

# Melatonin in elderly patients with insomnia:

Dr. Yotin. Chinvarun M.D. Ph.D. FAES

Lunch Symposium

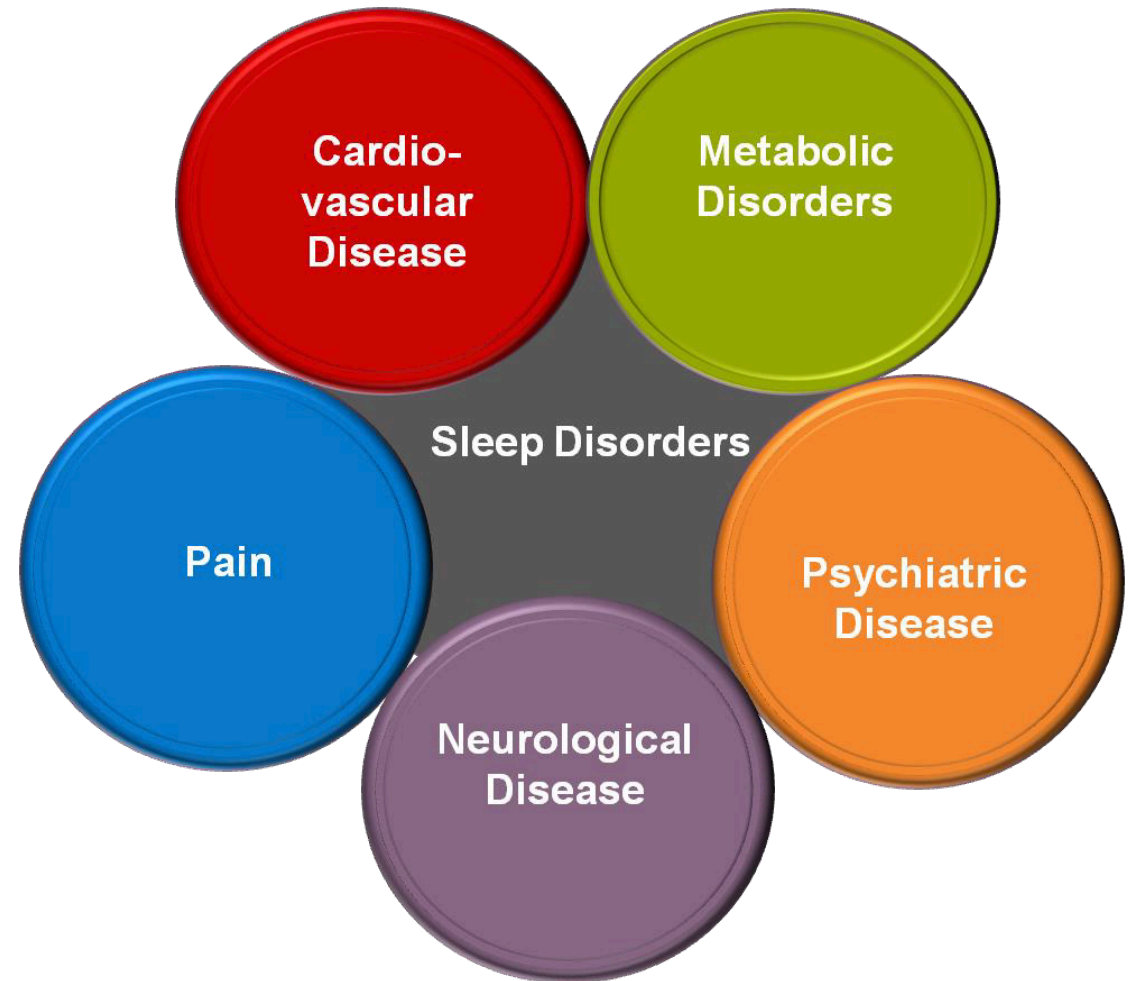


Sleep Neurology Society  
Annual Meeting 2020



# Introduction

Sleep is a vital process



7-8 hours of quality sleep per day reduces morbidity

# Introduction: Sleep and Hypertension

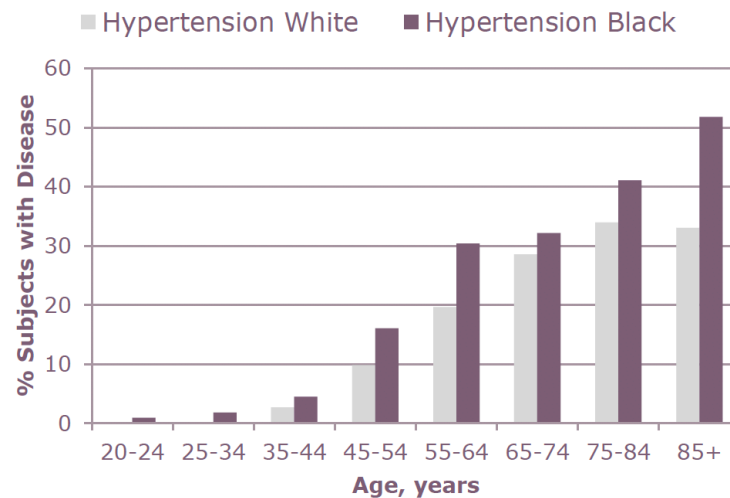
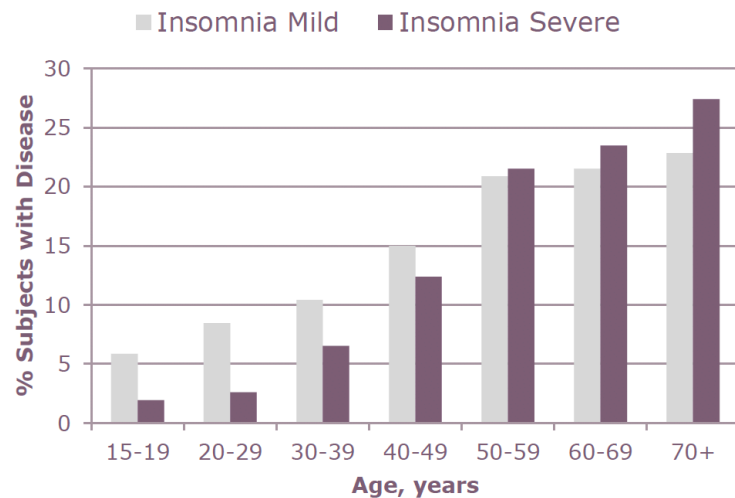
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The diurnal pattern of blood pressure is an important factor in determining cardiovascular complications in hypertensive patients.

Impaired nocturnal blood pressure fall is associated with a high risk of developing target organ damage<sup>1</sup> and morbid cardiovascular events

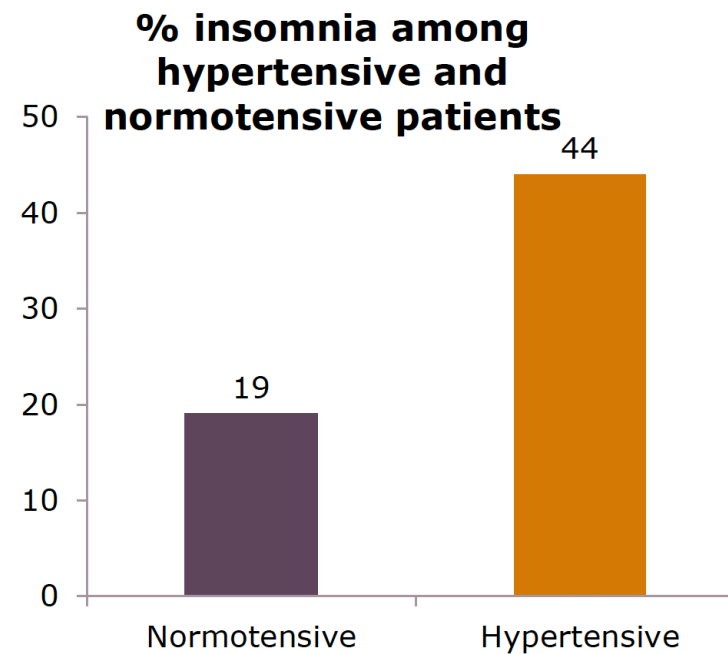
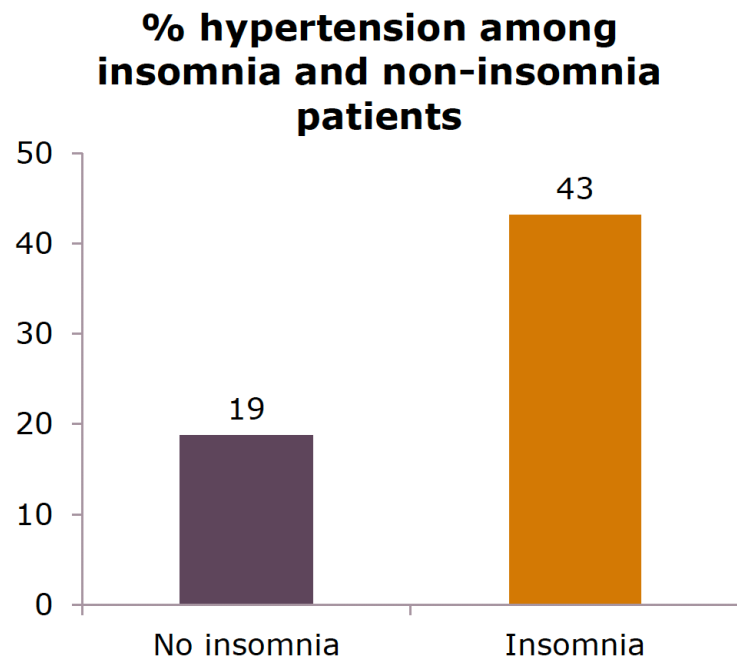
# Insomnia & Hypertension Increase with Age

