Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive

Diabetes Care 2011;34:1270-6.

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481 PHCL

When is the best time to take your medications?

- Many patients take all their once-daily BP meds in the morning.
- New evidence suggests that taking at least one BP med at bedtime improves BP control and decreases CV events in some patients.
- Researchers suspect that bedtime dosing may be especially useful for patients whose BP doesn’t “dip” at night like it should.
- However, lowering BP too much at night can lead to nocturnal hypotension and possibly orthostatic hypotension and falls.

Influence of Time of Day of Blood Pressure-Lowering Treatment on Cardiovascular Risk in Hypertens...
Hermida, Ramón C, PHD;Ayala, Diana E, MD, MPH, PHD;Mojón, Artemio;Fernández, José R, PHD
Diabetes Care; Jun 2011; 34, 6; ProQuest Central
pg. 1270

Clinical Care/Education/Nutrition/Psychosocial Research

ORIGINAL ARTICLE

Influence of Time of Day of Blood Pressure-Lowering Treatment on Cardiovascular Risk in Hypertensive Patients With Type 2 Diabetes

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consistently shown an association betwee
blunted sleep time blood pressure declin
and increased incidence of cardiovas

Introduction

- Circadian rhythms and chronobiology affect a variety of physiologic functions.
- Several drugs had been developed to address this (e.g., *Covera-HS). However, it has not led to significant* changes in the way drugs are administered.
- Very few antihypertensive meds have true 24-hour duration of activity.
- 24-hour ambulatory blood pressure monitoring (ABPM) has been shown to be more useful than office BP measurements when predicting cardiovascular (CV) events.

Diabetes Care 2011;34:1270-6.

Introduction

- Previous studies have indicated that sleep time (nocturnal) BP may be even more predictive of CV risk.

- Nocturnal hypertension is common with diabetes and CV risk is decreased in patients who “dip” at night.

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Objective and hypothesis

- To evaluate the administration of anti-hypertensives upon rising in the morning compared with taking at least one anti-hypertensive at bedtime.

- The nighttime dosing of BP medications would lead to better nocturnal control of hypertension.

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PICO

P	Hypertensive patients with type 2 diabetes on anti-hypertension medications
I	Bedtime treatment with ≥1 hypertension medications
C	Conventional therapy, in which all medications are ingested in the morning
O	Better blood pressure control and CV risk reduction

Methodology

Study design & Subjects

- Randomized, prospective, open-label, blinded endpoint trial occurred at a single center in Spain
  - Approved by the state Ethics Committee of Clinical Research.
  - All patients gave written informed consent.

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Methodology

Subjects:

- **Inclusion criteria**

  Spanish hypertensive patients with type 2 diabetes and > 17 years old

- **Exclusion Criteria**

  Pregnancy, drug or alcohol abuse, night or shift work, AIDS, type 1 diabetes, secondary hypertension, significant CV disease (unstable angina, heart failure, arrhythmia, nephropathy, or severe retinopathy), intolerance to ambulatory BP monitoring, or inability to follow procedures.

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Methodology

Subjects and diagnostic criteria

- The BP medications were chosen according to usual care practices.
- Hypertension was established by existing ABPM criteria: awake BP ≥ 135/85 mmHg or nocturnal BP ≥ 120/70 mmHg.
- Subjects received 48-hour ABPM at baseline, annually, or more frequently if the regimen was changed.
- All patients wore an actigraph to monitor their physical activity and correlate sleep-wake cycles with ABPM

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Methodology

Recruitment and Follow-up

- 448 Participant were randomized to ingest all their prescribed blood pressure–lowering medications upon awakening (232 patients) or ≥1 of them at bedtime (216 patients).
- There were no differences in the classes or number of anti-hypertensives used between the two groups.
- Median follow-up period was 5.4 years

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Methodology

Blindness

- Investigators were treatment blinded and reviewed the records annually for CV morbidity and mortality

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Outcomes

- **The Primary endpoint**
  - Total CVD morbidity and mortality including
    - MI, angina, coronary revascularization, heart failure, arterial occlusion of the lower extremities, thrombotic occlusion of the retinal artery, hemorrhagic stroke, ischemic stroke, and transient ischemic attack.
  - Major CVD events
    - Composite of CVD deaths, myocardial infarction, and stroke.

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Methodology

Statistical analysis

- Demographic and clinical characteristics were compared on an intention to- treat basis among groups of subjects randomized to the two treatment time groups by t test (quantitative variables) or nonparametric x2 test (proportions)

- Cox proportional-hazard model was developed to evaluate the effect of timing of drug administration and adjust for significant confounding variables.

