relationship between changes in ambulatory blood pressure and subsequent cardiovascular events of celecoxib vs naproxen and ibuprofen

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Changes in ambulatory 24-h SBP from baseline at 4 months resulted in a difference of -3.9 mm Hg (95% CI, -6.19, -1.61; P<0.001) between celecoxib and ibuprofen; of -1.8 mm Hg (95% CI, -4.15, 0.47; P=0.12) between celecoxib and naproxen, and of -2.1 mm Hg (95% CI, -4.36, 0.23; P=0.08) between naproxen and ibuprofen.

Systolic blood pressure
- Celecoxib (N=146): -0.3 (-2.25, 1.74)
- Ibuprofen (N=151): 3.7 (1.72, 5.58)
- Naproxen (N=147): 1.6 (-0.40, 3.57)

Diastolic blood pressure
- Celecoxib (N=146): 0.2 (-1.04, 1.37)
- Ibuprofen (N=151): 0.8 (-0.35, 1.99)
- Naproxen (N=147): 0.7 (-0.50, 1.90)

CI: confidence interval. IQR, interquartile range. SBP, systolic blood pressure.

PRECISION-ABPM: Change in Mean 24-hour Arterial Blood Pressure from Baseline at 4 Months

![Graph showing the change in mean 24-hour arterial blood pressure from baseline at 4 months for Celecoxib, Ibuprofen, and Naproxen.](image)

Celecoxib (n = 146)
Ibuprofen (n = 151)
Naproxen (n = 147)

LS mean change in ABP (mmHg)

Difference in LS mean change in ABP (mmHg)

Celecoxib vs. Ibuprofen: P=0.039
Celecoxib vs. Naproxen: P=0.214
Naproxen vs. Ibuprofen: P=0.413

LS, least squares. ABP, arterial blood pressure.

The percentage of patients with baseline normotension who had hypertension at month 4 was significantly greater for both ibuprofen and naproxen than for celecoxib (P=0.004 and P=0.035, respectively).

Hypertension defined as mean 24-hour SBP ≥130 mm Hg and/or DBP ≥80 mm Hg

DBP, diastolic blood pressure. SBP, systolic blood pressure
In PRECISION, the risk for hospitalization with hypertension increased by 69% with ibuprofen compared with celecoxib.
During a mean follow-up of 2.49 years, there were 22 APTC events (composite of CV death, nonfatal myocardial infarction or nonfatal stroke) including:

- 7 with celecoxib,
- 9 with ibuprofen, and
- 6 with naproxen

APTC, Anti-platelet Trialist Collaboration. CV, cardiovascular.

Celecoxib was significantly non-inferior to naproxen and ibuprofen on the APTC endpoints in both populations ITT & mITT.

Nissen S et al. NEJM 2016;  
*p value is for non-inferiority
The rate of death from any cause in the on-treatment analysis was significantly lower with celecoxib than with naproxen or ibuprofen.

(Statistical significance given by the 95% CI; P values not calculated)

Patients on celecoxib were ~35% and ~32% less likely to die from any cause than patients on naproxen or ibuprofen, respectively.
PRECISION – Conclusions

PRECISION has relevance for future assessments of non-CV drugs that may have pressor effects.
1. The nested BP study showed celecoxib less hypertension-Inducing than the 2 NSAID comparators.
2. Though CV outcomes were relatively few, there were fewer with celecoxib than with the comparators.
3. The outcomes of the nested study were thoroughly consistent with results of the larger study of which the nested study was a part.
4. For future evaluations, nesting a BP study within the larger Phase 3 trial, and prespecifying BP and CV outcomes, should help to define regulatory position about approval or, at least, about need to warn in label re: BP effects.
Session 1B: Interpreting Results of the PRECISION Study

10:30 am – 11:20 am

E-mail questions to pressor@duke.edu
What should be the threshold BP change for long term medications that triggers a requirement for CV safety data?

SBP $\geq$ 2 mm Hg compared to placebo

DBP $\geq$ 1 mm Hg compared to placebo
## Withdrawn medications and BP

<table>
<thead>
<tr>
<th>Drug/Daily dose</th>
<th>Year approved</th>
<th>Year withdrawn</th>
<th>Δ SBP (mm Hg)</th>
<th>Δ DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib (Vioxx) 12.5-50 mg</td>
<td>1999</td>
<td>2004</td>
<td>compared to placebo, 25 mg/day and 50 mg/day doses significantly increased SBP &gt; 20 mm Hg and value &gt; 140 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Valdecoxib (Bextra) 10-40 mg</td>
<td>2001</td>
<td>2005</td>
<td>2.0 - 2.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Sibutramine (Meridia) &lt; 5 mg</td>
<td>1997</td>
<td>2010</td>
<td>0.8</td>
<td>-0.5</td>
</tr>
<tr>
<td>&gt; 5 mg</td>
<td></td>
<td></td>
<td>1.7 - 4.7</td>
<td>2.0 - 3.7</td>
</tr>
</tbody>
</table>
**Diabetic medications: TZDs**

<table>
<thead>
<tr>
<th>Drug/Daily dose</th>
<th>Year approved</th>
<th>Δ SBP (mm Hg)</th>
<th>Δ DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone (Actos)</td>
<td>1999</td>
<td>-5 to -2</td>
<td>-3 to 0</td>
</tr>
<tr>
<td>(meta-analysis, 2006)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone (Avandia)</td>
<td>1999</td>
<td>-5 to -2</td>
<td>-3 to 0</td>
</tr>
<tr>
<td>(meta-analysis, 2006)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Diabetic medications: DPP-4 inhibitors

<table>
<thead>
<tr>
<th>Drug/Daily dose</th>
<th>Year approved</th>
<th>Δ SBP (mm Hg)</th>
<th>Δ DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin (Nesina) 25 mg</td>
<td>2013</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Linagliptin (Tradjenta) 5 mg</td>
<td>2011</td>
<td>-0.8</td>
<td>-0.1</td>
</tr>
<tr>
<td>Saxagliptin (Onglyza) 2.5 mg</td>
<td>2009</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2.3</td>
<td>-0.4</td>
</tr>
<tr>
<td>Sitagliptin (Januvia) 100 mg</td>
<td>2006</td>
<td>-0.6</td>
<td>-0.2</td>
</tr>
</tbody>
</table>
Diabetic medications: GLP-1 receptor agonists