- Approximately 40% of the 55+ population report insomnia and an overall dissatisfaction with quality of sleep<sup>1</sup>
- Approximately 30% of the 55+ population have hypertension<sup>2</sup>



# Hypertension and insomnia: a vicious cycle

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Roth, 2009 ; Thase, 2005; Pearson, Johnson, & Nahin, 2006; NIOH., 2005;Hoevenaar-Blom, Spijkerman, Kromhout, van den Berg, & Verschuren, 2011.Taylor, 2007

# Melatonin: influence cardiovascular system

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- Melatonin is a hormone normally secreted from the pineal gland at night.
  - It serves as the signal of darkness in the organism, and as such plays a pivotal role in the physiological regulation of circadian rhythms, including sleep
- Evidence from the last ten years suggests that melatonin may influence the cardiovascular system in humans
- Furthermore, exogenous melatonin has induced several hemodynamic effects in healthy men and women

# Melatonin: influence cardiovascular system

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- Melatonin rapidly metabolized, elimination half-life of 40–50 minutes
- Following oral administration of exogenous fast-release melatonin, peak plasma levels are reached 20–30 minutes after ingestion, maintained for 90 minutes and rapidly decline afterwards
- Fast release melatonin unable to provide melatonin for second half of night
- Controlled-release formulations circumvent fast clearance of hormone and provide melatonin profiles in blood more closely match normal physiological release

# Melatonin: influence cardiovascular system

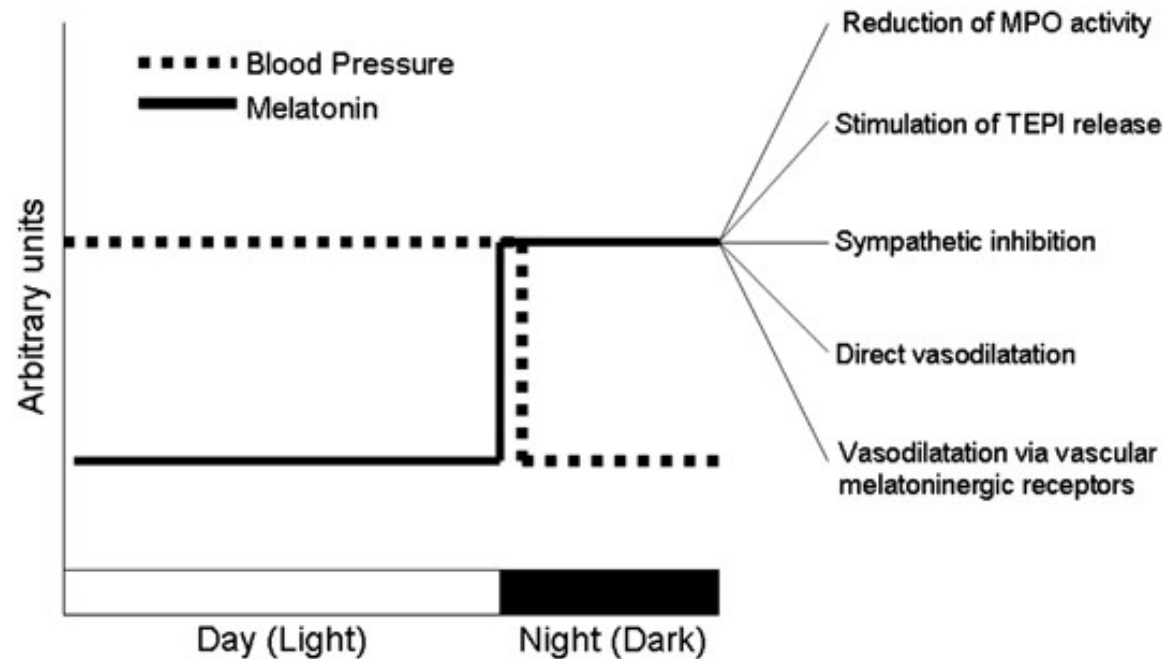
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- Therefore, in order for exogenous melatonin present during late part of night, it has to be administered via controlled-release preparation, or at very high doses
- Melatonin may lower blood pressure via several mechanisms
  - Vascular melatonergic receptors demonstrated and shown to be functionally linked with vasoconstrictor or vasodilatory effects of melatonin.<sup>5</sup>
  - Other neurohormonal properties of melatonin, such as sympathetic inhibition, contribute to its cardioprotective effects.<sup>25</sup>
  - Impaired nocturnal sympathetic suppression with sustained adrenergic activity during sleep reported in patients with nocturnal hypertension (nondippers).<sup>26,27</sup>



# Melatonin: influence cardiovascular system

Melatonin may lower  
blood pressure via several  
mechanisms



MPO, myeloperoxidase; TFPI, tissue factor pathway inhibitor.

## Melatonin: influence cardiovascular system

Administration of melatonin may therefore contribute to nocturnal suppression of the sympathetic nervous system

The reduction of the activity of oxidative enzyme, myeloperoxidase, by melatonin may also contribute to the vasoprotective and blood pressure-lowering effects of melatonin.<sup>28</sup>

Melatonin may also dilate peripheral arteries directly,<sup>5–7</sup> reducing peripheral resistance and leading to a nocturnal blood pressure fall

# Melatonin: influence cardiovascular system

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- Melatonin shown to stimulate release of tissue factor pathway inhibitor from vascular endothelium, which may suppress thrombosis and arterial restenosis
- A blunted nocturnal decrease in BP is independently associated with increased aortic stiffness in patients with nocturnal hypertension
- Carotid-femoral pulse wave velocity, a direct measure of aortic stiffness, become increasingly important for total cardiovascular risk estimation
- Even in dippers, absolute night-time BP associated more closely with pulse wave velocity than daytime blood pressure

# Melatonin: influence cardiovascular system

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- In a recent study, increased levels of melatonin during the night cause a decrease in velocity of aortic pulse wave
- Melatonin administration, compared with placebo, found to decrease pulse wave velocity and systolic BP in supine position in healthy young men.<sup>34</sup>
- A controlled-release melatonin approved in European Union and other countries Rx insomnia in patients aged 55 years and older

# Melatonin: influence cardiovascular system

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- The improvement in nocturnal hypertension appears to be related to mechanism of action of controlled-release melatonin and not to hypnotic action
- Zolpidem, most widely prescribed hypnotic drug, does not lower and may even increase nocturnal blood pressure

# Melatonin: influence cardiovascular system

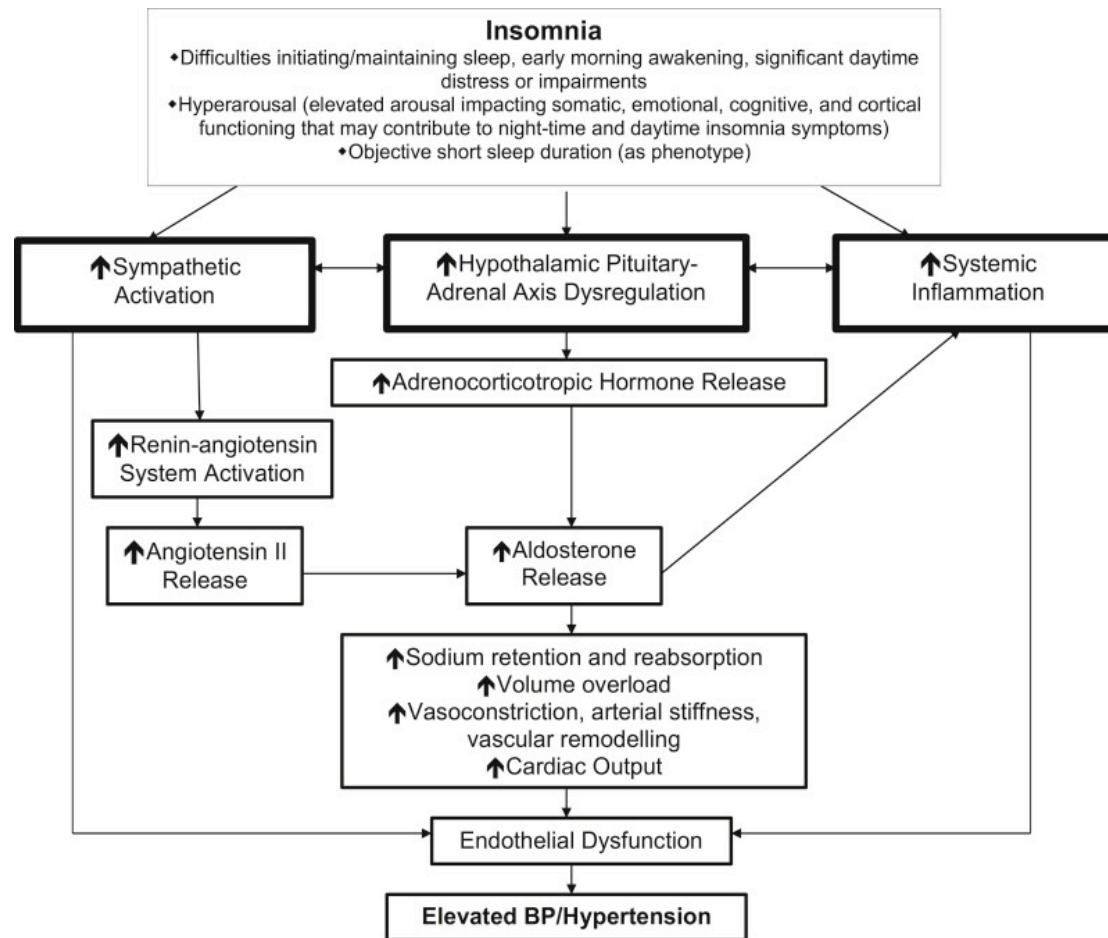
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- Addition of controlled-release melatonin at night to stable antihypertensive treatment may improve nocturnal blood pressure control
- Thus, because of its effects on nocturnal blood pressure, add-on controlled-release melatonin treatment is expected to reduce the cardiovascular risk in high-risk patients with nocturnal hypertension

