AGING, BLOOD PRESSURE & CARDIOVASCULAR DISEASE EVENT RISK

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Disclosures

- **Partner: Circadian Ambulatory Diagnostics**
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- **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:

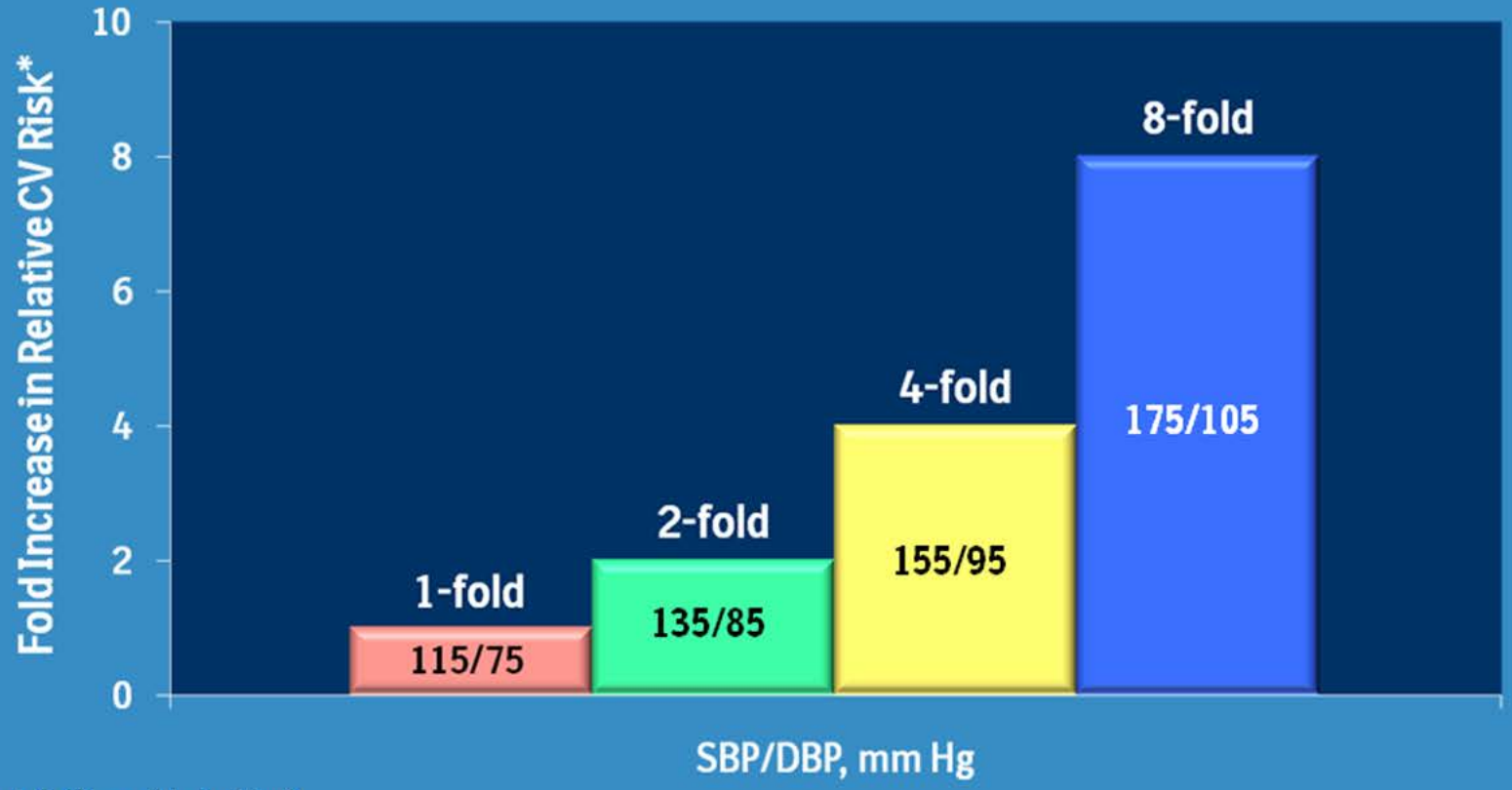
- **Accurate diagnosis of normal *vs.* elevated BP**
- **Accurate prognostication of future CVD events**

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).

Lewington S, et al. *Lancet*. 2002;360:1903-1913.

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 1.40[1]**

ABC-H Investigators 2015 report:

- **ABPM, especially nighttime SBP, significantly better predictor of future CVD events than daytime OBPM[2]**