<table>
<thead>
<tr>
<th>Drug/Dose</th>
<th>Year approved</th>
<th>Δ SBP (mm Hg)</th>
<th>Δ DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulaglutide (Trulicity)</td>
<td>2014</td>
<td>-2.7 to -1.7</td>
<td>0.2 to 0.5</td>
</tr>
<tr>
<td>0.75-1.5 mg/week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide (Bydureon)</td>
<td>2012</td>
<td>-4.7 to -1.1</td>
<td>-2.1 to 0.7</td>
</tr>
<tr>
<td>2 mg/week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide (Byetta)</td>
<td>2011</td>
<td>-3.6 to -0.8</td>
<td>-2.6 to -0.1</td>
</tr>
<tr>
<td>5-10 µg BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide (Victoza)</td>
<td>2010</td>
<td>-7 to -5.7</td>
<td>-3.6 to 0.5</td>
</tr>
<tr>
<td>0.6-1.8 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Diabetic medications: Sodium glucose transporters

<table>
<thead>
<tr>
<th>Drug/Daily dose</th>
<th>Year approved</th>
<th>Δ SBP (mm Hg)</th>
<th>Δ DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertugliflozin (Steglatro)</td>
<td>2017</td>
<td>-4.1 to -4.0</td>
<td>-1.9 to -1.6</td>
</tr>
<tr>
<td>5-15 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin (Jardiance)</td>
<td>2014</td>
<td>-4.0 to -3.3</td>
<td>-0.9 to -1.6</td>
</tr>
<tr>
<td>10-25 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin (Farxiga)</td>
<td>2014</td>
<td>-3.2</td>
<td>-1.3</td>
</tr>
<tr>
<td>10 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin (Invokana)</td>
<td>2013</td>
<td>-5.5 to -3.8</td>
<td>-2.4 to -1.8</td>
</tr>
<tr>
<td>100-300 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Naproxen

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Dose/day</th>
<th>N</th>
<th>Duration</th>
<th>Δ SBP vs base</th>
<th>Δ SBP vs placebo</th>
<th>Δ DBP vs base</th>
<th>Δ DBP vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klassen, 1993</td>
<td>750</td>
<td>~ 35</td>
<td>4 weeks</td>
<td></td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klassen, 1995</td>
<td>750</td>
<td>50</td>
<td>4 weeks</td>
<td></td>
<td>&lt; 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwartz, 2002</td>
<td>1000</td>
<td>17</td>
<td>4 weeks</td>
<td>3.1</td>
<td>4.4</td>
<td>-0.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Sowers, 2005</td>
<td>1000</td>
<td>128</td>
<td>12 weeks</td>
<td>- 0.7</td>
<td>- 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farkouh, 2008</td>
<td>1000</td>
<td>4,730</td>
<td>52 weeks</td>
<td>2.3</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baerwald, 2010</td>
<td>1000</td>
<td>156</td>
<td>13 weeks</td>
<td>0.5</td>
<td>2</td>
<td>0.1</td>
<td>2</td>
</tr>
<tr>
<td>Schnitzer, 2010</td>
<td>1000</td>
<td>147</td>
<td>13 weeks</td>
<td>- 1</td>
<td>2</td>
<td>- 0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Townsend, 2010</td>
<td>1000</td>
<td>131</td>
<td>2 weeks</td>
<td>3.7</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruschitzka, 2017</td>
<td>750-1000</td>
<td>147</td>
<td>16 weeks</td>
<td>1.9</td>
<td></td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>
The FDA should require CV safety data for drugs that, compared to placebo, increase SBP \(>2\) mm Hg or increase DBP \(>1\) mm Hg.
# Antidepressants

<table>
<thead>
<tr>
<th>Drug/Daily dose</th>
<th>Year approved</th>
<th>Δ SBP (mm Hg)</th>
<th>Δ DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levomilnacipran (Fetzima) 40-120 mg/day</td>
<td>2013</td>
<td>3.4 to 3.9</td>
<td>3.1 to 3.2</td>
</tr>
<tr>
<td>Milnacipran (Savella) 100-200 mg/day</td>
<td>2009</td>
<td>3.1 to 3.2</td>
<td>2.2 to 2.7</td>
</tr>
<tr>
<td>Desvenlafaxine (Pristiq) 50-100 mg/day</td>
<td>2008</td>
<td>3.3 to 3.7</td>
<td>2 to 2.1</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta) 40-80 mg/day</td>
<td>2004</td>
<td>1.6 to 3.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Bupropion XL (Wellbutrin XL)</td>
<td>2003</td>
<td>no data</td>
<td>no data</td>
</tr>
<tr>
<td>Venlafaxine XR (Effexor XR) 75-225 mg/day</td>
<td>1997</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Venlafaxine IR (Effexor) 25-375 mg/day</td>
<td>1993</td>
<td>no data</td>
<td>2.5 to 7.2</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin) 150 mg/day</td>
<td>1985</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.7 to 10.9</td>
<td>0.4 to 5.4</td>
</tr>
</tbody>
</table>
## ADD/ADHD medications

<table>
<thead>
<tr>
<th>Drug/Daily dose</th>
<th>Year approved</th>
<th>Δ SBP (mm Hg)</th>
<th>Δ DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisdexamfetamine (Vyvanse)</td>
<td>2007</td>
<td>“A modest increase in average blood pressure (about 2-4 mm Hg) is noted in the Warnings section of standard stimulant labeling.”</td>
<td></td>
</tr>
<tr>
<td>10-70 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focalin XR (Dexamethysphenidate)</td>
<td>2005</td>
<td>-0.3 to 4.1</td>
<td>-0.5 to 1.8</td>
</tr>
<tr>
<td>20-40 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine (Strattera)</td>
<td>2002</td>
<td>2.8</td>
<td>1.2</td>
</tr>
<tr>
<td>40-100 mg/day (data for adults)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamine salts XR</td>
<td>2001</td>
<td>2.3 to 6.3</td>
<td>1.3 to 2</td>
</tr>
<tr>
<td>(Adderall XR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-60 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focalin (Dexamethysphenidate)</td>
<td>2001</td>
<td>1.2 to 1.8</td>
<td>1.5 to 1.8</td>
</tr>
<tr>
<td>5-20 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylphenidate (Concerta)</td>
<td>2000</td>
<td>No data regarding mean change in SBD or DBP Compared to placebo “there appeared to be increases for diastolic and systolic blood pressure.” Referring to BP: “The sponsor chose to display these data graphically.”</td>
<td></td>
</tr>
<tr>
<td>18-54 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Miscellaneous drugs