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Methodology

- Event rates were expressed as the number per thousand patient-years and Kaplan-Meier survival curves were produced.
- BP responses as determined by ABPM were compared between the two groups.
- • Secondary analyses included individual components of the primary endpoint

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Results

	Awakening	Bedtime	P between groups
Demographic characteristics			
n	232	216	
Sex (% men)	59.1	54.6	0.345
Obstructive sleep apnea (%)	13.4	11.6	0.568
Metabolic syndrome (%)	86.6	86.6	0.984
Cigarette smoking (%)	8.6	7.9	0.773
Obesity (%)	66.8	64.8	0.656
Microalbuminuria (%)	28.0	26.9	0.782
Previous CVD events (%)	8.2	9.3	0.688
Duration of known diabetes (years)	8.9 ± 8.4	8.7 ± 8.0	0.804
Duration of known hypertension (years)	7.4 ± 8.2	7.6 ± 8.7	0.674
Anthropometric variables and clinic blood pressure			
Age (years)	62.5 ± 10.9	62.5 ± 10.7	0.935
Height (cm)	160.6 ± 9.2	159.3 ± 9.0	0.117
Weight (kg)	83.5 ± 16.9	81.1 ± 16.0	0.124
BMI (kg/m^2)		31.9 ± 5.2	0.631
Waist circumference (c		102.0 ± 11.6	0.442
Clinic SBP (mmHg)†		161.9 ± 22.2	0.085
Clinic DBP (mmHg)†		87.0 ± 12.3	0.303
Clinic PP (mmHg)†		74.9 ± 17.8	0.117
Clinic HR (bpm)†	75.6 ± 10.5	76.6 ± 13.7	0.391
Clinical laboratory test values			
HbA_{1c} (%)	6.9 ± 1.7	6.8 ± 1.7	0.627
Glucose (mg/dL)	157.2 ± 49.1	150.8 ± 51.2	0.178
Creatinine (mg/dL)	1.03 ± 0.25	1.01 ± 0.27	0.393
Uric acid (mg/dL)	6.1 ± 2.0	6.0 ± 1.6	0.271
Total cholesterol (mg/dL)	203.3 ± 45.7	202.7 ± 42.0	0.886
Triglycerides (mg/dL)	126.9 ± 63.2	120.6 ± 68.3	0.321
HDL cholesterol (mg/dL)	44.3 ± 13.6	46.6 ± 15.2	0.092
LDL cholesterol (mg/dL)	134.9 ± 38.1	131.7 ± 35.5	0.378
Fibrinogen (mg/dL)	357.7 ± 78.1	346.8 ± 88.3	0.265
Erythrocyte sedimentation rate (mm)	19.1 ± 16.8	17.6 ± 15.4	0.349
Glomerular filtration rate‡	71.0 ± 18.2	72.7 ± 17.1	0.206
Ambulatory blood pressure			
Duration of nocturnal rest (h)	9.2 ± 1.3	9.2 ± 1.2	0.902
Awake SBP mean (mmHg)	135.4 ± 17.9	135.9 ± 15.8	0.762
Asleep SBP mean (mmHg)	128.5 ± 21.7	129.2 ± 20.2	0.702
48-h SBP mean (mmHg)	133.2 ± 18.6	133.5 ± 16.5	0.837
Sleep time relative SBP decline (%)	5.2 ± 8.3	5.0 ± 8.7	0.779
Awake DBP mean (mmHg)	76.7 ± 11.0	77.3 ± 11.0	0.553
Asleep DBP mean (mmHg)	68.3 ± 11.4	69.3 ± 10.9	0.346
48-h DBP mean (mmHg)	73.9 ± 10.8	74.6 ± 10.6	0.538
Sleep time relative DBP decline (%)	10.7 ± 8.7	10.1 ± 8.9	0.432
Nondipper (%)	72.4	70.0	0.558

Data are means ± SD unless otherwise indicated. Metabolic syndrome is determined by the National Cho