[1]Piper et al., *Ann Intern Med*. 2015;162:192-204

[2]ABC-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

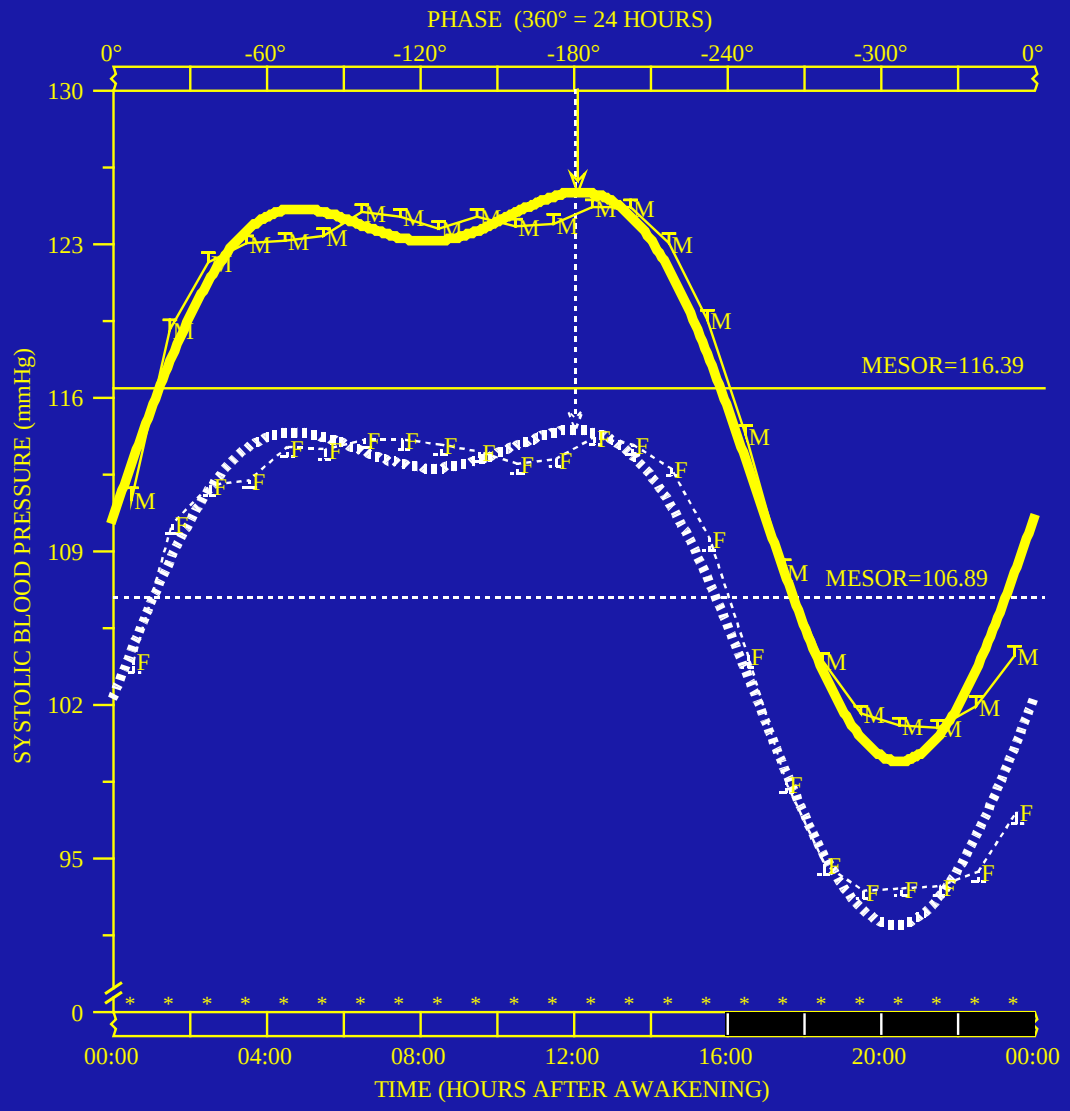
Significance:

- **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 NORMOTENSIVE SUBJECTS

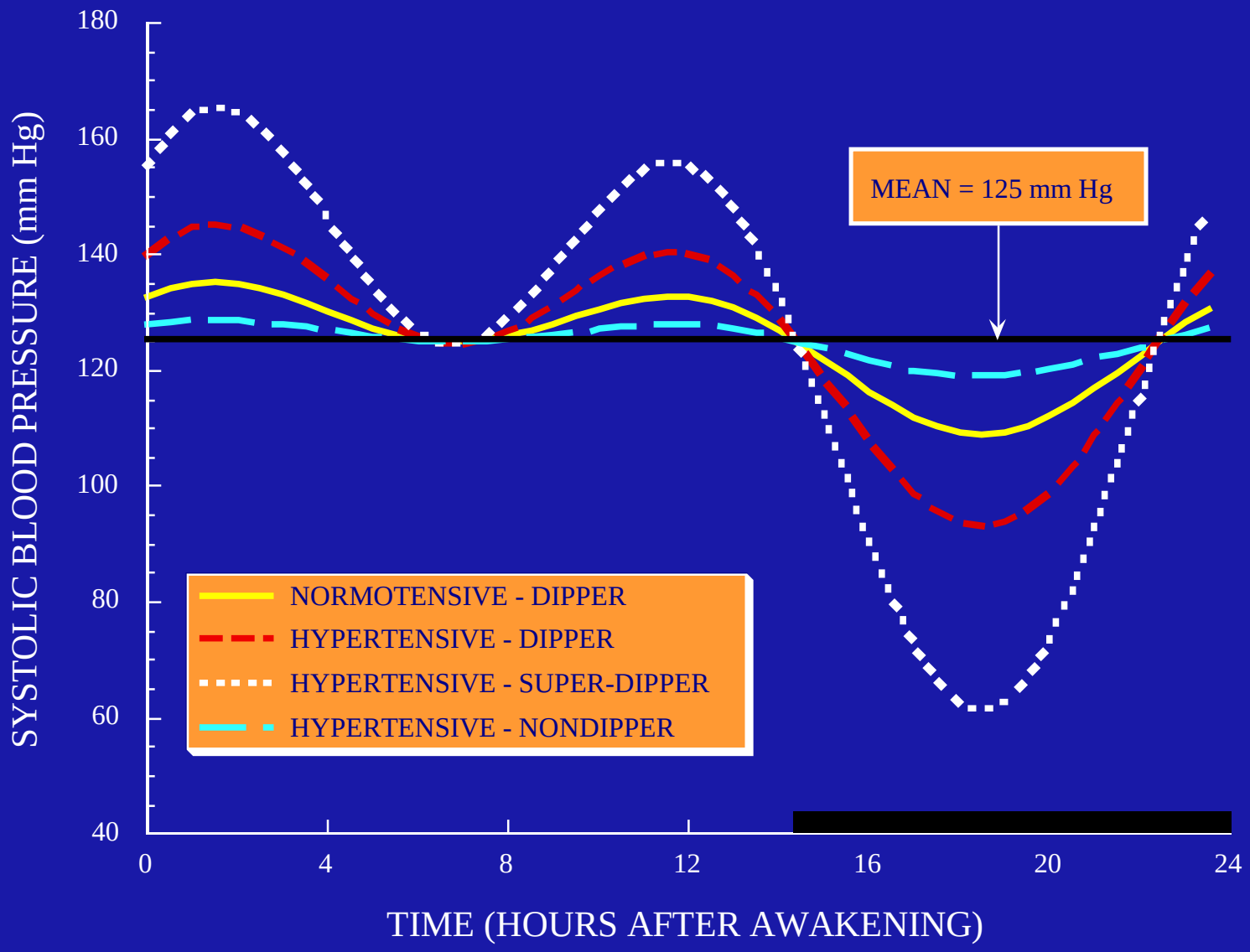


M ——— M MALES

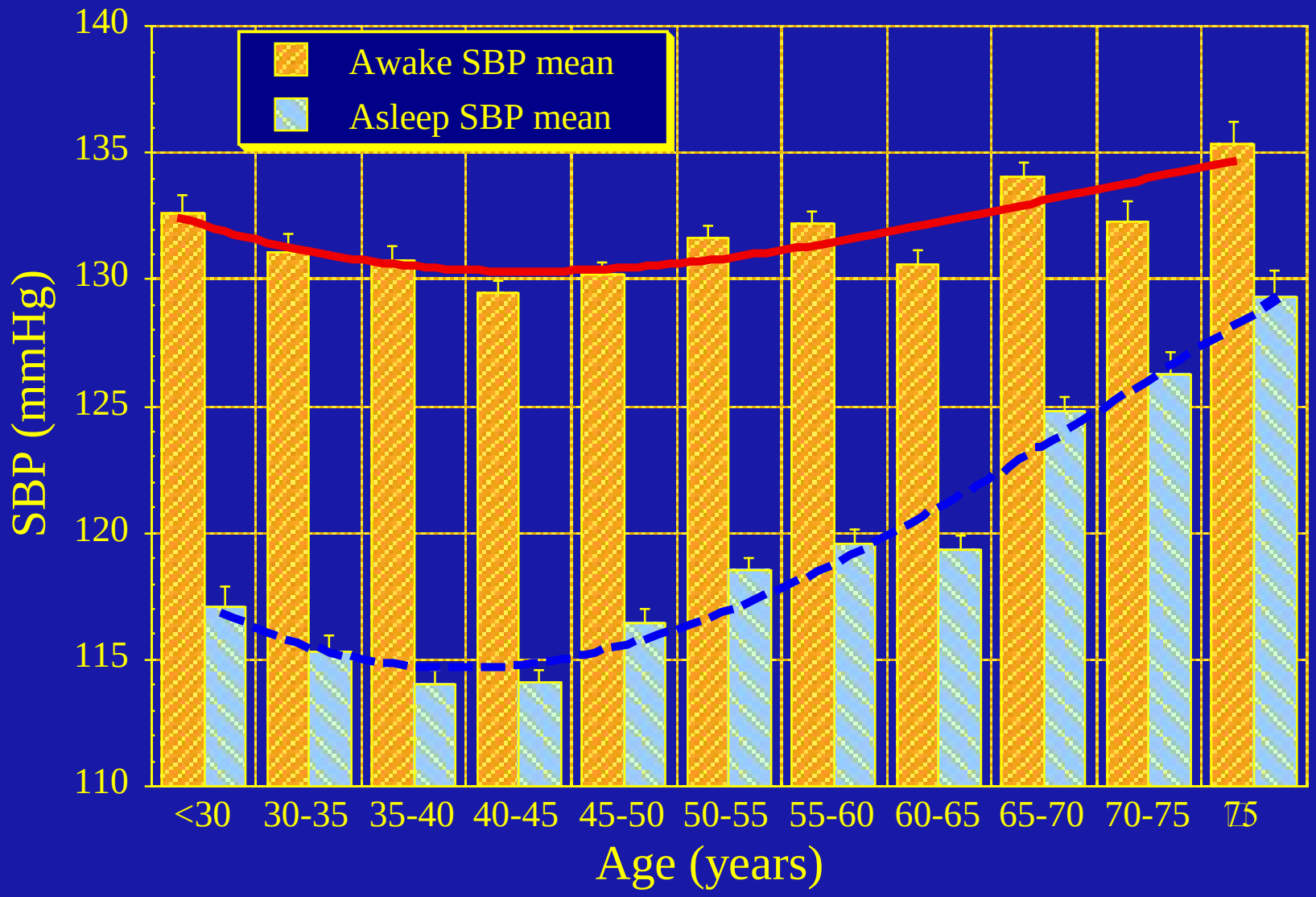
F ---------- F FEMALES