**Why is insomnia linked to hypertension?**

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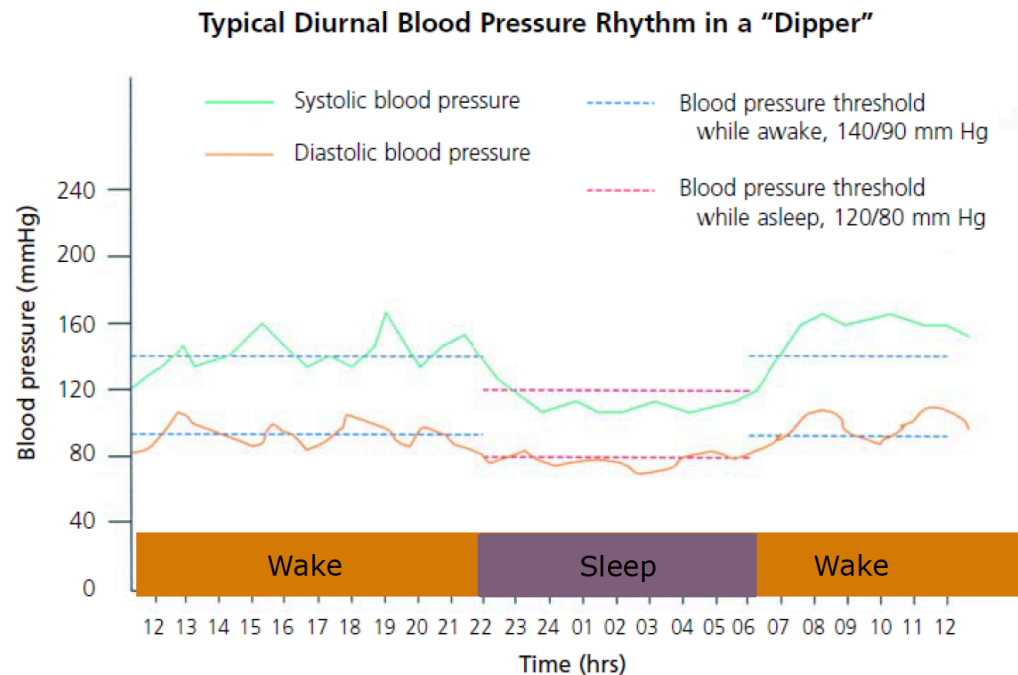






# Circadian rhythm in blood pressure regulation

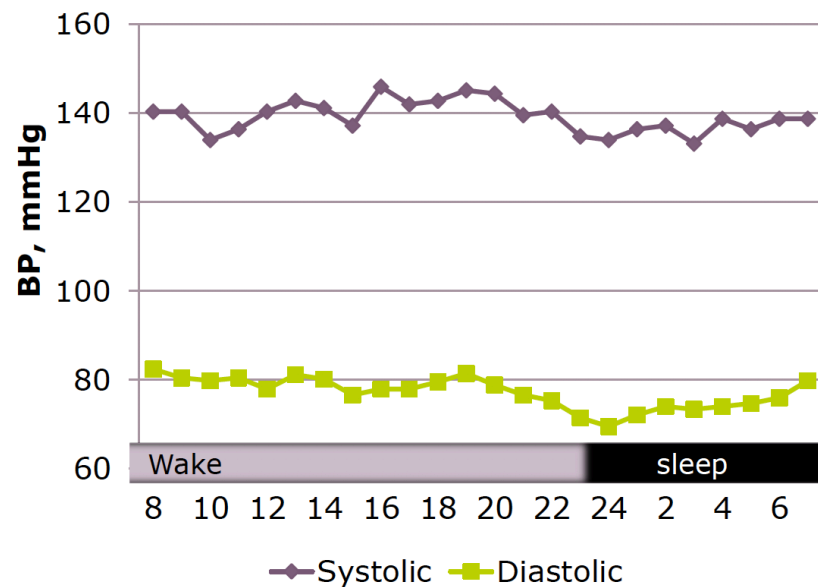
- Blood pressure falls during sleep and rises rapidly just before the time of awakening
- Circadian Rhythm in Blood Pressure is essential for Cardiovascular health



# Failure to reduce blood pressure during the night is associated with poor sleep

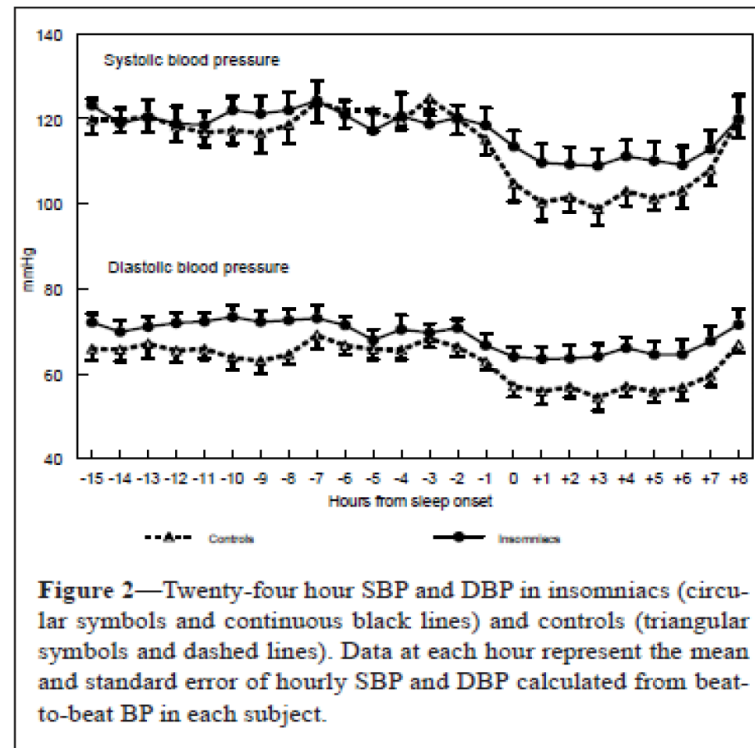
- Every second patient with hypertension is a non dipper
- Nocturnal hypertension is significantly higher in older than younger patients (63.1% vs. 41.1%;  $p < .001$ ).
- **Non dippers have poor quality of sleep**

Non-dippers display blunted circadian BP rhythm



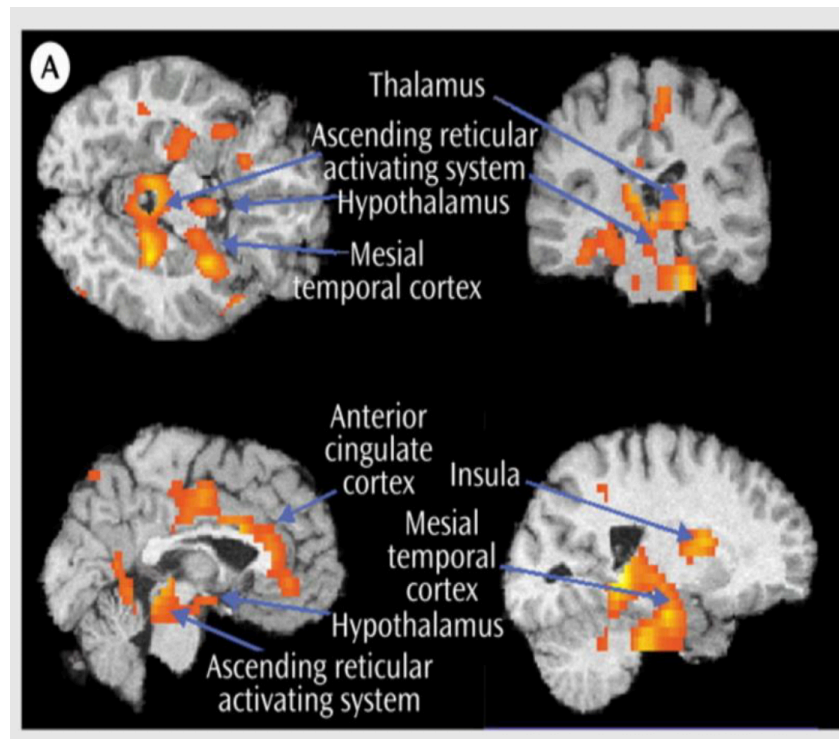
# The circadian rhythm of blood pressure is blunted in patients with insomnia

- Blood pressure is not reduced at night in insomnia even in normotensive patients
- If blood pressure when asleep drops by less than 10% from wake blood pressure the patient is a non-dipper



# Insomnia is a syndrome of brain hyperarousal during the night

- Brain structures that did not show decreased metabolic rate from waking to sleep states in patients with insomnia.
- Differences in all regions shown reached statistical significance at the  $p < 0.05$ , corrected, level.

