AGING, BLOOD PRESSURE & CARDIOVASCULAR DISEASE EVENT RISK

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Disclosures

• Partner: Circadian Ambulatory Diagnostics
• Consultant: Spot On Sciences (Austin, Texas)
• Consultant: National Toxicology Program, US Dept. Health & Human Services
Outline

• Accuracy of daytime office blood pressure (BP) measurement (OBPM) vs. 24-hour ambulatory BP monitoring (ABPM) to diagnose hypertension

• Accuracy of cardiovascular disease (CVD) event prediction by daytime OBPM vs. ABPM-derived awake or asleep BP means

• Trend in awake & asleep SBP & DBP with aging

• Male/female difference in BP diagnostic thresholds & relevance to CVD risk reduction of women

• Differential reduction of CVD events by treatment that targets normalization of daytime OBPM vs. asleep BP vs. awake BP
Part I: Merit of 24-hour ABPM vs. Daytime OBPM to Diagnose Hypertension & Assess CVD Risk

Significance:

• Accurate diagnosis of normal vs. elevated BP
• Accurate prognostication of future CVD events

State of art knowledge:

• ABPM more consistent and accurate than OBPM & better predictor of future CVD events
Each 20/10 mm Hg Increase in BP Doubles CV Mortality Risk

- Meta-analysis of 61 prospective, observational studies
- 1 million adults
- 12.7 million person-years

*Individuals aged 40–69 years (N = 1 million).
Continued

US Prevention Services Task Forces 2015 report:

• Confirmation of daytime OBPM-diagnosed hypertension by out-of-office measurement poor - as low as 35% & generally no better than 75%¹

• ABPM predicts long-term CVD events *independently* of OBPM: Hazard ratio = 1.28 to 1.40¹

ABC-H Investigators 2015 report:

• ABPM, especially nighttime SBP, significantly better predictor of future CVD events than daytime OBPM²

¹Piper et al., *Ann Intern Med.* 2015;162:192-204
²ABC-Investigators et al., *J. Hypertens.* 2015;32:2332-40
Merit of OBPM vs. ABPM-Derived Awake vs. Asleep BP to Predict Future CVD Events

• 2005 Dublin 8.4 yr median duration trial (5292 pts): ABPM superior to daytime OBPM as predictor of CVD & all-cause mortality, nighttime SBP strongest predictor\(^1\)

• 2008 European CVD events trial (3468 pts): ABPM-derived daytime & nighttime SBP means predicted CVD & all-cause, coronary heart disease & stroke mortality independently from daytime OBPM. When the SBPs simultaneously entered into statistical model, nighttime SBP predicted all outcomes, whereas daytime SBP did not add prognostic precision\(^2\)

\(^1\)Dolan et al., *Hypertension*. 2005;46:156-61
\(^2\)Fagard et al., *Hypertension* 2008;51:55-61
Part II: ABPM-Derived Asleep BP Parameters

Significance:

• Asleep systolic BP (SBP) mean more strongly correlated with CVD events than awake or 24-hour SBP means
• Incidence of elevated asleep SBP increases steadily after 45 yrs of age
• Studies suggest diagnostic hypertension thresholds for women should be lower than current ones

State of art knowledge:

• ABPM plus pt diary/wrist actigraphy to denote actual sleep & awake spans is the only way to assess sleep SBP & DBP means
SBP IN NORMOTENSIONIVE SUBJECTS

PATTERNS OF BLOOD PRESSURE VARIABILITY

SYSTOLIC BLOOD PRESSURE (mm Hg)

MEAN = 125 mm Hg

- NORMOTENSIVE - DIPPER
- HYPERTENSIVE - DIPPER
- HYPERTENSIVE - SUPER-DIPPER
- HYPERTENSIVE - NONDIPPER

TIME (HOURS AFTER AWAKENING)
Change in awake and asleep SBP means with age in hypertensive individuals.
Change in sleep-time relative SBP decline with age in hypertensive individuals.