<table>
<thead>
<tr>
<th>Drug/Daily dose</th>
<th>Year approved</th>
<th>Δ SBP (mm Hg)</th>
<th>Δ DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armodafanil (Nuvigil)</td>
<td>2007</td>
<td>1 to 4</td>
<td>1 to 3</td>
</tr>
<tr>
<td>50-250 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modafanil (Provigil)</td>
<td>1998</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>100 mg (single dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudoephedrine (Sudafed)</td>
<td></td>
<td>0 to 3.2</td>
<td>-0.5 to 5.5</td>
</tr>
<tr>
<td>various doses, short term use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td></td>
<td>0 to 10</td>
<td>0 to 10</td>
</tr>
</tbody>
</table>
Session 1B: Interpreting Results of the PRECISION Study

10:30 am – 11:20 am

E-mail questions to pressor@duke.edu
Panelist and Reactant
(Session IB)

William B White, MD
Professor of Medicine
Calhoun Cardiology Center
University of Connecticut School of Medicine
Effects of NSAIDs on Ambulatory Blood Pressure in Patients with Hypertension: the Patient Population Might Matter

Table 2  Subanalysis for the change from baseline in 24-h MSABP at week 4 by age group and antihypertensive treatment subgroups (intention-to-treat population)

<table>
<thead>
<tr>
<th></th>
<th>Luminasaib 100 mg o.d.</th>
<th></th>
<th>Ibuprofen 600 mg t.i.d.</th>
<th></th>
<th>Estimated difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>LSM (SE) change from baseline</td>
<td>n</td>
<td>LSM (SE) change from baseline</td>
<td>Estimated difference (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>By age subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;64 years</td>
<td>195</td>
<td>-2.6 (0.59)</td>
<td>185</td>
<td>1.6 (0.59)</td>
<td>-4.1 (-5.7 to -2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>65–74 years</td>
<td>132</td>
<td>-2.9 (0.78)</td>
<td>133</td>
<td>2.9 (0.82)</td>
<td>-5.8 (-7.8 to -3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥75 years</td>
<td>36</td>
<td>-3.8 (1.60)</td>
<td>41</td>
<td>2.5 (1.58)</td>
<td>-6.3 (-11.1 to -1.5)</td>
<td>0.011</td>
</tr>
<tr>
<td>Antihypertensive treatment subgroups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitor monotherapy</td>
<td>39</td>
<td>-4.8 (1.34)</td>
<td>37</td>
<td>3.7 (1.38)</td>
<td>-8.2 (-12.1 to -4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARB monotherapy</td>
<td>53</td>
<td>-3.5 (1.16)</td>
<td>45</td>
<td>4.6 (1.26)</td>
<td>-8.1 (-11.5 to -4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-Blocker monotherapy</td>
<td>35</td>
<td>-3.0 (1.09)</td>
<td>22</td>
<td>2.8 (1.37)</td>
<td>-5.8 (-9.3 to -2.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diuretic monotherapy</td>
<td>12</td>
<td>-1.5 (2.30)</td>
<td>17</td>
<td>2.1 (1.93)</td>
<td>-3.6 (-9.8 to 2.6)</td>
<td>0.241</td>
</tr>
<tr>
<td>CCB monotherapy</td>
<td>17</td>
<td>-1.0 (1.44)</td>
<td>17</td>
<td>1.8 (1.44)</td>
<td>-2.8 (-6.9 to 1.40)</td>
<td>0.184</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CCB, calcium-channel blocker; CI, confidence interval; LSM, least squares mean; MSABP, mean systolic ambulatory blood pressure; o.d., once daily; SE, standard error; t.i.d., three times daily.

MacDonald TM et al. J Hypertens 2008; 26: 1695-1704
Higher Doses of Celecoxib (200 mg BID) versus Placebo on Ambulatory Blood Pressure in Patients on Lisinopril

Celecoxib versus Placebo on Ambulatory Blood Pressure in Patients on Lisinopril – Outliers

Acetaminophen Raises Ambulatory Blood Pressure

Inhibition has potential implications in determining drug safety in patients treated with NSAIDs, concomitant COX-1

Figure 2. Difference in mean 24-hour ambulatory blood pressure (Delta BP, mm Hg) between baseline and treatment with acetaminophen.
Session 1B: Interpreting Results of the PRECISION Study

10:30 am – 11:20 am

E-mail questions to pressor@duke.edu
Session 1C: Pressor Risk & Tolerance Among Diverse Development Programs

11:20 am – 12:10 pm

E-mail questions to pressor@duke.edu
PRESSOR RISK & TOLERANCE AMONG DIVERSE DEVELOPMENT PROGRAMS

George L. Bakris, MD
Professor of Medicine
Director, Am. Heart Assoc Comprehensive Hypertension Center
University of Chicago Medicine
Chicago, IL
QUESTION

• Is there a blood pressure increase of concern applicable across development programs or should each development program take its risk tolerance into consideration?
CHRONIC CONDITIONS REQUIRING CHRONIC TREATMENT WITH BP RAISING MEDICATIONS

1. chronic pain (NSAIDs, opioids)
2. psychiatric disorders (antidepressants, Ritalin, Adderall and similar drugs)
3. Chemotherapy (VEGF inhibitors) and Immunosuppressants (Cyclosporine, Tacrolimus)
4. weight loss drugs
5. Birth Control (Estrogens)
6. Chronic sinus congestion

Modifiers of BP raising effect of these classes: Some also affected by level of sodium intake
STABILITY TRIAL

- Tested Darapladib a reversible oral inhibitor of LpA₂ in a double-blind placebo controlled trial in 15,000+ patients with established coronary heart disease.

- BP variability was assessed by the standard deviation (SD) of systolic BP, the SD of diastolic BP, maximum BP, and minimum BP, from 5 measurements (baseline and months 1, 3, 6, and 12) during the first year after randomization.

