

Does the bedtime dosing of antihypertensive medications decrease the risk of cardiovascular death in nonhospitalized adults with hypertension?

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CONTEXT

The known relationship between cardiovascular death and uncontrolled hypertension has led to further research to study blood pressures in ambulatory hypertensive patients. Multiple studies have shown that bedtime versus awakening dosing of antihypertensives have led to significantly improved ambulatory blood pressure control.

OBJECTIVE

Assess the evidence for bedtime compared to awakening dosing of antihypertensive medications for the primary endpoint of reducing cardiovascular mortality.

DESIGN

Evidence-based review.

PubMed search using keywords: “bedtime hypertension treatment” “timing of antihypertensives” “reduce cardiovascular death.” 18 articles were reviewed and narrowed to 3 RCTs.

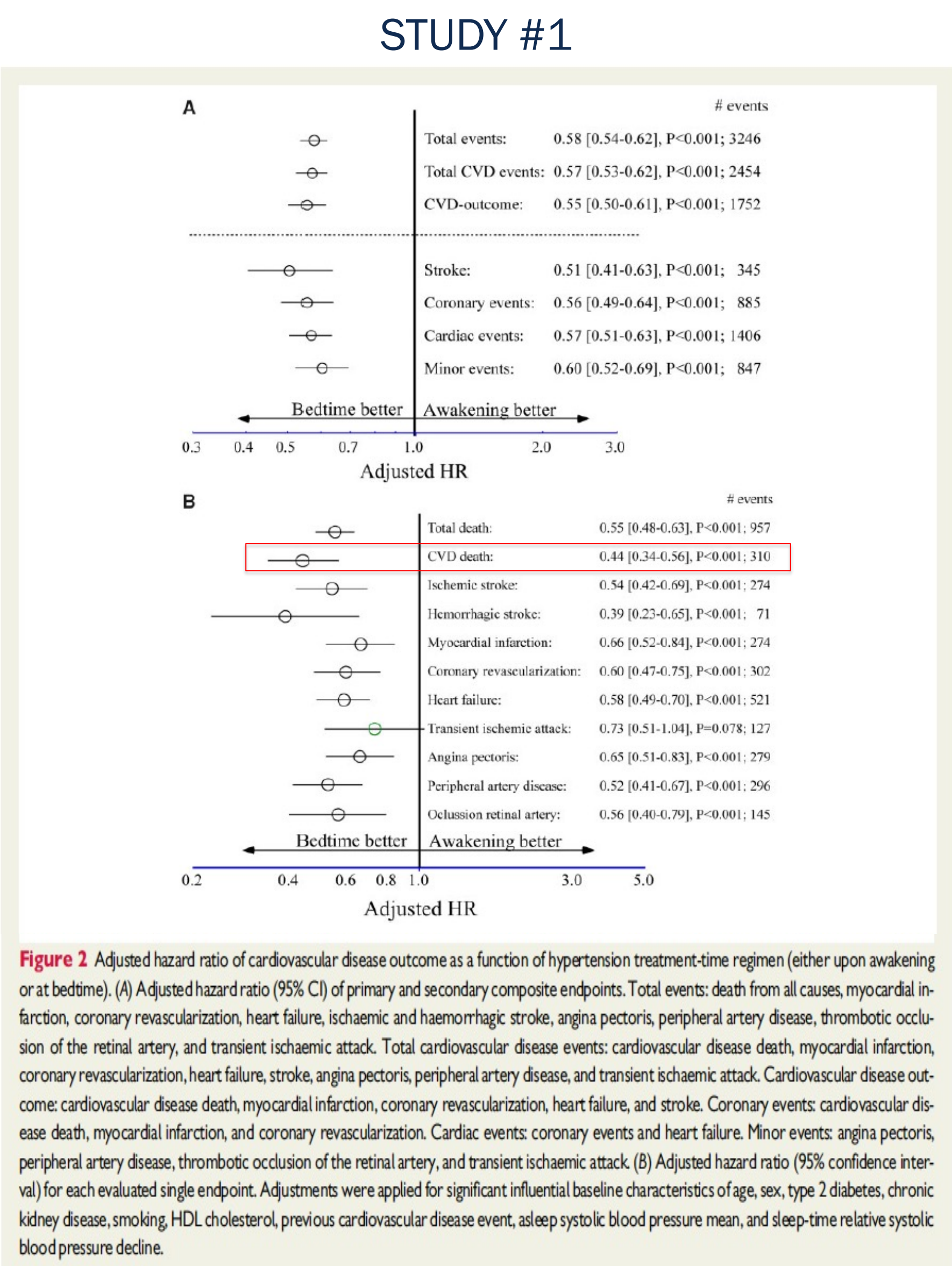
PATIENTS

21,688 Caucasian Spanish women and men aged ≥ 18 years of age with a diagnosis of hypertension according to ABP criteria.