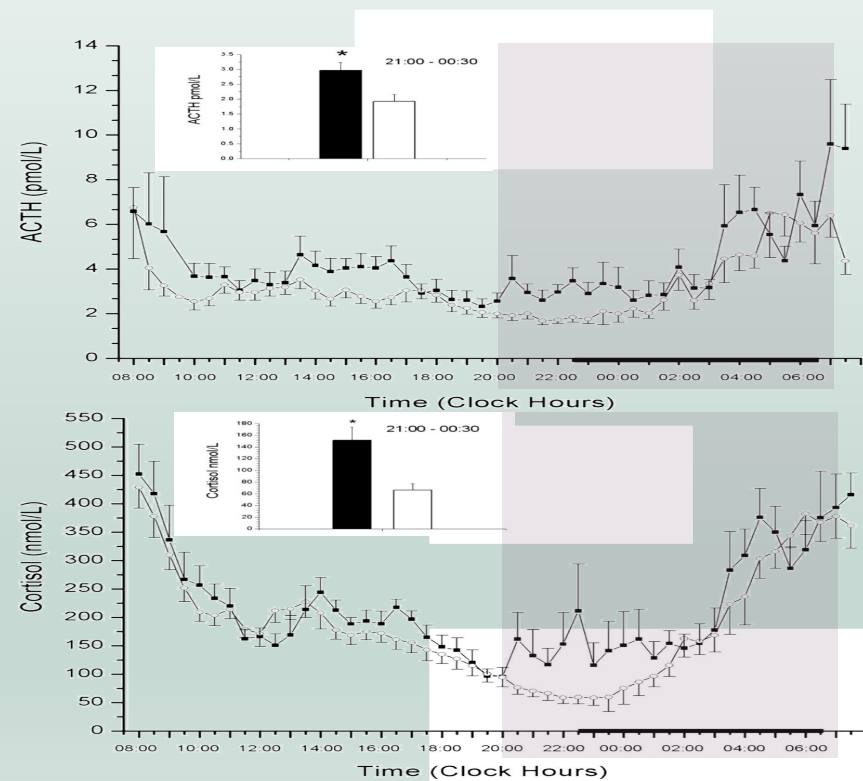


# The hyperarousal is associated with high hypothalamic pituitary adrenal (HPA) axis activity

The 24-h plasma ACTH (top) and cortisol (bottom) concentrations in insomnia patients (■) and controls (○).

The thick black line on the abscissa indicates the sleep recording period.

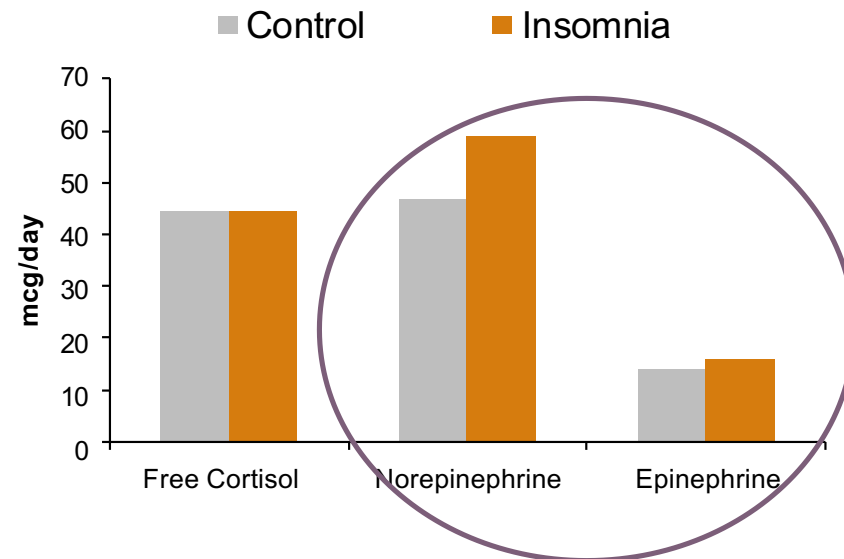
Error bar indicates standard error (SE).  
\*  $P < .01$ .



# The hyperarousal is associated with high sympathetic activity

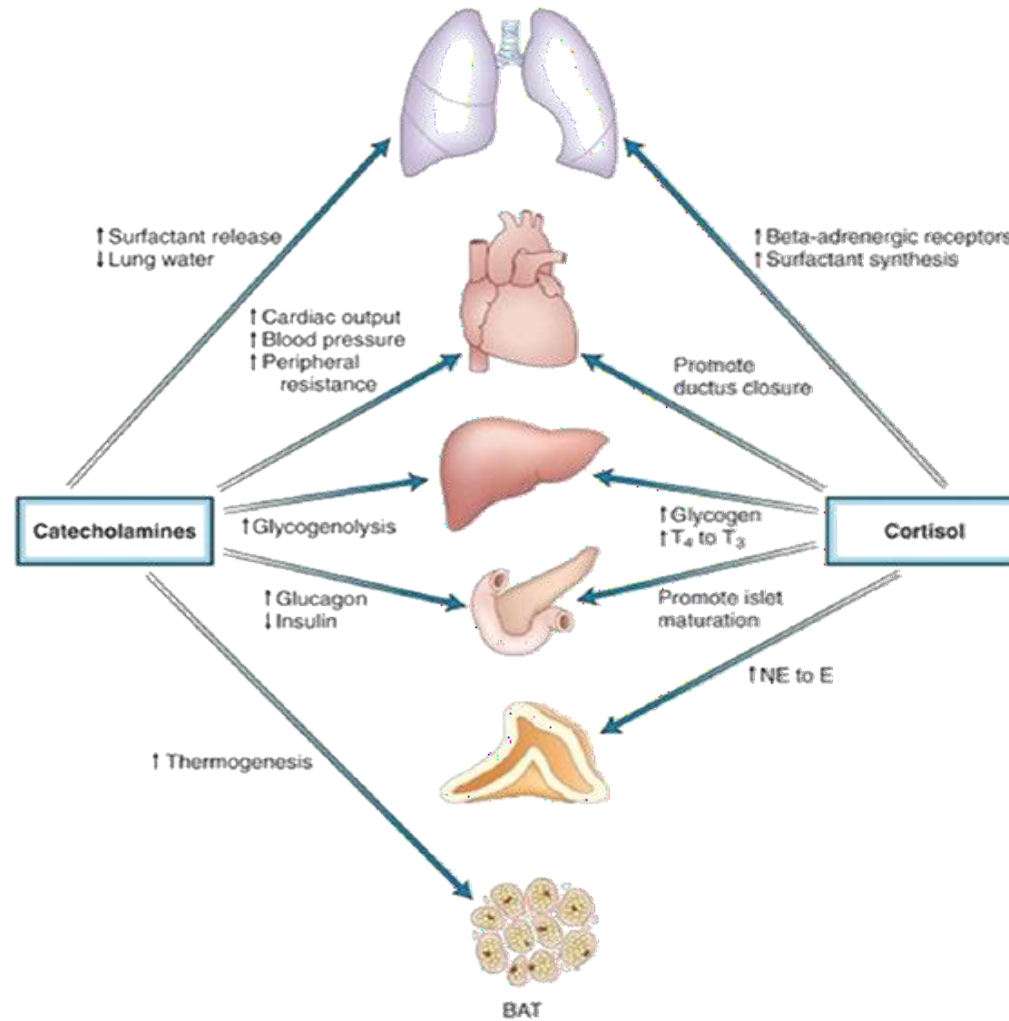
Catecholamines such as norepinephrine, which are markers of hyperarousal, are elevated in patients with insomnia

**Endocrine Measures in urine**



# Insomnia and Cortisol and Catecholamine

Insomnia causes increase in cortisol and catecholamines and consequently increases BP

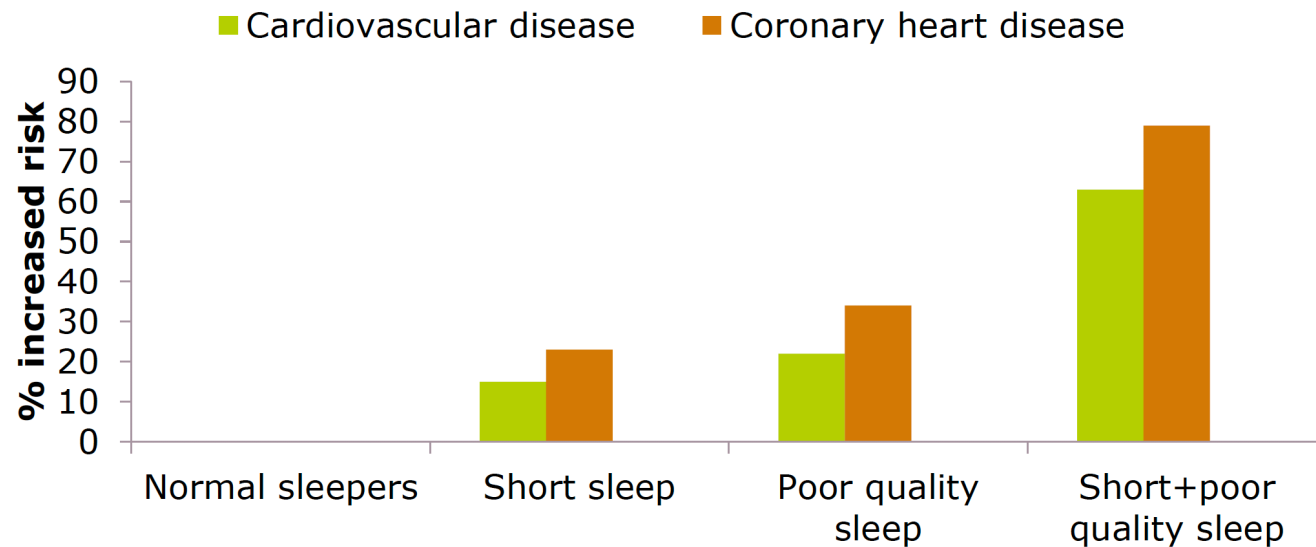


**Why should we  
treat  
insomnia in  
hypertensive  
patients?**





## Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: The MORGEN Study

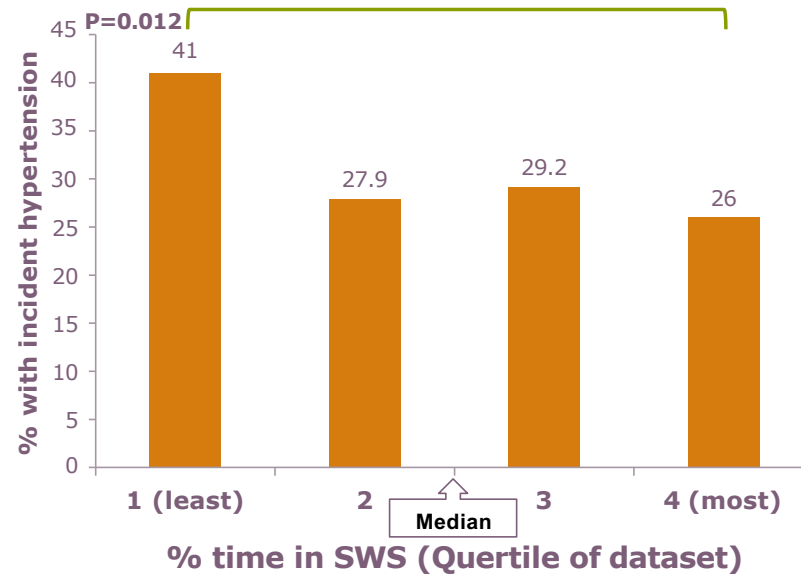


20,432 men and women aged 20-65 y with no history of CVD. 10-15 years of follow-up in the Netherlands,

# Decreased Slow Wave Sleep Increases Risk of Developing Hypertension in Elderly Men

Percentage time in SWS was inversely associated with incident hypertension, independent of sleep duration and fragmentation, and sleep-disordered breathing.