- **Primary outcome was MACE after the first year of treatment**

Baseline characteristics of STABILITY trial by tertiles of SD of systolic BP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total population</th>
<th>1st tertile (&lt;7.16 mmHg)</th>
<th>2nd tertile (7.16–10.95 mmHg)</th>
<th>3rd tertile (≥10.95 mmHg)</th>
<th>P-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 13 794</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.0 (59.0–71.0)</td>
<td>63.0 (57.0–70.0)</td>
<td>64.0 (59.0–70.0)</td>
<td>66.0 (60.0–72.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>2540 (18.4%)</td>
<td>685 (15.0%)</td>
<td>790 (17.4%)</td>
<td>1065 (22.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index-kg/m²</td>
<td>28.3 (25.5–31.7)</td>
<td>28.2 (25.5–31.6)</td>
<td>28.4 (25.7–31.8)</td>
<td>28.3 (25.5–31.6)</td>
<td>0.98</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5317 (38.5%)</td>
<td>1664 (36.5%)</td>
<td>1720 (37.8%)</td>
<td>1933 (41.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10 806 (78.3%)</td>
<td>3596 (79.0%)</td>
<td>3575 (78.6%)</td>
<td>3635 (77.5%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Black</td>
<td>300 (2.2%)</td>
<td>101 (2.2%)</td>
<td>86 (1.9%)</td>
<td>113 (2.4%)</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific</td>
<td>2393 (17.3%)</td>
<td>774 (17.0%)</td>
<td>778 (17.1%)</td>
<td>841 (17.9%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>295 (2.1%)</td>
<td>82 (1.8%)</td>
<td>110 (2.4%)</td>
<td>103 (2.2%)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>2472 (17.9%)</td>
<td>932 (20.5%)</td>
<td>788 (17.3%)</td>
<td>752 (16.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Former</td>
<td>7028 (50.9%)</td>
<td>2273 (49.9%)</td>
<td>2382 (52.4%)</td>
<td>2373 (50.6%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>4293 (31.1%)</td>
<td>1348 (29.6%)</td>
<td>1378 (30.3%)</td>
<td>1567 (33.4%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 716 (77.7%)</td>
<td>3272 (71.9%)</td>
<td>3531 (77.6%)</td>
<td>3913 (83.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average systolic BP (mmHg)</td>
<td>130.6 (121.8–140.0)</td>
<td>128.2 (119.2–137.0)</td>
<td>129.6 (121.4–139.2)</td>
<td>134.2 (125.0–143.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average diastolic BP (mmHg)</td>
<td>78.4 (72.8–83.8)</td>
<td>78.0 (72.6–83.0)</td>
<td>78.4 (72.8–83.6)</td>
<td>79.0 (73.2–84.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Adjusted cumulative incidence for the primary composite outcome MACE, by tertile of SD of SYSTOLIC BP

Adjusted cumulative incidence for the primary composite outcome MACE, by tertile of SD of DIASTOLIC BP

### Panel B

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>Hazard Ratio</th>
<th>95% Wald Confidence Limits</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st tertile (&lt;4.67 mmHg: reference)</td>
<td>1.07</td>
<td>0.83 - 1.36</td>
<td>0.96</td>
</tr>
<tr>
<td>2nd tertile (4.67-7.00 mmHg)</td>
<td>1.35</td>
<td>1.07 - 1.70</td>
<td></td>
</tr>
<tr>
<td>3rd tertile (&gt;=7.00 mmHg)</td>
<td>1.41</td>
<td>1.14 - 1.75</td>
<td></td>
</tr>
<tr>
<td><strong>Non Diabetic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st tertile (&lt;4.67 mmHg: reference)</td>
<td>1.07</td>
<td>0.85 - 1.35</td>
<td>0.19</td>
</tr>
<tr>
<td>2nd tertile (4.67-7.00 mmHg)</td>
<td>1.29</td>
<td>1.08 - 1.53</td>
<td></td>
</tr>
<tr>
<td>3rd tertile (&gt;=7.00 mmHg)</td>
<td>1.41</td>
<td>1.14 - 1.75</td>
<td></td>
</tr>
<tr>
<td><strong>History of Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st tertile (&lt;4.67 mmHg: reference)</td>
<td>1.23</td>
<td>0.82 - 1.84</td>
<td>0.19</td>
</tr>
<tr>
<td>2nd tertile (4.67-7.00 mmHg)</td>
<td>1.89</td>
<td>1.29 - 2.76</td>
<td></td>
</tr>
<tr>
<td>3rd tertile (&gt;=7.00 mmHg)</td>
<td>1.89</td>
<td>1.29 - 2.76</td>
<td></td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st tertile (&lt;4.67 mmHg: reference)</td>
<td>1.32</td>
<td>0.83 - 2.10</td>
<td>0.35</td>
</tr>
<tr>
<td>2nd tertile (4.67-7.00 mmHg)</td>
<td>1.84</td>
<td>1.21 - 2.81</td>
<td></td>
</tr>
<tr>
<td>3rd tertile (&gt;=7.00 mmHg)</td>
<td>1.84</td>
<td>1.21 - 2.81</td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st tertile (&lt;4.67 mmHg: reference)</td>
<td>1.04</td>
<td>0.86 - 1.24</td>
<td>0.14</td>
</tr>
<tr>
<td>2nd tertile (4.67-7.00 mmHg)</td>
<td>1.32</td>
<td>1.11 - 1.56</td>
<td></td>
</tr>
<tr>
<td>3rd tertile (&gt;=7.00 mmHg)</td>
<td>1.32</td>
<td>1.11 - 1.56</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline systolic BP &lt; 120 mmHg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st tertile (&lt;4.67 mmHg: reference)</td>
<td>1.00</td>
<td>0.68 - 1.47</td>
<td>0.14</td>
</tr>
<tr>
<td>2nd tertile (4.67-7.00 mmHg)</td>
<td>1.67</td>
<td>1.19 - 2.36</td>
<td></td>
</tr>
<tr>
<td>3rd tertile (&gt;=7.00 mmHg)</td>
<td>1.67</td>
<td>1.19 - 2.36</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline systolic BP between 120-140</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st tertile (&lt;4.67 mmHg: reference)</td>
<td>1.24</td>
<td>0.98 - 1.57</td>
<td>0.14</td>
</tr>
<tr>
<td>2nd tertile (4.67-7.00 mmHg)</td>
<td>1.43</td>
<td>1.13 - 1.80</td>
<td></td>
</tr>
<tr>
<td>3rd tertile (&gt;=7.00 mmHg)</td>
<td>1.43</td>
<td>1.13 - 1.80</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline systolic BP &gt; 140 mmHg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st tertile (&lt;4.67 mmHg: reference)</td>
<td>0.84</td>
<td>0.61 - 1.15</td>
<td>0.14</td>
</tr>
<tr>
<td>2nd tertile (4.67-7.00 mmHg)</td>
<td>1.12</td>
<td>0.85 - 1.48</td>
<td></td>
</tr>
<tr>
<td>3rd tertile (&gt;=7.00 mmHg)</td>
<td>1.12</td>
<td>0.85 - 1.48</td>
<td></td>
</tr>
</tbody>
</table>
IS THERE A BLOOD PRESSURE INCREASE OF CONCERN APPLICABLE ACROSS DEVELOPMENT PROGRAMS OR SHOULD EACH DEVELOPMENT PROGRAM TAKE ITS RISK TOLERANCE INTO CONSIDERATION?