EXCLUSION CRITERIA

Pregnancy, history of drug/alcohol abuse, shift work employment, diagnosis of acquired immunodeficiency syndrome (AIDS), type 1 diabetes, secondary hypertension, CVD disorders (primarily unstable angina pectoris, heart failure, life-threatening arrhythmia, nephropathy, and grade III–IV retinopathy), intolerance to ABPM measurement, and inability to communicate and comply with all of the study requirements

RESULT TABLES



STUDY #3

Table 2—Final characteristics of patients investigated according to treatment time (either all hypertension medications upon awakening or ≥1 medications at bedtime)

	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
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

Data are means ± SD. Event rates (95% CIs) are expressed as the number/1,000 patient-years, i.e., ratio of the observed number of events to the total number of patient-years of exposure. Total events include death (from all causes), cardiovascular events (myocardial infarction, angina pectoris, and coronary revascularization), cerebrovascular events (stroke and transient ischemic attack), heart failure, and other events (acute arterial occlusion of lower extremities and thrombotic occlusion of the retinal artery). Major events include cardiovascular deaths, myocardial infarction, ischemic stroke, and hemorrhagic stroke. Comparison of event rates between treatment time groups was done by the Mantel log-rank test. The sleep time relative blood pressure decline, an index of blood pressure dipping, is defined as the percent decline in mean blood pressure during nocturnal sleep relative to the mean blood pressure during daytime activity, and calculated as: [(awake blood pressure mean – asleep blood pressure mean)/awake blood pressure mean] × 100. HR, heart rate; Nondipper, patients with sleep time relative SBP decline <10% using data sampled by ABPM for 48 consecutive hours; PP, pulse pressure. *Number of events is shown in parentheses. †Values correspond to the average of six conventional blood pressure measurements obtained for each subject at the clinic before starting ABPM.

STUDY #2

TABLE 2 Final characteristics of patients investigated according to treatment-time (either all hypertension medications upon awakening or ≥1 medications at bedtime)