Selective deprivation of SWS may contribute to adverse blood pressure in older men.

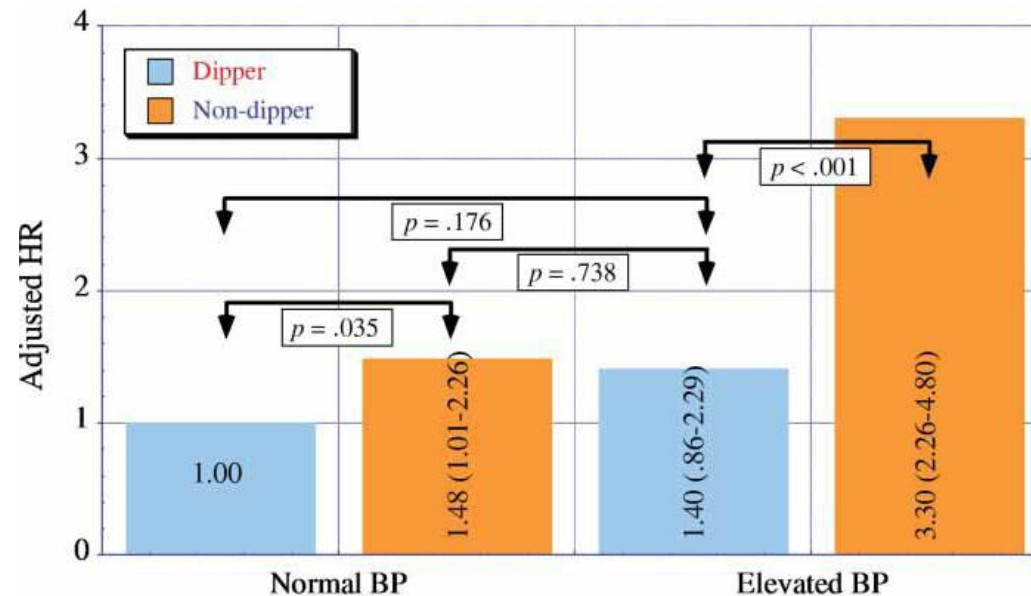


Odds ratio: 1.81 [95% CI: 1.18 to 2.80].

# Failure to reduce blood pressure during the night is associated with high cardiovascular (CVD) risk

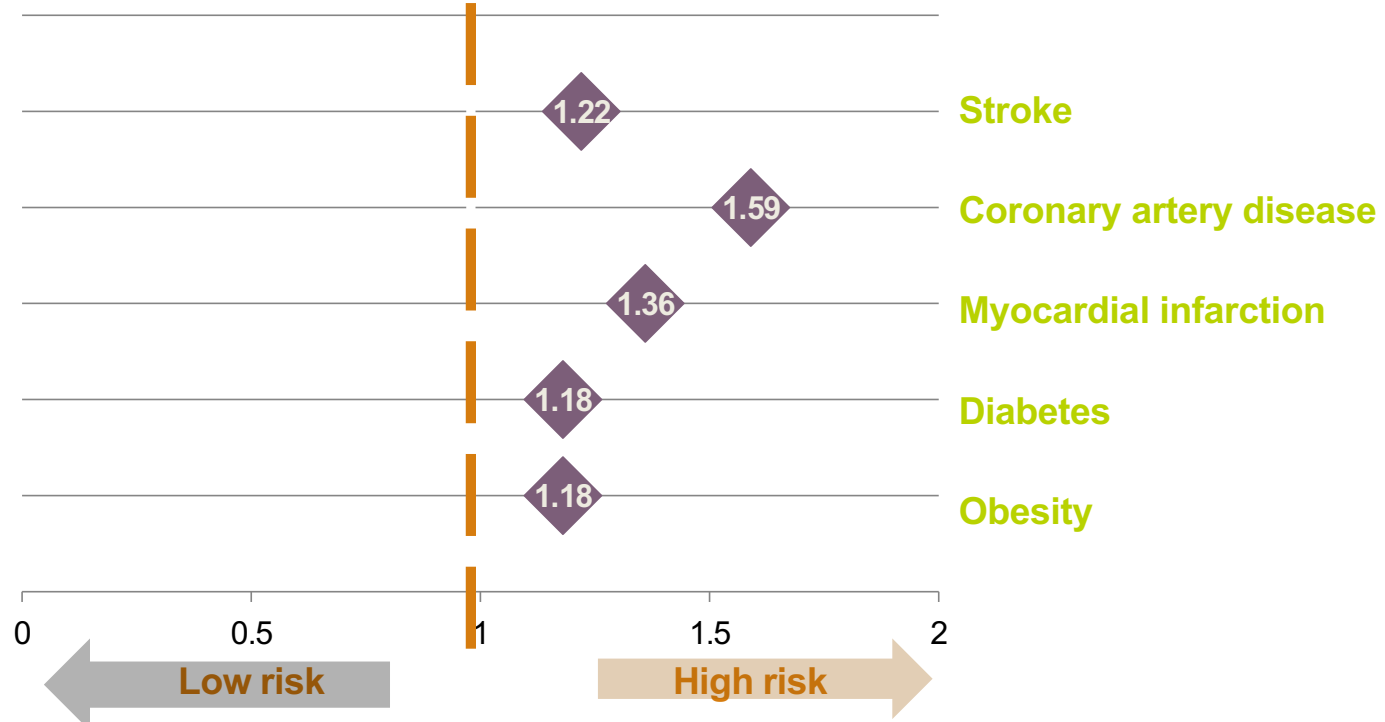
Adjusted HRs (95% CIs) of total CVD events in **treated** patients

elevated sleep-time blood pressure is a better predictor of cardiovascular risk than awake or 24-h blood pressure means



# We need to treat the sleep disorder for better cardiovascular health

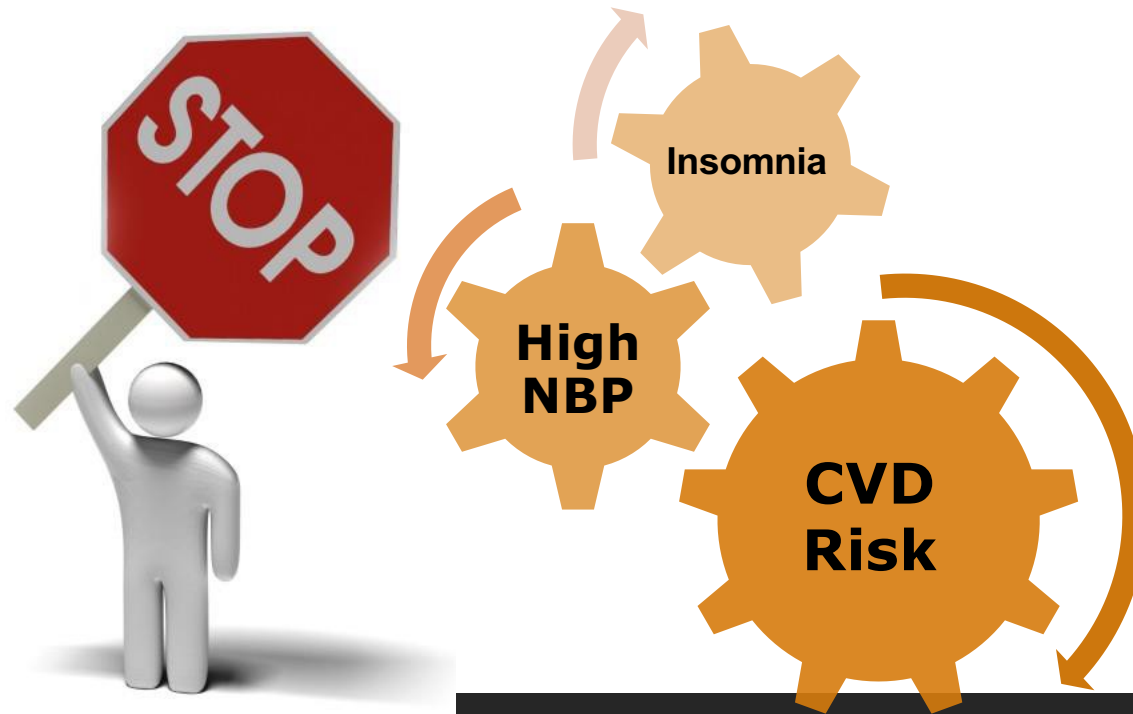
Odds Ratio predicted by sleep disturbance



Grandner, Jackson, Pak, & Gehrman, 2012

# Insomnia leads to high Nocturnal BP (NBP) and elevated CVD risks

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# **How should we treat insomnia in hypertensive patients?**

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## **What do we expect from an effective treatment of insomnia in hypertensive patients?**