* p<0.05 AMONG GROUPS

PATTERNS OF BLOOD PRESSURE VARIABILITY

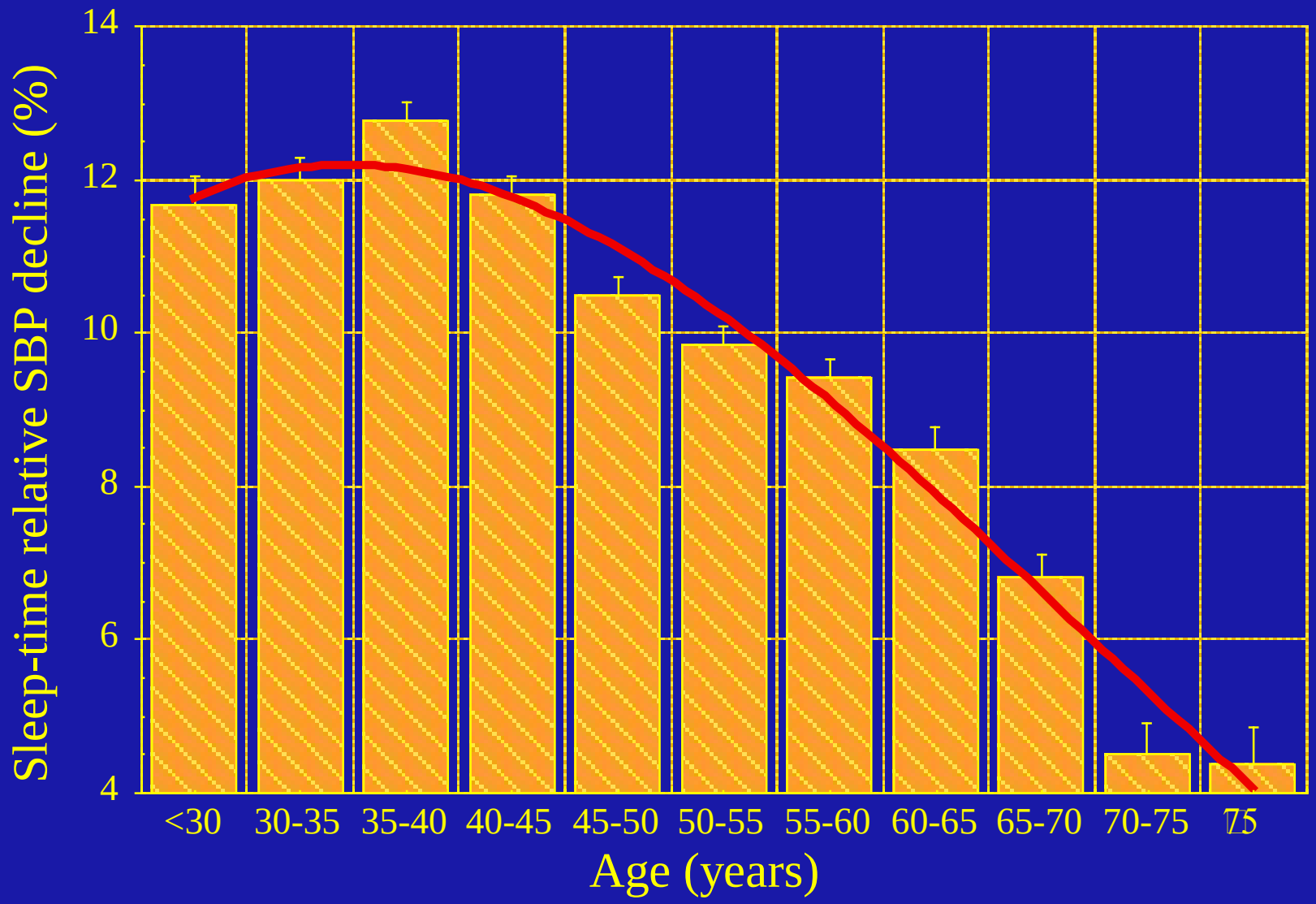


Change in awake and asleep SBP means with age in hypertensive individuals.