NS results

Results

Outcomes

	Awakening	Bedtime	P between groups
n	232	216	
Primary end points*			
Total events	54.24 (68)	19.80 (23)	<0.001
Major events	17.55 (22)	5.16 (6)	<0.001
Secondary end points*			
Total death	6.38 (8)	2.58 (3)	0.097
Cardiovascular death	4.79 (6)	0.86 (1)	0.038
Other cause	1.60 (2)	1.72 (2)	0.968
Cardiovascular events	15.95 (20)	6.89 (8)	0.008
Cerebrovascular events	6.38 (8)	0.86 (1)	0.010
Heart failure	13.56 (17)	6.02 (7)	0.020
Other events	11.96 (15)	3.44 (4)	0.005

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Results

	Awakening	Bedtime	P between groups
Hypertension treatment			
Number of medications	2.6 ± 1.1	2.4 ± 1.2	0.145
1 Medication (%)	23.7	28.7	0.229
2 Medications (%)	15.9	19.4	0.332
≥3 Medications (%)	60.3	51.9	0.070
ARB (%)	63.4	67.1	0.403
ACEI (%)	27.2	20.4	0.159
Calcium channel blocker (%)	50.0	49.1	0.845
α-Blocker (%)	29.7	28.7	0.809
β-Blocker (%)	21.1	22.2	0.777
Diuretic (%)	63.4	56.5	0.137
Clinic and ambulatory blood pressure			
Clinic SBP (mmHg)†	150.3 ± 28.6	147.9 ± 21.3	0.309
Clinic DBP (mmHg)†	80.5 ± 16.3	78.6 ± 14.3	0.187
Clinic PP (mmHg)†	69.8 ± 18.2	69.3 ± 14.7	0.742
Clinic HR (bpm)†	73.6 ± 13.8	74.6 ± 14.2	0.453
Awake SBP mean (mmHg)	127.1 ± 17.8	126.8 ± 14.6	0.861
Asleep SBP mean (mmHg)	122.4 ± 21.8	115.0 ± 17.1	<0.001
48-h SBP mean (mmHg)	125.5 ± 18.3	122.8 ± 15.0	0.097
Sleep time relative SBP decline (%)	3.7 ± 10.3	9.4 ± 7.8	<0.001
Awake DBP mean (mmHg)	70.5 ± 10.8	71.0 ± 10.7	0.621
Asleep DBP mean (mmHg)	63.7 ± 11.3	60.2 ± 10.1	<0.001
48-h DBP mean (mmHg)	68.2 ± 10.4	67.4 ± 10.1	0.406
Sleep time relative DBP decline (%)	9.3 ± 11.4	14.9 ± 9.2	<0.001
Nondipper (%)	76.3	49.5	<0.001
Controlled ambulatory blood pressure (%)	50.9	62.5	0.013
Controlled awake blood pressure (%)	75.4	72.2	0.439
Controlled asleep blood pressure (%)	54.7	70.8	<0.001

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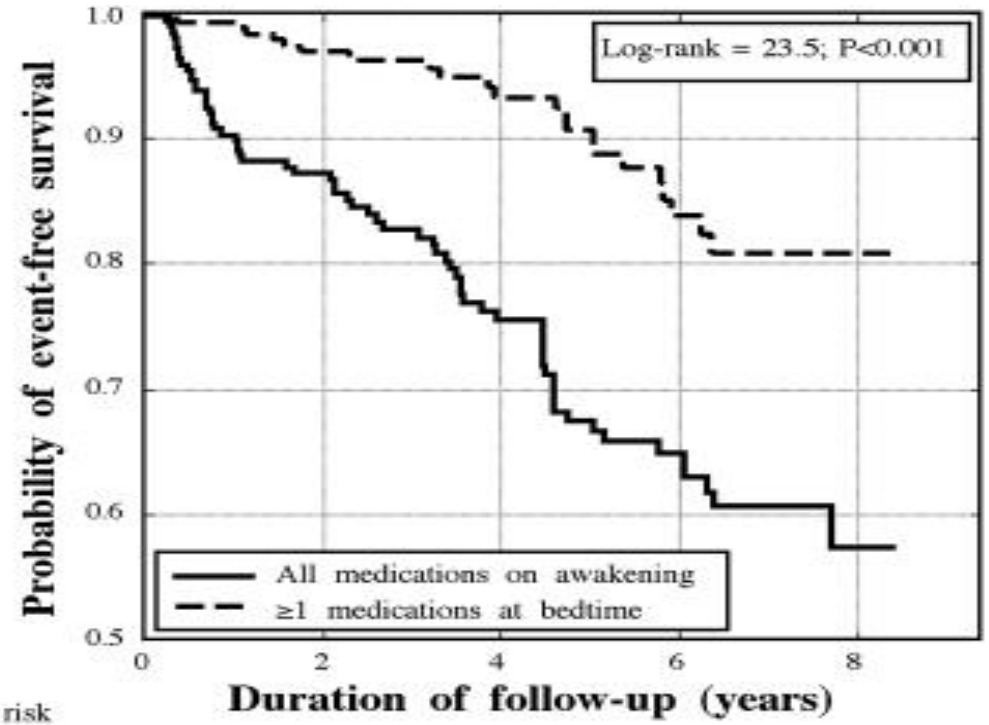
Results