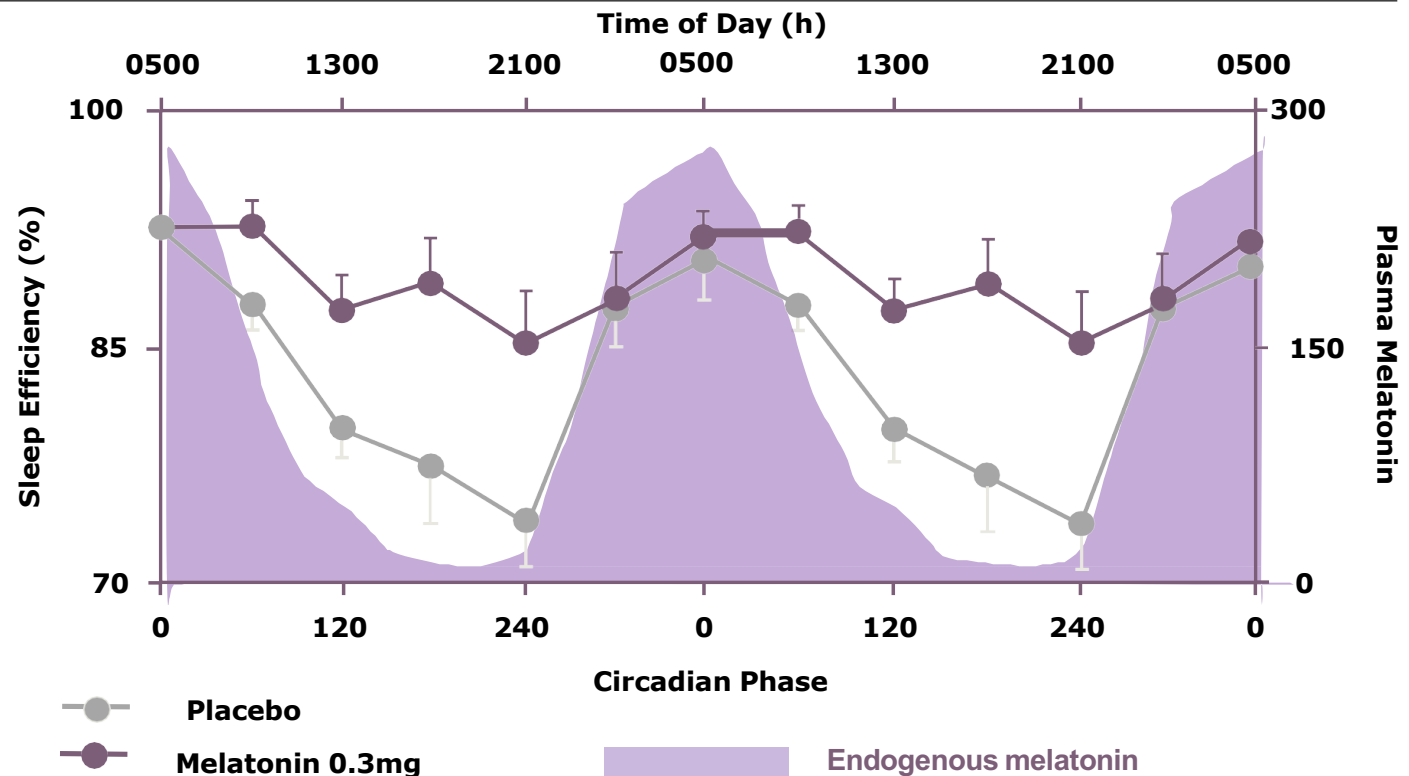
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- Restore physiological sleep
  - Adjust the sleep/wake cycle
  - Restore circadian rhythm in blood pressure regulation
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# Melatonin is an endogenous regulator of sleep and the circadian clock

**Melatonin** is regulated not only by that **circadian** oscillator but acts as a darkness signal, providing feedback to the oscillator.

**Melatonin** has both a soporific effect and an ability to entrain the **sleep-wake rhythm**.



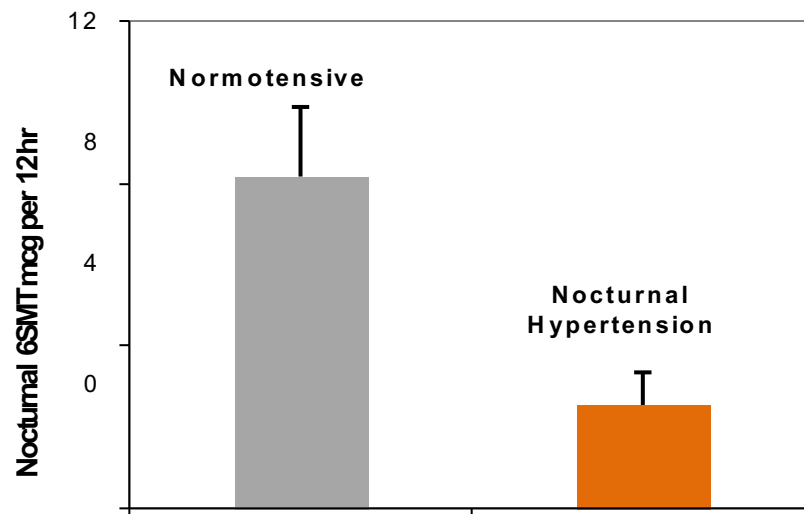
Wyatt, Dijk, Ritz-de Cecco, Ronda, & Czeisler, 2006)



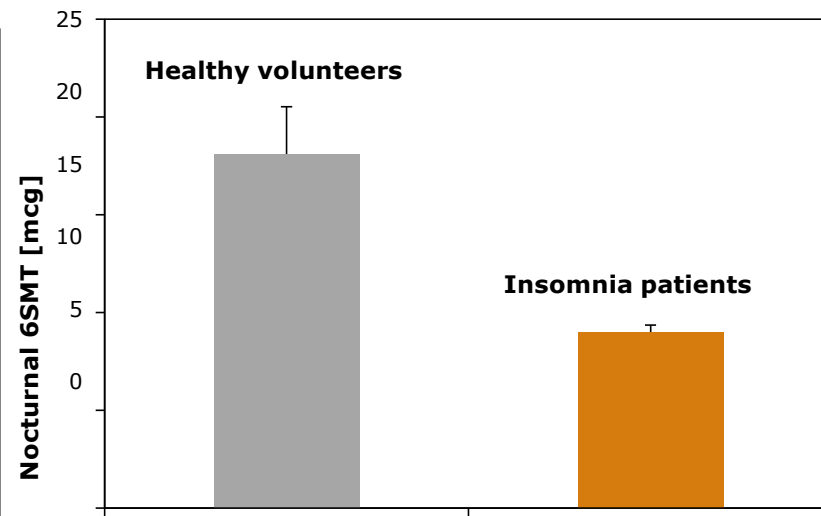
# Low melatonin is causally linked to poor sleep and nocturnal hypertension

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**Nondippers make less melatonin**



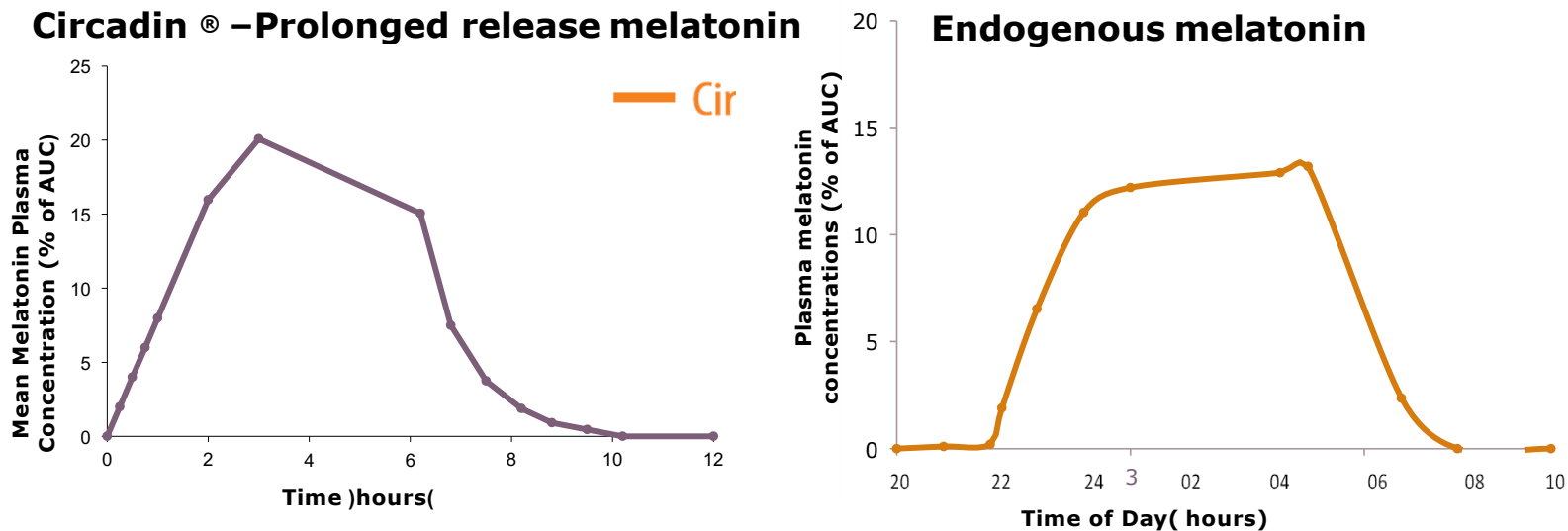
**Insomnia patients make less melatonin**



Scheer, Montfrans, Someren, Mairuhu, & Buijs, 2004 ; Jonas, Garfinkel, Zisapel, Laudon, & Grossman, 2003; Grossman, 2004; Marchiando & Elston, 2003 ; Pasqualini, Foroni, Salvioli, & Mussi, 2004 ; Hermida & Diana E. Ayala, 2012, Leger, Laudon, & Zisapel, 2004