Hermida et al., *Chronobiol Int.* 2013;30:176-91

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*

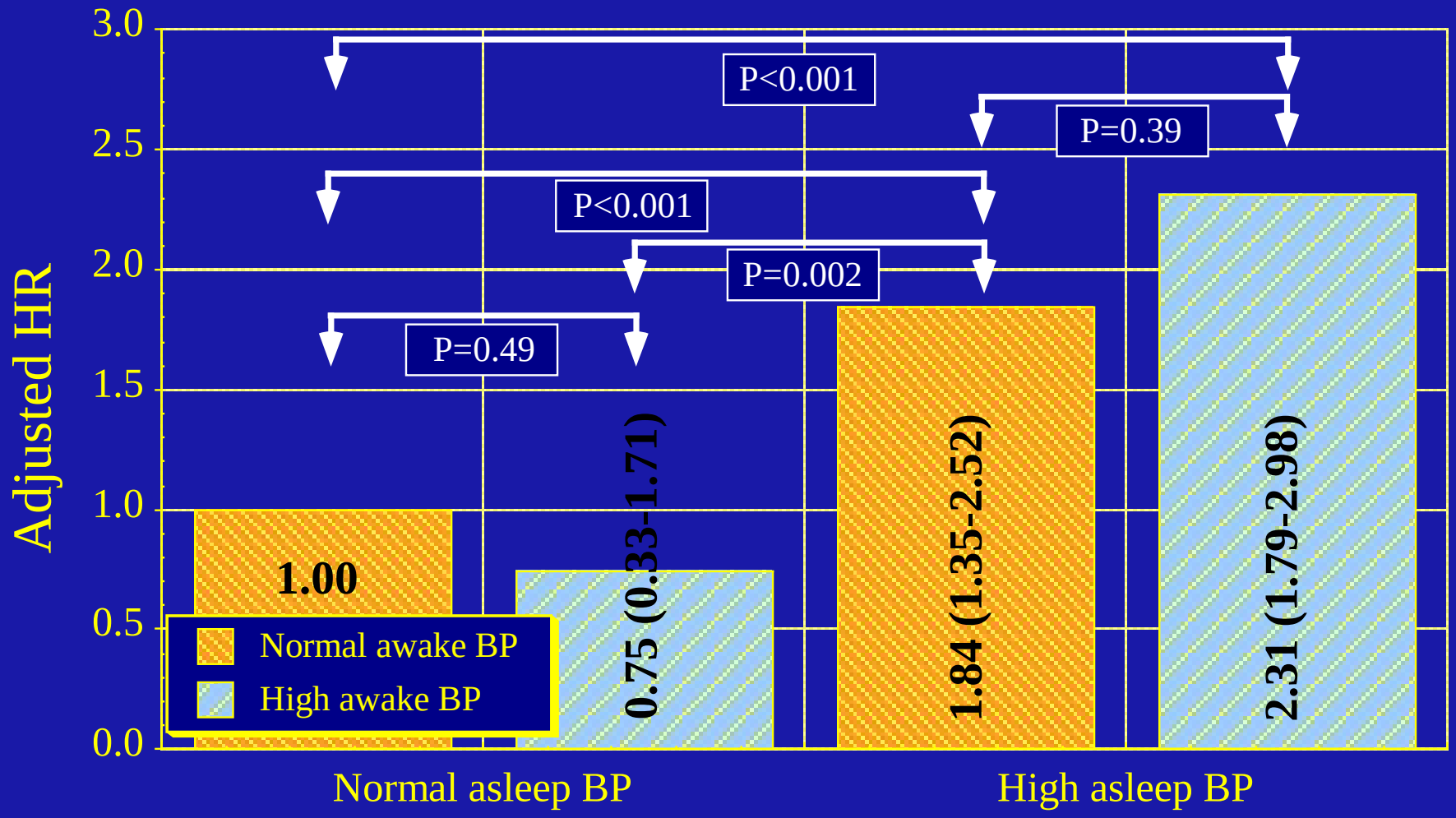
What Is the Best Predictor of CVD Events: ABPM-Derived Asleep *vs.* Awake BP?

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

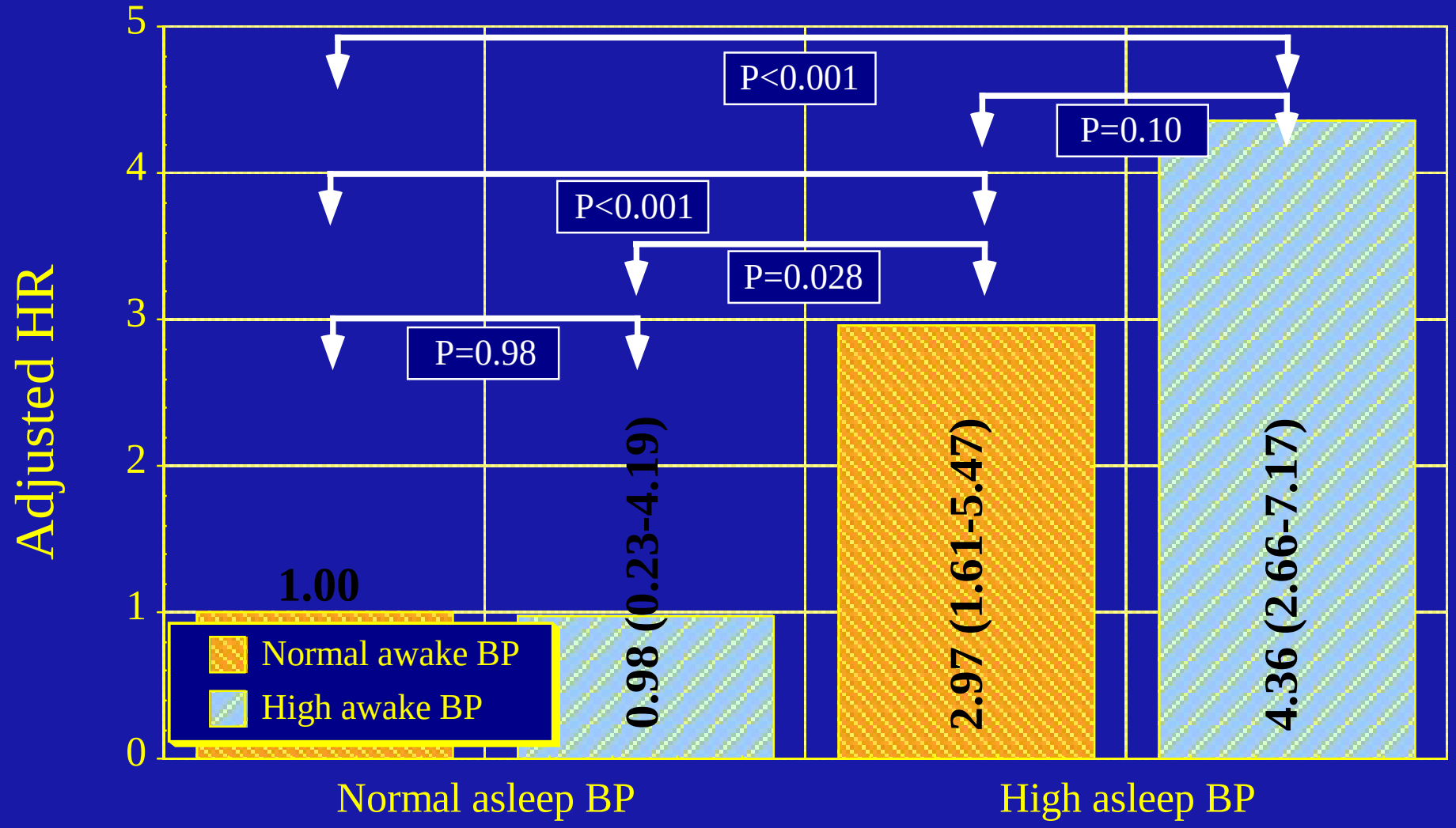
*Hermida et al., *J Am Coll Cardiol.* 2011;58:1165-73