• I would propose for discussion that "Each Development Program should assess risk tolerance". In the data I showed the clinical benefit was weighed against the BP-related risk.

• The risk in the study shown and others regarding weight loss drugs i.e. sibutramine and other classes is not idiosyncratic, in contrast to QTc increases. Thus, the risk is highly dependent on multiple factors, including the CV risk of the cohort involved, BP of the group, and duration of treatment.
Session 1C: Pressor Risk & Tolerance Among Diverse Development Programs

11:20 am – 12:10 pm

E-mail questions to pressor@duke.edu
Session 1D: Placebo Control Groups in ABPM Studies

1:00 pm – 1:50 pm

E-mail questions to pressor@duke.edu
Placebo control in ABPM studies

Tzu-Yun McDowell
Division of Cardiovascular and Renal Products
OND/CDER
Disclaimer

• This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
A. Control Group

In general, it is desirable to include a placebo group as the control group. ABPM measurements, as noted, are not influenced by observer bias and provide precision. Nevertheless, there can be changes in blood pressure with time that could obscure drug effects, making inclusion of a placebo group desirable.

FDA encourages sponsors to seek further discussion on this issue, including the arguments for and against using a placebo group as the control in ABPM studies.
ABPM Research Database

• Two FDA ABPM databases were combined to assess the impact of placebo
  – ABPM study database for antihypertensives: 16 studies, which were initiated between 1986 and 1994 with > 20 subjects per arm.
  – Recent ABPM study database: 6 studies, which were initiated between 2008 and 2017

• Of the 22 studies, 11 studies included a placebo arm for a total of 456 subjects.
Are there changes in BP with time that could obscure drug effects, making inclusion of a placebo group desirable?

• Objective:
  – Evaluate the consistency of the change from baseline in placebo arms between studies

• Methods:
  – 11 studies with the placebo arm (N = 456) from the ABPM research database
    • With baseline data and at least one post-baseline time point
    • Each study included between 1 and 3 post-baseline visits
    • Median study duration: ~6 weeks
  – Mean change from baseline for systolic and diastolic blood pressure
    • 24 hour
    • daytime\(^1\) (9am-9pm)
    • nighttime\(^1\) (1am-6am)

\(^1\) O’Brien et al. J Hypertens 2013
Diurnal BP pattern is consistent over time for baseline and placebo visit for normotensive and hypertensive subjects.

Hourly average BP overtime by study and visit.

Systolic BP

Diastolic BP
No difference in average systolic BP between baseline and placebo visit for hypertensive and normotensive subjects

Similar findings for Diastolic BP
No difference between baseline and placebo-visits

Change from baseline for 24-hour Systolic BP

The overall estimate is calculated based on the first post-baseline visit from each study.
No difference between baseline and placebo-visits

Change from baseline for 24-hour Diastolic BP

Similar findings for daytime and nighttime Diastolic BP

The overall estimate is calculated based on the first post-baseline visit from each study.
Results are in general consistent among subgroups of interest

Change from baseline for 24-hour Systolic BP

<table>
<thead>
<tr>
<th></th>
<th>Mean ± 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>≥ 65 years (n = 73)</td>
<td>-0.8 (-3.0, 1.5)</td>
</tr>
<tr>
<td>&lt; 65 years (n = 343)</td>
<td>0.1 (-0.7, 1.0)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White (n = 331)</td>
<td>-0.3 (-1.2, 0.5)</td>
</tr>
<tr>
<td>Black (n = 61)</td>
<td>2.1 (-0.1, 4.3)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female (n=219)</td>
<td>0.1 (-1.0, 1.2)</td>
</tr>
<tr>
<td>Male (n = 197)</td>
<td>-0.2 (-1.3, 1.0)</td>
</tr>
</tbody>
</table>

This analysis was based on the pooled ABPM data

Similar findings for Diastolic BP
Inclusion of the placebo arm results in a larger study to exclude an increase in blood pressure.
Points to consider

• Lack of placebo effect on ABPM was reported in literature\(^2, 3, 4\)
• Nature of study design supports that placebo effect is less likely
  – Minimal interactions between the patient, clinician and treatment environment
  – Minimize potential observer bias, white-coat syndrome or other study-related factors
• Early study\(^4\) showed that placebo effect may present in the earliest part of ABPM
  – Some avoid the effect by excluding the first few hours of ABPM data
  – This approach is not clearly described or adopted in many studies
  – But it should have minimal impact on 24-hour or daytime average
• Are there different concerns regarding placebo effect for an efficacy ABPM study vs. safety ABPM study?

Scenarios where a placebo group is helpful

• Targeting “high risk” patient population (e.g. SBP ≥160 mmHg)
  – Control regression to the mean phenomenon
  – Study design consideration – avoid using baseline ABPM data to assess inclusion criteria. A separate screening visit with cuff measurements of ABPM is recommended.

  ![Diagram showing regression to the mean](image)

  If we select subjects based on extreme blood pressures (high or low), in subsequent measurement they will have blood pressure closer to the mean

• Assess a long-term effect – control potential seasonal changes in blood pressure
Summary

• The diurnal pattern appears to be consistent over time and there was no difference in the 24-h, daytime, and nighttime average systolic and diastolic BP between placebo visits and corresponding baseline.
Acknowledgements

• Lars Johannesen
• Norman Stockbridge
• Dalong Huang
• Fortunato Senatore
• Naomi Lowy
• Mona Fiuzat

• Christine Garnett
• Jose Vicente
• Preston Dunnmon
• Ellis Unger
• Meg Pease-Fye
Session 1D: Placebo Control Groups in ABPM Studies

1:00 pm – 1:50 pm

E-mail questions to pressor@duke.edu
Session 1D: Placebo Control Groups in ABPM Studies

1:00 pm – 1:50 pm

E-mail questions to pressor@duke.edu
Part II: ABPM Study Design, Efficiency, and Appropriateness

Sessions 2, & 3
9:30 am – 1:50 pm
Session 2: Design of Efficient Ambulatory Blood Pressure Monitoring Studies

1:50 pm – 2:40 pm

E-mail questions to pressor@duke.edu
Design of Efficient Ambulatory Blood Pressure Monitoring Studies

Lars Johannesen
Division of Cardiovascular and Renal Products
OND/CDER
Disclaimer

• This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Overview

• Summary of key protocol features of contemporary studies in ABPM research database:
  – Primary endpoint
  – Inclusion of placebo
  – Number of BP readings per hour
  – Definition for valid ABPM session

• Evaluation of impact of key protocol features on
  – Study size to exclude 4 mmHg increase when true effect is 0 mmHg
  – False negative rate: number of studies that fail to detect a 4 mmHg increase when the true effect is 4 mmHg

• Design considerations of an efficient ABPM study
ABPM Research Database

• The ABPM research database includes 22 studies initiated between 1986 and 2017 and has > 20 subjects per arm.