CVD risk



No. at risk				
Awakening	232	198	119	76
Bedtime	216	206	124	77

Event-free survival was significantly higher in the bedtime (P <0.001).

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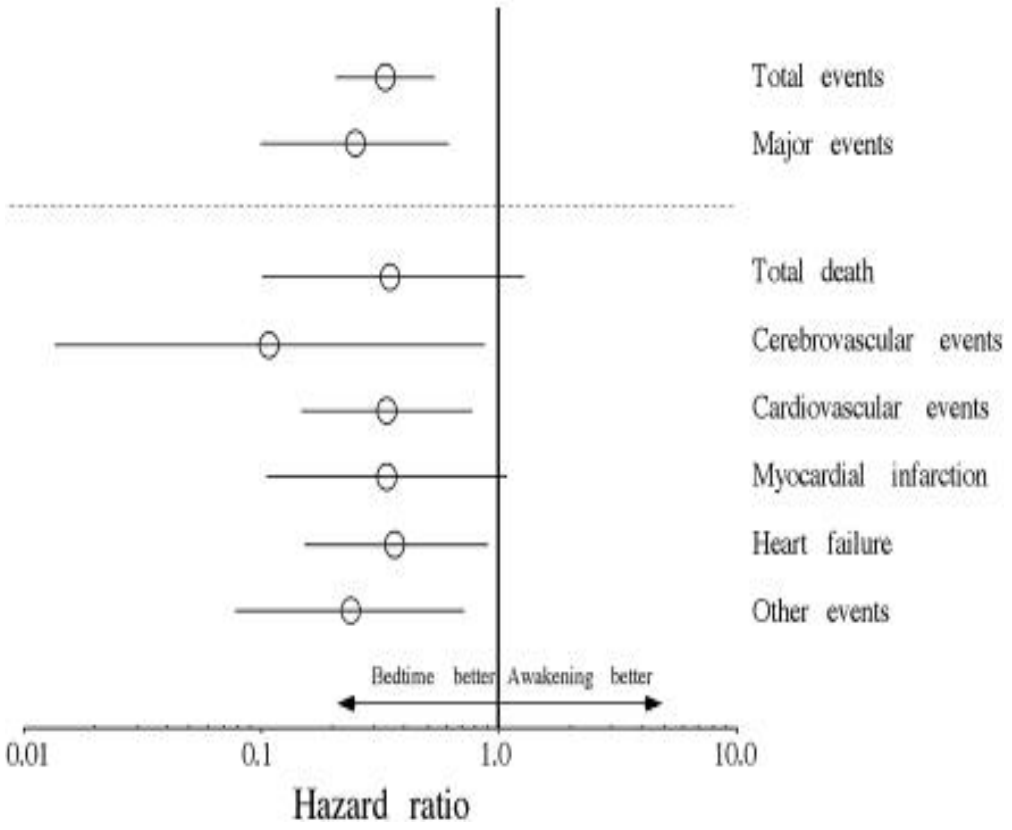
Results

CVD risk



Significantly lower risk in bedtime group:

- Total events (HR 0.33 [95% CI 0.21–0.54];
- Major CV events (HR 0.25, 95% CI 0.10 to 0.61).

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Conclusion

- For every 5 mmHg decrease in nocturnal BP there was a 12% reduction in CV risk.

- Bedtime administration of anti-hypertensives was associated with a significant decrease in CV disease in patients with type 2 diabetes and hypertension.

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External validity

- The subjects studied in this trial were from a single Spanish site.
- Their demographic characteristics are similar to those seen in many practices
- The results may be generalizable to all patient populations

Strength

- This trial had adequate power to detect relatively small differences in the primary outcome.
- All of the prespecified study and points were adjudicated by a blinded group of investigators.

Weakness

- Open label study, Randomization method is not clear
- BP treatments were not standardized.
- The study occurred at a single site in Spain.
- The investigators did not measure adverse events in this trial


THANK
YOU SO
MUCH!