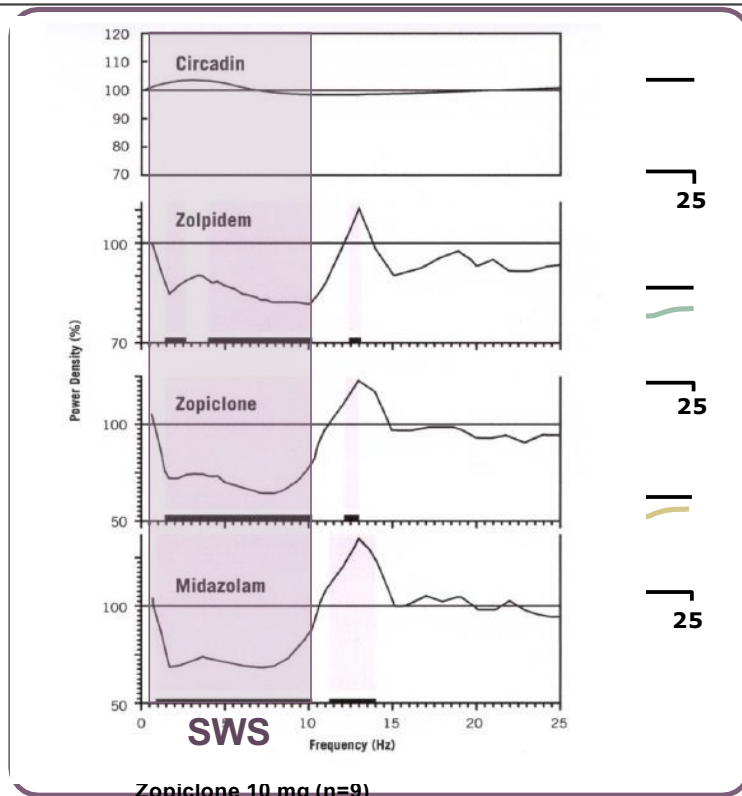
# Circadin®- Melatonin replacement therapy

- Circadin® releases melatonin over a predefined extended period of time
- circumvents both the build-up of high levels and the fast clearance of melatonin.

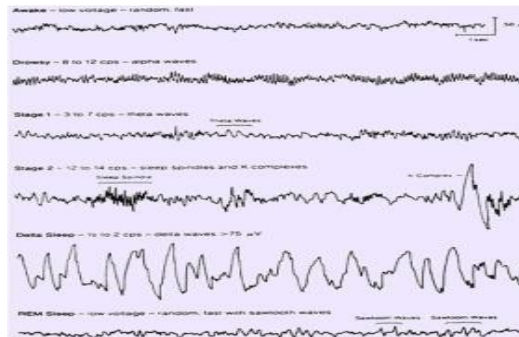


1. Adapted from Arendt, Bojkowski, Franey, Wright, & Marks, 1985
2. EPAR. Assessment report for Circadin. Procedure No.EMA/H/C/695,200

# BAD and Z Drugs suppress whereas Circadin® preserves Slow Wave Sleep



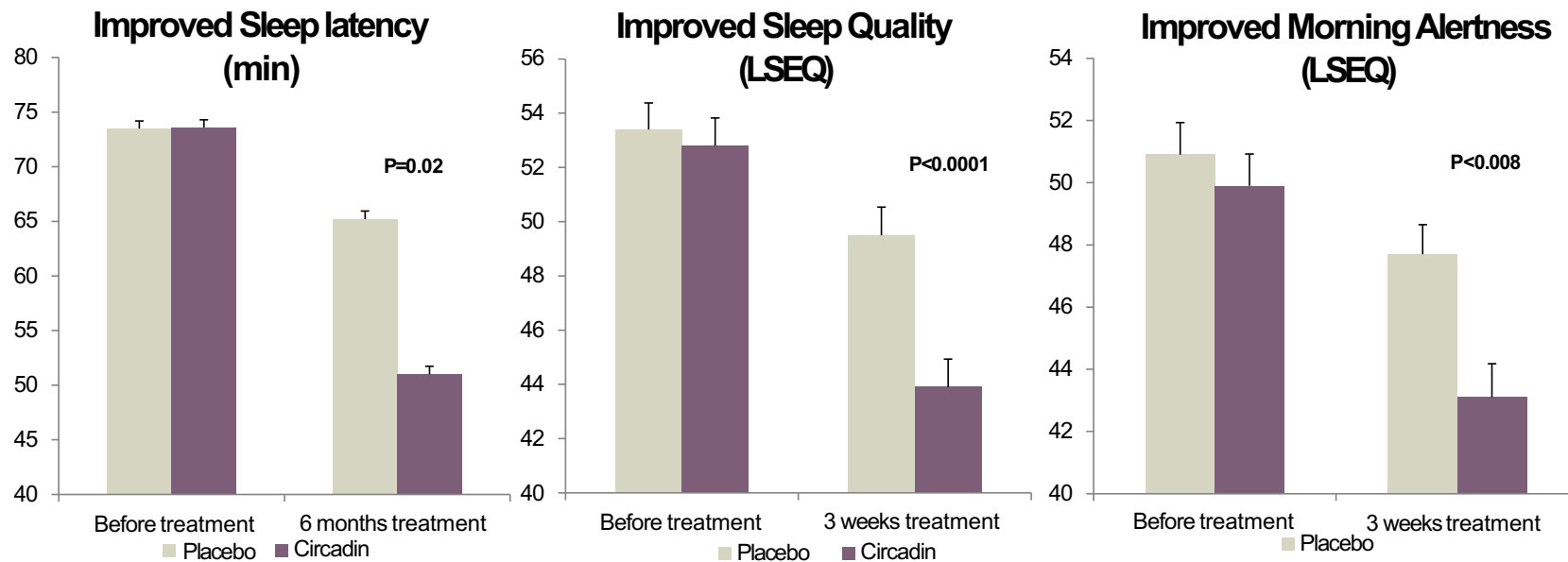
- Circadin® preserves physiological sleep structure and architecture<sup>1</sup>
- The suppression of low frequency deep sleep which is typically caused by hypnotics<sup>2,3,4</sup> does not occur with Circadin®



<sup>1</sup>Luthringer R et al. *Int Clin Psychopharmacol* (2009).

<sup>2</sup>Trachsel L et al. *Neuropharmacol* (1990). <sup>3</sup>Brunner D et al. *Psychopharmacol* (1991). <sup>4</sup>Borbély and Tobler (1989)

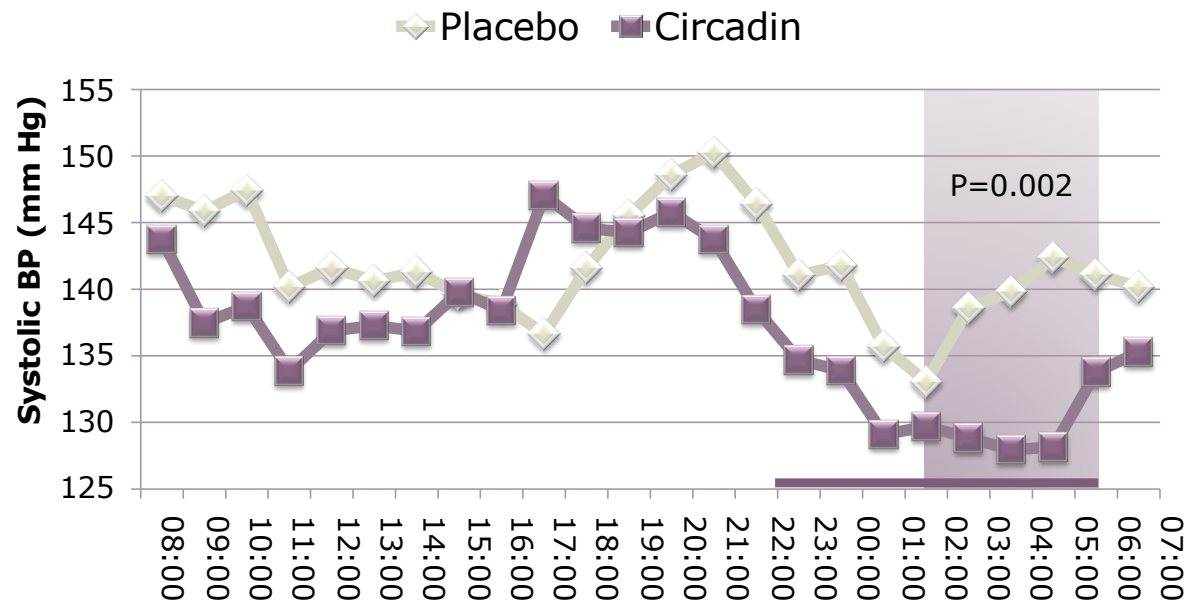
# Add-on Circadin® improves sleep quality and the sleep/wake cycle in patients with hypertension



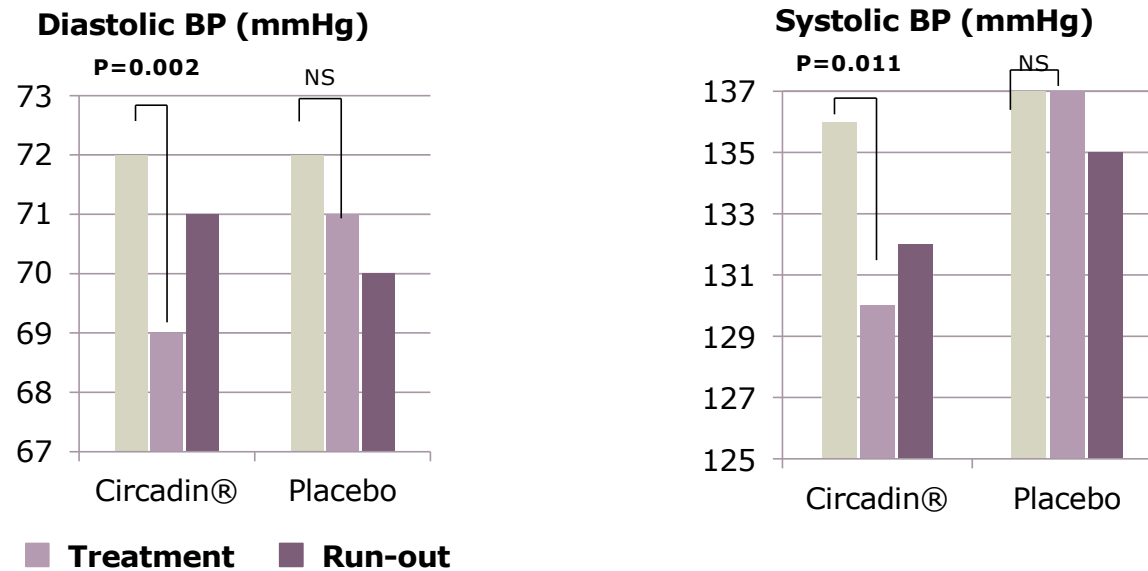
**Circadin® is the only insomnia drug that preserves physiological sleep structure and architecture**