• Of the 22 studies, 11 studies included a placebo arm for a total of 456 subjects. The median study duration was 6 weeks.

• Each study included 1 to 3 post-baseline visits and a median number of 3 (night) and 4 (day) BP measurements per hour.
## Examples of contemporary studies in ABPM Research database

<table>
<thead>
<tr>
<th></th>
<th>PRECISION-ABPM&lt;sup&gt;1&lt;/sup&gt;</th>
<th>SYNERGY&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>24-h mean systolic BP</td>
<td>24-h mean systolic BP</td>
</tr>
<tr>
<td>Placebo</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Planned subjects per arm</td>
<td>180</td>
<td>76 (monotherapy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>152 (combination)</td>
</tr>
<tr>
<td>Powered to exclude</td>
<td>3 mmHg</td>
<td>3 mmHg</td>
</tr>
<tr>
<td>Planned number of BP</td>
<td>6a to 10p: 3 per h</td>
<td>8a to 10p: 4 per h</td>
</tr>
<tr>
<td>readings per hour</td>
<td>10p to 6a: 2 per h</td>
<td>10p to 8a: 2 per h</td>
</tr>
<tr>
<td>Validity criteria</td>
<td>Not described in publication</td>
<td>70% of measurements being obtained every 30 min or more</td>
</tr>
</tbody>
</table>

<sup>1</sup> Ruschitzka et al. Eur Heart J 2017  
<sup>2</sup> Weber et al. Blood Press Monit 2018
Pattern of drug effect: constant shift vs. time-varying

• Most studies in ABPM research database show a constant-shift within day or 24-h.
Simulation study

• Placebo subjects in the ABPM research database were resampled to generate new ABPM studies to evaluate the impact of key protocol features.

• From the simulated studies, the study size required to exclude a 4 mmHg increase (power) and number of studies that fail to detect a 4 mmHg increase (false negative rate) was calculated.
  – Drug effect was added as a constant increase in the 24-h average BP of 4 mmHg.

• Simulations were conducted for systolic and diastolic BP and MAP. Only systolic BP is included in the presentation as similar findings were observed for diastolic BP and MAP.
ABPM study metrics evaluated in the simulation study

• The simulation study includes average BP calculated within three time-windows:
  • 24–h
  • Day¹: 9a to 9p
  • Night¹: 1a to 6a

¹: O'Brien et al. J Hypertens 2013
Inclusion of the placebo arm results in a larger study to exclude an increase in blood pressure

<table>
<thead>
<tr>
<th>Time window</th>
<th>SD (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h</td>
<td>8.5</td>
</tr>
<tr>
<td>Day</td>
<td>9.4</td>
</tr>
<tr>
<td>Night</td>
<td>11.6</td>
</tr>
</tbody>
</table>
The European Society of Hypertension describes 5 criteria to determine if an ABPM session needs to be repeated.

- The criteria are centered around ensuring a specific number of overall valid measurements and not the timing of missing data.

- Additionally, the criteria are not based on firm data.

European Society of Hypertension Criteria

1. 70% of expected measurements during 24-h
2. 20 valid day time measurements (9a to 9p)
3. 7 valid night measurements (1a to 6a)
4. Measurements every 30 min
5. (research purposes): at least 2 valid daytime and 1 valid nighttime measurement per hour

References:
Missing hourly ABPM data is isolated and tends to be more frequent at night.

Each row represents a Subject ordered by number of missing hours.

Black color indicates no valid ABPM measurements for that hour.

Same order across visits.
Validity Criteria is too conservative: impact on accuracy and precision of BP estimate

Accuracy of estimated treatment effect

Precision of estimated treatment effect

*Based on 100 subjects for 24-h average BP
Validity Criteria is too conservative: impact on power and percent of inconclusive studies

*Based on 100 subjects for 24-h average BP
Number of measurements within each hour impacts sample size minimally

Subjects required to maintain 80% power to exclude 4 mmHg

*Based on subjects with ≥ 3 measurements at baseline/post baseline
## Design Considerations for Efficient ABPM Study

<table>
<thead>
<tr>
<th></th>
<th>Suggestion</th>
<th>Additional considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>24-h average BP</td>
<td>If time-varying drug effect, consider other time-windows</td>
</tr>
<tr>
<td><strong>Placebo control</strong></td>
<td>No</td>
<td>• Long duration of study&lt;br&gt;• High BP used as inclusion criteria</td>
</tr>
<tr>
<td><strong>BP threshold to exclude</strong></td>
<td>Depends on therapeutic area and target patient population</td>
<td></td>
</tr>
<tr>
<td><strong>Number of BP readings per hour</strong></td>
<td>At least 2 measurements per hour</td>
<td></td>
</tr>
<tr>
<td><strong>Validity criteria</strong></td>
<td>50% of expected measurements within individual</td>
<td>If time-varying drug effect, consider strategies to minimize missing data around peak effect</td>
</tr>
</tbody>
</table>
Acknowledgements

- Tzu-Yun McDowell
- Norman Stockbridge
- Dalong Huang
- Fortunato Senatore
- Naomi Lowy
- Mona Fiuzat
- Christine Garnett
- Jose Vicente
- Preston Dunnmon
- Ellis Unger
- Meg Pease-Fye
Session 2: Design of Efficient Ambulatory Blood Pressure Monitoring Studies

1:50 pm – 2:40 pm

E-mail questions to pressor@duke.edu
ASSESSMENT OF PRESSOR EFFECTS OF DRUGS
GUIDANCE FOR INDUSTRY

COMMENTS

Charles T Benson, M.D., Ph.D.
Eli Lilly & Co
February 4, 2018
• What is the evidence we are currently missing drugs with Pressor effects? What is the evidence that dog CV safety misses bp? Or other animal studies? Ibuprofen is a very old example.

• Thorough BP study? All drugs for chronic use? Specific, well characterized antibodies? No non clinical signal? Low risk population(s)?

• Do we have triplicate phase 1 concentration response data that demonstrates that we cannot detect a signal?

• Law of unintended consequences. TBP (thorough BP) in early phase with knock on effects. Same as TQT. Do you have to move up DDI or special population studies? Perfect storm of interactions? Since chronic, impact of DDI and special populations?