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



Hermida et al. *J Am Coll Cardiol.* 2011;58:1165-73.

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



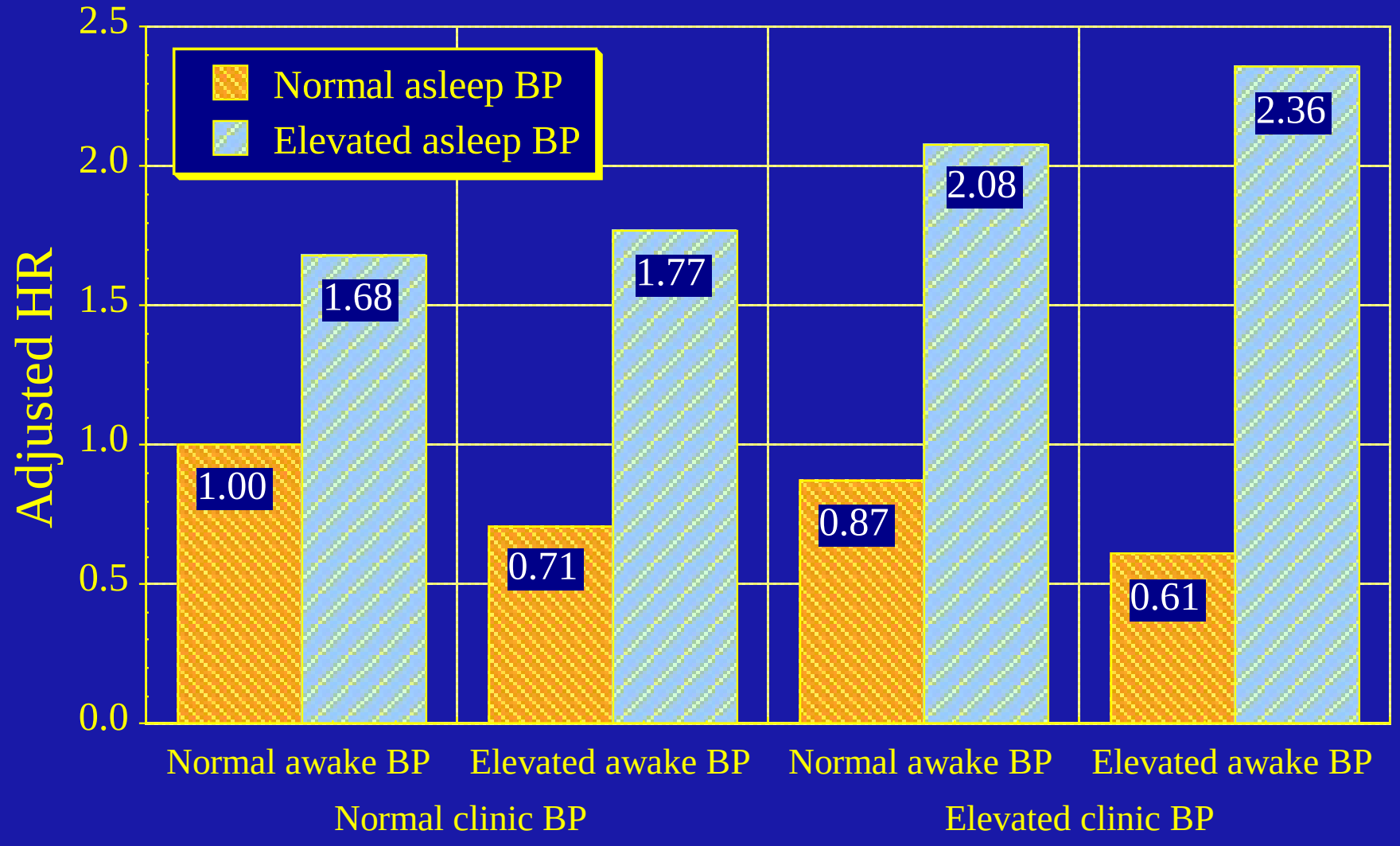
Hermida et al., *J Am Coll Cardiol*. 2011;58:1165-73
Hermida et al., *Chronobiol Int.* 2013;30(3):355-410