Hermida et al. *Chronobiol Int.* 2013;30:176-91
Elevated Asleep BP & Non-Dipping & BP Patterning Is Common

- Aging (≥60% in elderly >age 65 yrs)
- Resistant hypertension (~80%)
- Type 2 diabetes (>75%)
- Chronic renal disease (~70%)
- Sleep disorders: insomnia, obstructive sleep apnea, etc. (??)
- Chronic pain syndromes that disturb sleep (??)
- Chronic nocturnal COPD that disturbs sleep (??)
- Chronic nocturia that disturbs sleep (??)
- Neurological conditions that disturb sleep (??)
- Metabolic syndrome (??)
- Previous CVD events (??)
MAPEC Outcomes Trial
(1626 Female/1728 Male Day-Active Pts)*

Prospective clinical trial to compare differential merit of:

• Daytime OBPM vs. ABPM-derived awake & asleep BP parameters to predict future CVD events

• Targeting control of awake vs. asleep BP by bedtime therapy (full dose of ≥1 conventional hypertension medications) vs. typical morning therapy for BP control & CVD event reduction

*Hermida et al., Chronobiol Int. 2010;27:1629-51
MAPEC Trial Methods

• At inclusion & annually, pts assessed for 48 consecutive hours by ABPM: Δt=20 min 07:00 to 23:00 & Δt=30 min overnight

• Physical activity monitored by wrist actigraphy (Δt=1 min) to accurately derive per pt awake & asleep SBP & DBP means

• ABPM integrated into primary pt care medicine & done at least annually to enable detection of relationship between BP parameters & 24-hour patterning that immediately preceded a CVD event.
MAPEC Trial Outcomes
(Blue=Major; Blue + Black=Total CVD events)

• CVD event outcomes:
  – Myocardial infarction
  – Hemorrhagic stroke
  – Ischemic stroke
  – CVD death
  – Coronary revascularization
  – Heart failure

• Additional registered events:
  – Angina pectoris
  – Transient ischemic attacks
  – Acute arterial occlusion of lower extremities
  – Thrombotic occlusion of retinal artery
  – Non-CVD death
What Is the Best Predictor of CVD Events: ABPM-Derived Asleep vs. Awake BP?

Patients of MAPEC Trial divided into 4 groups according to ABPM-derived awake & asleep SBP & DBP means at final evaluation before CVD event:

- **Normal awake** SBP/DBP means: <135/85 mmHg
- **Normal asleep** SBP/DBP means: <120/70 mmHg

*Hermida et al., *J Am Coll Cardiol.* 2011;58:1165-73*
Adjusted hazard ratio of total CVD events
Classification by awake and asleep BP means

Adjusted hazard ratio of major CVD events
Classification by awake and asleep BP means

Hermida et al., *J Am Coll Cardiol.* 2011;58:1165-73
Hermida et al., *Chronobiol Int.* 2013;30(3):355-410
Simultaneous Evaluation of OBPM & Awake & Asleep BP for Best Predictor of Future CVD Events

MAPEC Trial Pts of the same 4 groups categorized according to awake & asleep BP now additionally classified by normal vs. elevated daytime OBPM

- **Normal daytime OBPM:** <140/90 mmHg
- **Elevated daytime OBPM:** ≥140/90 mmHg
Adjusted HR of total CVD events in the MAPEC Study. Classification by clinic, awake, and asleep BP means.
# Diagnostic ABPM Thresholds (mmHg)

<table>
<thead>
<tr>
<th>ABPM-Derived</th>
<th>Men ≥18 yrs</th>
<th>Women ≥18 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>135</td>
<td>125</td>
</tr>
<tr>
<td>DBP</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>Asleep mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>120</td>
<td>110</td>
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<tr>
<td>DBP</td>
<td>70</td>
<td>65</td>
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</table>
Part III: Bedtime Hypertension Therapy to Optimize BP Control & Reduce CVD Risk

Significance:

• Asleep SBP mean more strongly correlated with CVD event risk than awake SBP or daytime OBPM values

State of art knowledge:

• Conventional long-acting BP-lowering medications when ingested at bedtime vs. morning are more effective in normalizing entire BP 24-hour pattern

• Conventional hypertension therapy ingested at bedtime substantially reduces CVD event risk
## Ingestion-Time Differences in Effect of 6 Classes of Hypertension Therapies on Asleep BP