• Risk of false positives in small studies and all studies (even large ones with small pretest probability). TQT all over again. More false positive than true positives. Must take prior information and probability into consideration. This has been demonstrated with simple statistics on PPV and NPV.
COMMENTS

• “ABPM in early, small studies, “. When? Phase 1 or phase 2? Remember cost is multiplied due to most drugs not working. Very glad positive control is not mentioned.

• 2-3mmHg is stated multiple times. “Few mm” … exclude 4 mm with 60-220 subjects sample size … with 20% false positive rate… this is not small

• “Is there a specific, identified increase applied across development programs that is cause for concern, or should each development program have its own threshold as it takes risk tolerance into consideration?”
  • Yes. Both. Should be an absolute cutoff to r/o risk. This should be based on a lack of a non clinical signal, mechanism of action, concentration response with triplicate measurement… The second cutoff can be negotiated based on non clinical, mechanism of action, indication, unmet medical need ,
  • The first cutoff should be, in most cases, accomplished by cuff BP in office. In the rare case where the population is high risk, the drug is high prior probability, the benefits are minimal compared to the potential for a BP risk…

• “The study should be carried out in a patient population with characteristics similar to the intended target patient population (i.e., similar demographic and disease-specific characteristics).”
  • Why ? We do we think there is an interaction between patients and healthy volunteers such that we would miss a signal?
• Although BP is important, many safety signals are also important.

• Exploration of signals generated by non-clinical data, mechanism of action, and early phase has been a reasonably successful approach to safety in drug development.

• Applying a Thorough BP may have unintended consequences similar to the TQT study, with unknown study characteristics that may include poor positive predictive values in the case of a low prior probability...
Session 2: Design of Efficient Ambulatory Blood Pressure Monitoring Studies

1:50 pm – 2:40 pm

E-mail questions to pressor@duke.edu
Break

2:40 pm – 2:50 pm
Session 3: Methodological Options & Outstanding Issues in Pressor Study Design for Reliable Evidence Development

2:50 pm – 3:40 pm

E-mail questions to pressor@duke.edu
Is Ambulatory Blood Pressure Monitoring the Right Blood Pressure Metric for Assessing Risk?

Daichi Shimbo, MD
The Hypertension Center
Columbia University Medical Center
Disclosure

- No financial conflicts of interest
- Vice Chair of the American Heart Association Scientific Statement on Measurement of Blood Pressure in Humans
- Chair of the American Heart Association / American Medical Association / Center for Disease Control and Prevention Policy Statement on Self-Measured Blood Pressure
- Voting Member of the Association for the Advancement of Medical Instrumentation
Limitations of Office BP Measurement

- **Office BP:** Auscultatory and oscillometric methods
- **Reliance on a well trained person using standardized procedures**
- **Quality control issues**
  - Letting air out of cuff too rapidly (auscultatory)
  - Digit bias (rounding to nearest 5 or 10 mmHg) (auscultatory)
  - Failure to allow 5 minutes rest
  - Patient position and arm position
  - Expectation bias
Limitations of Office BP Measurement

- Limited reliability due to the small number of readings
- Use an average of 2+ readings obtained on 2+ visits to estimate an individual’s level of BP (2017 ACC/AHA High BP guideline)
- More confidence is gained by increasing the number of visits with readings than by increasing the number of readings within a visit

Whelton et al. Hypertension. 2017
Kronish et al. Am J Hypertens. 2018
Issue Related to Ecological Validity

• Does it matter what someone’s BP is in the clinic setting?

• Are we using clinic BP, even when measured well, as an estimate of the person’s BP during everyday life?
  – “True” BP
Out-of-clinic BP Monitoring

Two types:
- Ambulatory Blood Pressure Monitoring (ABPM)
- Home Blood Pressure Monitoring (HBPM)

- Measure of “True” or “Ecological” BP
- Less reliant on training of clinical personnel
- Many more readings than in the office setting
Clinic BP: 126/88 mmHg; Awake BP: 133/90 mmHg and 24-hour BP: 129/87 mmHg

24-Hour ABPM Measures “True” BP

Office BP Followed by 24-hour ABPM

Mean daytime (awake) BP
Mean 24-hour BP
Mean nighttime (sleep) BP

## Ambulatory Systolic BP and Cardiovascular Disease (CVD) Outcomes: Meta-Analysis of Prospective Cohort Studies

Conen et al. J Hypertens. 2008;26:1290-1299

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N</th>
<th>24-hour BP</th>
<th>Daytime BP</th>
<th>Sleep BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR_{multivariable}</td>
<td>HR_{incremental}</td>
<td>N</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>9</td>
<td>1.27 (1.18–1.38)</td>
<td>1.21 (1.10–1.33)</td>
<td>4</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>1.33 (1.24–1.42)</td>
<td>1.33 (1.22–1.44)</td>
<td>3</td>
</tr>
<tr>
<td>CV death</td>
<td>6</td>
<td>1.45 (1.23–1.70)</td>
<td>1.19 (1.13–1.26)</td>
<td>5</td>
</tr>
<tr>
<td>Total mortality</td>
<td>6</td>
<td>1.20 (1.10–1.31)</td>
<td>1.12 (1.07–1.17)</td>
<td>5</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>3</td>
<td>1.18 (1.06–1.31)</td>
<td>1.17 (1.09–1.26)</td>
<td>3</td>
</tr>
</tbody>
</table>

Data are summarized HRs (95% CIs). HR_{incremental} denotes additional adjustment of the multivariable model for office BP. All HRs are per 10-mmHg increase in systolic BP, BP, blood pressure; CVD, cardiovascular disease. N, number of studies included in the analysis.

Before adjustment for research grade office BP

After adjustment for research grade office BP

Conen et al. J Hypertens. 2008;26:1290-1299
<table>
<thead>
<tr>
<th>Clinic Pressure</th>
<th>Ambulatory Pressure (Daytime)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 140/90 mmHg</td>
<td>White Coat Hypertension</td>
</tr>
<tr>
<td>&lt; 140/90 mmHg</td>
<td>Sustained Hypertension</td>
</tr>
<tr>
<td>&lt; 135/85 mmHg</td>
<td>Sustained Normotension</td>
</tr>
<tr>
<td>≥ 135/85 mmHg</td>
<td>Masked Hypertension</td>
</tr>
</tbody>
</table>

*Alternatively 24-hour (using 130/80 mmHg threshold)
HBPM or Self-measured BP (SMBP)
HBPM Measures “Ecological” BP