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

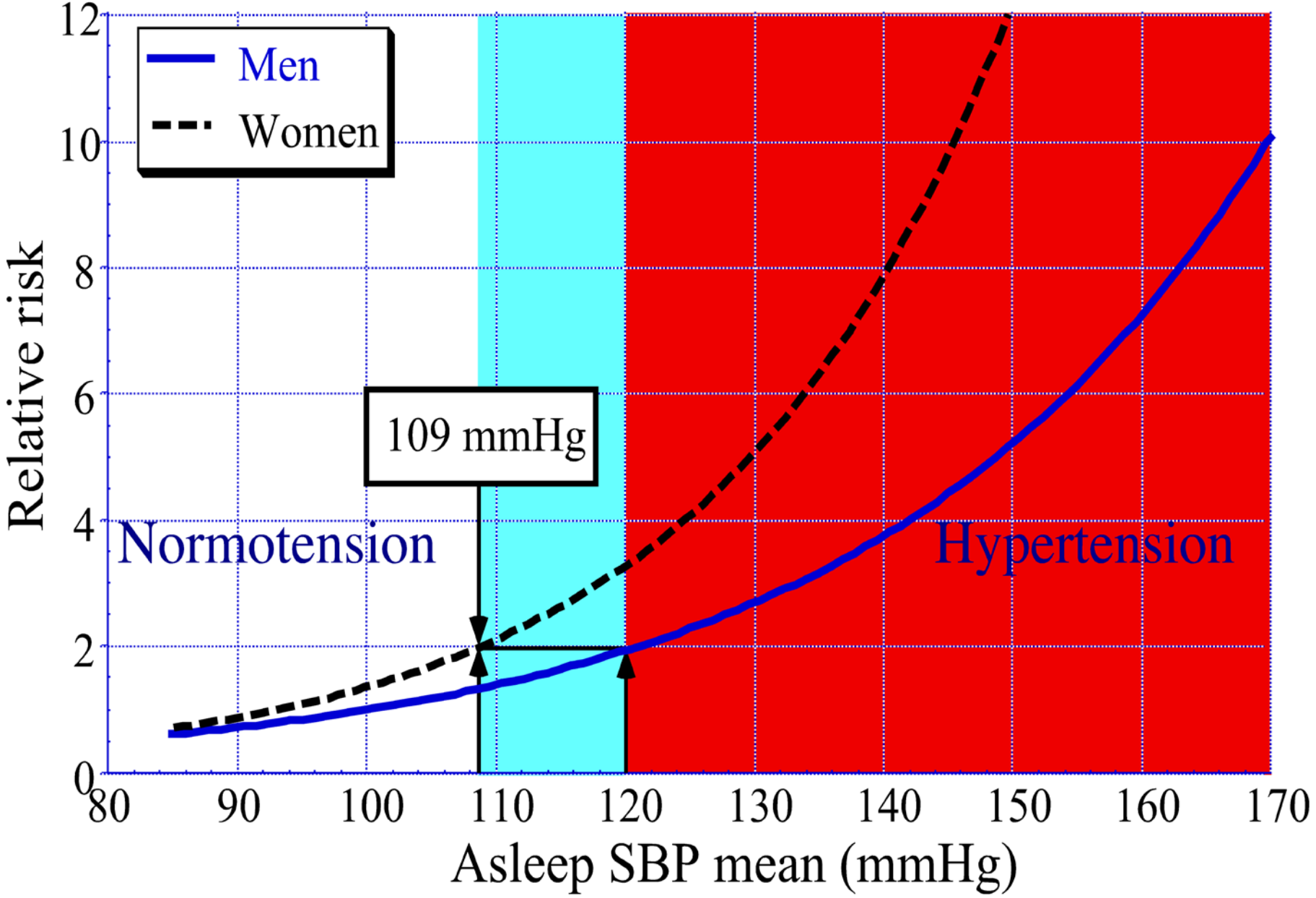
- ***Normal daytime OBPM*: <140/90 mmHg**
- ***Elevated daytime OBPM*: ≥140/90 mmHg**

Adjusted HR of **total CVD events** in the MAPEC Study. Classification by clinic, awake, and asleep BP means.