Lemoine et al., 2012; Luthringer, et al, 2009

# Add-on Circadin® restores circadian rhythm in blood pressure regulation



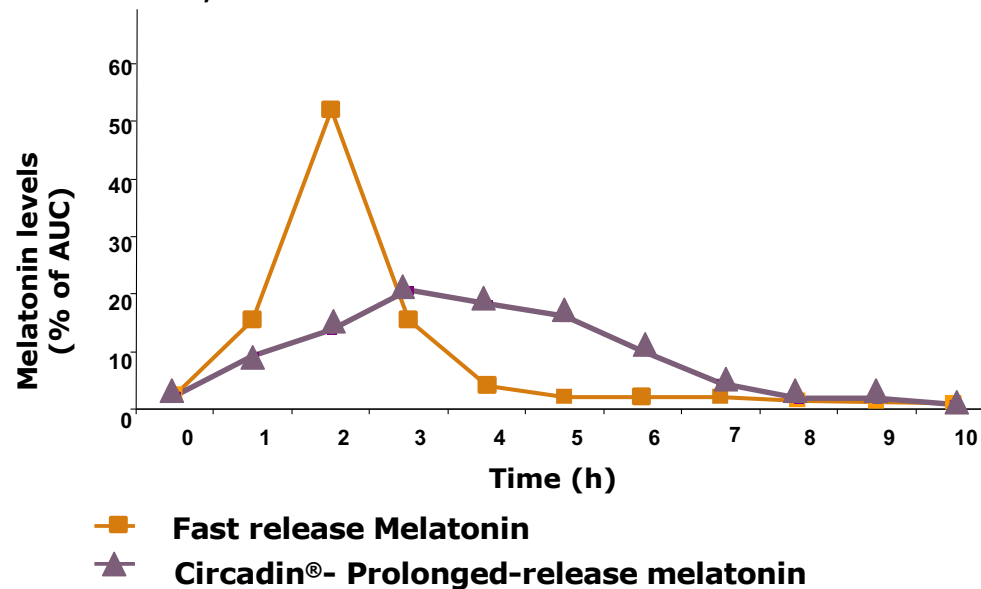
# Add-on Circadin® improves Blood Pressure Control in nocturnal hypertension



A decrease of 5 mmHg in mean asleep systolic blood pressure or 2.1 mmHg in diastolic blood pressure saved 1585 CV events per 100,000 patient years.

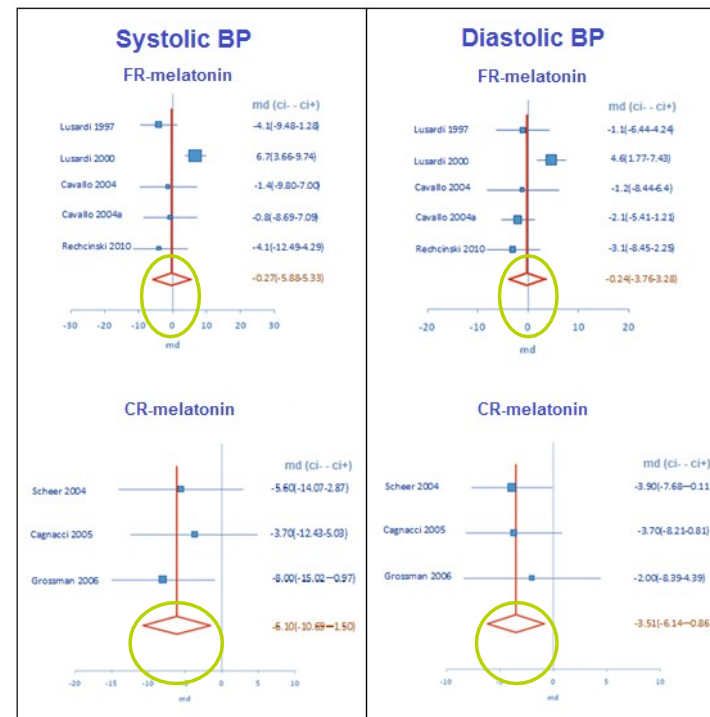
# Pharmacokinetics of Circadin® vs. Immediate-Release Melatonin

Immediate-release melatonin has a **rapid onset** to high levels and is rapidly metabolised, and does not cover the second half of the night



# Circadin® improves nocturnal hypertension whereas immediate release melatonin is ineffective

Add-on controlled release (CR) melatonin to anti-hypertensive therapy is effective and safe in ameliorating nocturnal hypertension whereas fast release (FR) melatonin is ineffective





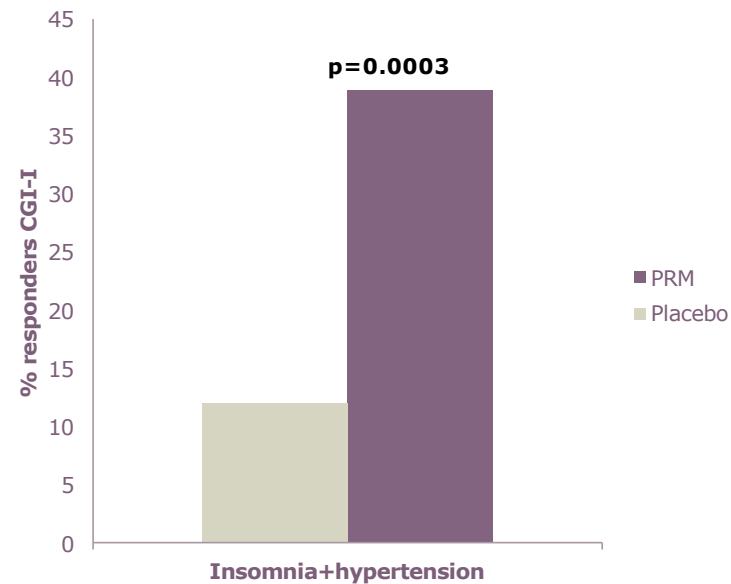
# Safety Analysis

	With CVD abnormalities (N = 650)			Without CVD abnormalities (N = 1184)			With CVD abnormalities (N = 632)			Without CVD abnormalities (N = 926)		
	N	%	Rate of patients with AE per 100 Pt weeks of therapy	N	%	Rate of patients with AE per 100 Pt weeks of therapy	N	%	Rate of patients with AE per 100 Pt weeks of therapy	N	%	Rate of patients with AE per 100 Pt weeks of therapy
<b>MedDRA system organ class/preferred term</b>												
<b>Any event</b>	272	(41.8)	3.668	645	(54.5)	2.996	231	(36.6)	8.536	371	(40.1)	5.088

Circadin® has an excellent safety profile for insomnia in patients with cardiovascular comorbidity.

# Circadin® Improves Clinical Global Impression in Patient with Hypertension

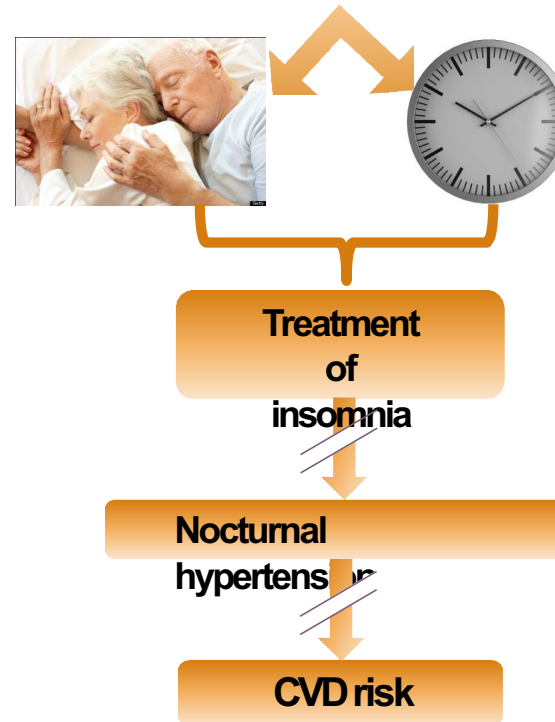
- Long term treatment with Circadin® (6M)
- % patients rated as improved or greatly improved by the physician (CGI-I) following Circadin (6 months) treatment was about 40%, 4 times higher than with placebo



# Add-on Circardin in hypertensive therapy

Through its activity on sleep and the circadian clock,

Add-on Circadin to anti-hypertensive therapy can improve clinical outcome in hypertensive patients with insomnia



# In summary

- One in two patients with hypertension has insomnia
- Concomitant treatment of insomnia and hypertension is essential for Cardiovascular health
- BZDs/Z drugs suppress SWS and may increase hypertension risk
- Melatonin is the physiological regulator of circadian rhythms and sleep

# In summary

- Insomnia patients and non-dippers have low melatonin levels
- IR melatonin cannot provide the Circadian signal throughout the night
- Circadin® (PR melatonin) restores physiological sleep, adjusts the biological clock and restores circadian rhythm in blood pressure regulation and is therefore the optimal treatment for insomnia in hypertensive patients