Average home BP: 116/79 mmHg
Office BP with CVD Events

### Systolic BP

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>N</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office</td>
<td>Any CV event</td>
<td>391</td>
<td>86</td>
<td>0.96 (0.83, 1.11)</td>
</tr>
<tr>
<td></td>
<td>CV mortality</td>
<td>2081</td>
<td>162</td>
<td>1.01 (0.92, 1.12)</td>
</tr>
<tr>
<td></td>
<td>CV mortality</td>
<td>1789</td>
<td>52</td>
<td>1.00 (0.85, 1.17)</td>
</tr>
<tr>
<td>Subtotal</td>
<td><em>I</em>-squared = 0.0%, <em>P</em> = 0.841</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Home**

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>N</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fagard (2005)</td>
<td>Any CV event</td>
<td>391</td>
<td>86</td>
<td>1.17 (1.02, 1.33)</td>
</tr>
<tr>
<td>Niiranen (2010)</td>
<td>Any CV event</td>
<td>2081</td>
<td>162</td>
<td>1.22 (1.09, 1.37)</td>
</tr>
<tr>
<td>Ohkubo (1998)</td>
<td>CV mortality</td>
<td>1789</td>
<td>52</td>
<td>1.23 (1.00, 1.51)</td>
</tr>
<tr>
<td>Subtotal</td>
<td><em>I</em>-squared = 0.0%, <em>P</em> = 0.848</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Diastolic BP

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>N</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office</td>
<td>Any CV event</td>
<td>391</td>
<td>86</td>
<td>0.91 (0.81, 1.03)</td>
</tr>
<tr>
<td>Niiranen (2010)</td>
<td>Any CV event</td>
<td>2081</td>
<td>162</td>
<td>1.06 (0.97, 1.16)</td>
</tr>
<tr>
<td>Ohkubo (1998)</td>
<td>CV mortality</td>
<td>1789</td>
<td>52</td>
<td>1.03 (0.90, 1.16)</td>
</tr>
<tr>
<td>Subtotal</td>
<td><em>I</em>-squared = 49.7%, <em>P</em> = 0.137</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Home**

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>N</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fagard (2005)</td>
<td>Any CV event</td>
<td>391</td>
<td>86</td>
<td>1.24 (1.11, 1.40)</td>
</tr>
<tr>
<td>Niiranen (2010)</td>
<td>Any CV event</td>
<td>2081</td>
<td>162</td>
<td>1.15 (1.05, 1.26)</td>
</tr>
<tr>
<td>Ohkubo (1998)</td>
<td>CV mortality</td>
<td>1789</td>
<td>52</td>
<td>1.07 (0.91, 1.24)</td>
</tr>
<tr>
<td>Subtotal</td>
<td><em>I</em>-squared = 20.4%, <em>P</em> = 0.285</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ABPM and HBPM

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A&lt;sup&gt;SR&lt;/sup&gt;</td>
<td>1. Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension (Table 11) and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions (1-4).</td>
</tr>
</tbody>
</table>

SR indicates systematic review.

**COR: Class of recommendation**

**LOE: Level of evidence**
Diagnosis and Management of Hypertension

Siu A. Ann Intern Med. 2015;163:778-86
Hypertension treatment trials have been largely based on office BP goals: treating office BP versus BP on ABPM?

What are the treatment goals for out-of-clinic BP?

Which is better for CVD risk prediction: ABPM or HBPM?

Sleep BP: a target that is separate from awake BP?
Clinical Pharmacology Considerations for Evaluating Pressor Effects

Raj Madabushi, PhD
Team Lead, Guidance and Policy Team
Office of Clinical Pharmacology
OTS/CDER

The views expressed in this presentation are personal opinion and do not reflect the official policy of the FDA
Clinical Pharmacology

Multidisciplinary science concerned with translation of the relationships between drugs and humans*

Pharmacology
Pharmacokinetics
Pharmacodynamics
Exposure-Response

Use
Analysis
Study Design

Pharmacology

• Common reported mechanisms for pressor effects
  – Centrally acting: sympathomimetics, antidepressants, stimulants, weight loss drugs
  – Salt or water retention: NSAIDs, oral contraceptives containing estrogens and progestins
  – Reduced NO activity and increased endothelin production: VEGF inhibitors, calcineurin inhibitors, glucocorticoids

• Consideration of the mechanism of action can help inform the choice of:
  – Study duration
  – Study population
Pharmacology

• Study duration:
  – Shorter duration studies may be possible for some mechanisms that manifest acute effects
    Eg: duloxetine\(^1\), sunitinib\(^2\)
  – Longer duration trials may be necessary for mechanisms that are slowly evolving
    Eg: ibuprofen\(^3\)

• Study population:
  – Based on the mechanism of action, a sensitive study population can be identified for evaluating the pressor effects
    Eg: Healthy volunteer studies demonstrated pressor effects for mirabegron and duloxetine

Dose/Exposure-Response

- Dose/Concentration-blood pressure relationship can be an evidence of pressor effect

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202611Orig1s000ClinPharmR.pdf
Dose/Exposure-Response

• Unlike CQT analysis, summary exposure measures at steady-state such as average concentration or area under plasma concentration time curve (AUC) may be more relevant for evaluating exposure-response.

• Characterizing exposure-blood pressure relationship can be useful to predict the pressor effects in drug interaction scenarios and inform dosing.

• Extrapolating the relationship to unstudied populations can be challenging.
Summary

• Clinical pharmacology considerations are critical for designing pressor effect studies

• Understanding the pharmacology of the pressor effect can inform the choice of the study population, duration of the study and potential mitigation strategies

• Evaluation of dose/exposure-blood pressure relationships provide valuable evidence of pressor effects and can inform use with concomitant medications
Acknowledgements

• Lars Johannesen
• Mike Pacanowski
• Kevin Krudys
• Atul Bhattaram
• Christine Garnett
• Norman Stockbridge
• Issam Zineh
Thank You!
The graphs show the changes in mean blood pressure and heart rate as measured by teletransmitted results of home monitoring in patients with metastatic renal-cell carcinoma who were treated with two cycles of sunitinib at a dose of 50 mg daily for 4 weeks (shaded area), followed by 2 weeks without treatment. The results are shown separately for systolic and diastolic blood pressure.
Session 3: Methodological Options & Outstanding Issues in Pressor Study Design for Reliable Evidence Development

2:50 pm – 3:40 pm

E-mail questions to pressor@duke.edu
Part III: Reflection & Open Audience Feedback

Session 4
3:40 pm – 4:30 pm
Session 4: Open Audience Feedback

3:40 pm – 4:30 pm

E-mail questions to pressor@duke.edu
Closing Remarks

Dr. Doug Throckmorton, Deputy Center Director for Regulatory Programs

4:30 pm