Hermida et al., *J Am Coll Cardiol.* 2011;58:1165-73

Figure 3


Men
Women
109 mmHg
Normotension
Hypertension
Relative risk
Asleep SBP mean (mmHg)
0
2
4
6
8
10
12
80
90
100
110
120
130
140
150
160
170

Diagnostic ABPM Thresholds (mmHg)

ABPM-Derived	Men ≥18 yrs	Women ≥18 yrs
Awake mean		
SBP	135	125
DBP	85	80
Asleep mean		
SBP	120	110
DBP	70	65

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**

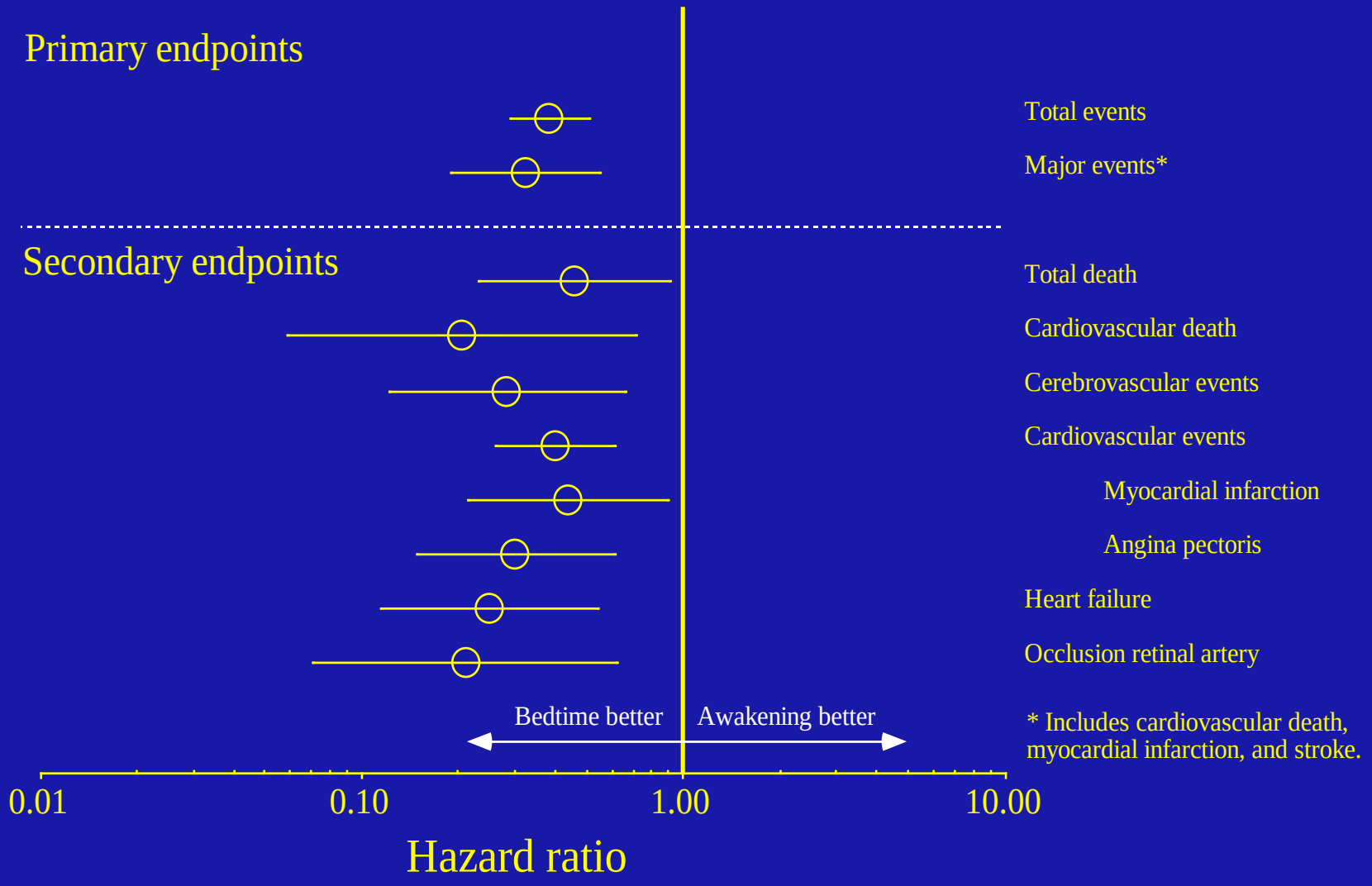
State of art knowledge:

- **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

Class Medication	Dose mg	No. Pts	Reduction: asleep SBP/DBP mean		Sleep-time relative SBP/DBP decline	
			Awakening R_x	Bedtime R_x	Awakening R_x	Bedtime R_x
ACEIs Ramipril	5	115	-4.5/-4.1	-13.5/-11.5*	-3.3/-1.8	3.4/4.9*
Spirapril	6	165	-5.7/-4.6	-12.8/-8.6*	-2.5/-2.7	4.1/4.5*
ARBs Valsartan	160	200	-12.9/-8.1	-21.1/-13.9*	0.4/0.9	7.2/7.1*
Telmisartan	80	215	-8.3/-6.4	-13.8/-9.7*	-1.6/-1.0	3.1/3.9*
CCB Nifedipine GITS	30	238	-7.5/-5.1	-12.8/-7.8*	-0.7/-0.2	1.0/1.5‡
α-Blocker Doxazosin GITS	4	39	0.7/-1.3	-8.2/-6.5†	-2.3/-2.4	1.9/1.9‡
β-Blocker Nebivolol	5	173	-7.9/-7.4	-10.2/-8.1	-3.6/-3.0	-1.2/-1.4‡
Diuretic Torasemide	5	113	-4.3/-2.5	-12.5/-8.0*	-1.6/-0.7	-1.3/-0.2

Age, diabetes and sex-adjusted hazard ratio as a function of treatment-time (≥1 medication at bedtime compared to all medication upon awakening) in hypertensive subjects (MAPEC study)



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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.