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
<th>Dose (mg)</th>
<th>No. Pts</th>
<th>Reduction: asleep SBP/DBP mean</th>
<th>Sleep-time relative SBP/DBP decline</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Awakening $R_x$</td>
<td>Bedtime $R_x$</td>
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<tr>
<td>ACEIs</td>
<td>Ramipril</td>
<td>5</td>
<td>115</td>
<td>-4.5/-4.1</td>
<td>-13.5/-11.5*</td>
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<td></td>
<td></td>
<td>3.4/4.9*</td>
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<tr>
<td></td>
<td>Spirapril</td>
<td>6</td>
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<td>-5.7/-4.6</td>
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<td>-2.5/-2.7</td>
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<td></td>
<td>4.1/4.5*</td>
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<tr>
<td>ARBs</td>
<td>Valsartan</td>
<td>160</td>
<td>200</td>
<td>-12.9/-8.1</td>
<td>-21.1/-13.9*</td>
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<td>0.4/0.9</td>
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<td></td>
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<td>-1.6/-1.0</td>
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<td></td>
<td></td>
<td>3.1/3.9*</td>
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<tr>
<td>CCB</td>
<td>Nifedipine GITS</td>
<td>30</td>
<td>238</td>
<td>-7.5/-5.1</td>
<td>-12.8/-7.8*</td>
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<td>-0.7/-0.2</td>
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<td></td>
<td></td>
<td>1.0/1.5‡</td>
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<tr>
<td>α-Blocker</td>
<td>Doxazosin GITS</td>
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<td>0.7/-1.3</td>
<td>-8.2/-6.5†</td>
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<td>-2.3/-2.4</td>
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<td>1.9/1.9‡</td>
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<tr>
<td>β-Blocker</td>
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<td>173</td>
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<td>1.2/-1.4‡</td>
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<tr>
<td>Diuretic</td>
<td>Torasemide</td>
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<td>1.3/-0.2</td>
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</table>
Age, diabetes and sex-adjusted hazard ratio as a function of treatment-time (medication at bedtime compared to all medication upon awakening) in hypertensive subjects (MAPEC study)

- Primary endpoints
  - Total events
  - Major events*
- Secondary endpoints
  - Total death
  - Cardiovascular death
  - Cerebrovascular events
  - Cardiovascular events
    - Myocardial infarction
    - Angina pectoris
    - Heart failure
    - Occlusion retinal artery

* Includes cardiovascular death, myocardial infarction, and stroke.
Conclusions

• Hypertension in adults should be established by 24-hour ABPM

• ABPM-derived asleep SBP mean -- not awake SBP mean or daytime OBPM -- most significant & independent predictor of future CVD events

• Elevated asleep BP & nocturnal non-dipping BP patterning increase steadily after age >45 yrs

• Diagnostic thresholds that differentiate elevated from normal BP appear to be lower for women than men

• Targeting asleep SBP by bedtime vs. upon wakening ingestion of conventional BP medications reduces CVD events substantially
Gaps in Knowledge

• It is unknown if chronic co-morbidities that disrupt sleep elevate asleep (& awake) BP & future CVD event risk
• It is unknown how sleep length affects asleep BP and future CVD event risk
• It is unknown to what extent increase of CVD events with age in women is due to misdiagnosis throughout life of elevated BP because of reliance on population & male-based SBP & DBP thresholds
• It is unknown if a bedtime treatment strategy entailing conventional medications is appropriate for all forms of hypertension
Research Questions

• Does asleep SBP best predict future CVD events across all races & women & men?

• Is incidence of elevated asleep BP & CVD risk greater in short vs. long sleepers & does it vary by race, age, & sex?

• Do chronic medical conditions that disrupt sleep result in elevated asleep SBP & higher CVD event risk?

• Do all obstructive sleep apnea & other sleep-disordered pts have elevated asleep BP & CVD risk?

• Do awake & asleep hypertension states entail different mechanisms, CVD event risk & is bedtime *(chrono)*therapy with conventional BP-lowering medications best for all types of hypertension?
Acknowledgements

Most materials of this presentation were derived from the MAPEC outcomes trial (Ambulatory Blood Pressure Monitoring to Predict Cardiovascular Events); appreciation is extended to the primary investigators, particularly Drs. Ramon Hermida & Diana Ayala, & the many dedicated participating doctors, nursing & patients.