Variable*	Awakening	Bedtime	p between groups
Patients, n		1084	1072
Primary endpoints, events/1000 patient-yr (event-number in parenthesis)			
Total events	27.80 (187)	11.95 (68)	<.001
Total death	4.16 (28)	2.11 (12)	.008
Cardiovascular	2.08 (14)	0.55 (3)	.006
Other cause	2.08 (14)	1.58 (9)	.250
CVD events	11.00 (74)	5.27 (30)	<.001
Cerebrovascular events	3.57 (24)	1.23 (7)	.001
Heart failure	4.91 (33)	1.41 (8)	<.001
Other events	4.16 (28)	1.95 (11)	.004
Hypertension treatment			
Number of medications	2.1 ± 1.2	2.0 ± 1.4	.302
1 medication, %	43.4	43.0	.868
2 medications, %	16.3	15.9	.766
≥ 3 medications, %	40.3	41.1	.697
ARB, %	58.8	60.1	.535
ACEI, %	20.3	17.1	.055
CCB, %	38.1	40.6	.239
α-Blocker, %	16.1	17.2	.488
β-Blocker, %	22.7	20.0	.122
Diuretic, %	53.9	45.8	<.001
Clinic and ambulatory BP			
Clinic SBP, mm Hg†	144.4 ± 23.0	142.6 ± 20.1	.065
Clinic DBP, mm Hg†	81.4 ± 13.2	81.1 ± 12.1	.693
Clinic PP, mm Hg†	63.0 ± 16.2	61.5 ± 14.6	.024
Clinic HR, beats/min†	72.4 ± 13.0	73.0 ± 13.1	.345
Awake SBP mean, mm Hg	124.9 ± 15.1	125.3 ± 12.9	.546
Asleep SBP mean, mm Hg	116.1 ± 17.9	110.9 ± 13.9	<.001
48-h SBP mean, mm Hg	122.1 ± 15.1	120.8 ± 12.6	.029
Sleep-time relative SBP decline, %	7.0 ± 9.1	11.4 ± 7.3	<.001
Awake DBP mean, mm Hg	74.7 ± 10.4	75.9 ± 10.2	.005
Asleep DBP mean, mm Hg	65.2 ± 10.4	63.1 ± 9.4	<.001
48-h DBP mean, mm Hg	71.6 ± 9.8	71.9 ± 9.5	.475
Sleep-time relative DBP decline, %	12.3 ± 10.7	16.6 ± 8.7	<.001
Non-dipper, %	61.6	34.4	<.001
Controlled ambulatory BP, %	52.8	62.2	<.001
Changes in clinic and ambulatory BP from baseline			
Clinic SBP, mm Hg	−10.0 ± 17.7	−13.1 ± 19.7	<.001
Clinic DBP, mm Hg	−6.0 ± 10.7	−7.4 ± 10.8	.004
Clinic PP, mm Hg	−4.0 ± 11.2	−5.7 ± 12.2	.001
Clinic HR, beats/min	−1.6 ± 10.6	−1.9 ± 11.1	.410
Awake SBP mean, mm Hg	−9.4 ± 13.3	−8.9 ± 13.4	.401
Asleep SBP mean, mm Hg	−6.6 ± 12.5	−11.8 ± 13.2	<.001
48-h SBP mean, mm Hg	−8.6 ± 12.8	−9.7 ± 12.5	.028
Sleep-time relative SBP decline, %	−1.5 ± 6.7	2.9 ± 7.4	<.001
Awake DBP mean, mm Hg	−7.2 ± 8.5	−6.5 ± 8.9	.035
Asleep DBP mean, mm Hg	−5.2 ± 8.3	−7.9 ± 8.5	<.001
48-h DBP mean, mm Hg	−6.6 ± 7.9	−6.8 ± 8.1	.534
Sleep-time relative DBP decline, %	−1.4 ± 7.8	3.1 ± 8.3	<.001

*CVD events include myocardial infarction, angina pectoris, and coronary revascularization. Cerebrovascular events include hemorrhagic stroke, ischemic stroke, and transient ischemic attack. Other events include acute arterial occlusion of the lower extremities, rupture of aortic aneurisms, and thrombotic occlusion of the retinal artery. Comparison of event rates between groups was done by the Mantel log-rank test. The sleep-time relative BP decline, an index of BP dipping, is defined as the percent decline in mean BP during the hours of nocturnal sleep relative to the mean BP during the hours of diurnal activity, and calculated as: [(awake BP mean – asleep BP mean)/awake BP mean] × 100. Non-dipper: patients with sleep-time relative SBP decline <10%, using data sampled by ABPM for 48 consecutive hours.

†Note. Values are shown as mean ± SD.

‡Values correspond to the average of six conventional BP measurements obtained for each subject at the clinic before starting ABPM.

OVERVIEW

Author	NNT	p-Value
Hermida et al. 2020 (Study 1)	No NNT, HR 0.44	p<0.001
Hermida et al. 2010 (Study 2)	98.97	p=0.006
Hermida et al. 2011 (Study 3)	47.1	p=0.038

VALIDITY

Author	Randomized	Concealed Randomization	Intention to treat	Equal Baseline Characteristics	Equal Treatment	Blinded?	Follow-up Complete?	Result
Hermida et al. 2020 (Study 1)	Yes	No	Yes	Yes	Yes	Blinded end point	Yes	Statistically Significant
Hermida et al. 2010 (Study 2)	Yes	No	Yes	Yes	Yes	Blinded end point	Yes	Statistically Significant
Hermida et al. 2011 (Study 3)	Yes	No	Yes	Yes	Yes	Blinded end point	Yes	Statistically Significant

CONCLUSION

In nonhospitalized adult patients with uncomplicated hypertension who took antihypertensive medications at bedtime, the incidence of cardiovascular death was decreased.

Clinical Recommendation	SOR	Reference
Bedtime dosing of antihypertensive medications decreases the risk of cardiovascular death in nonhospitalized adults with hypertension.	B	Article 1: (Hermida 2020), Article 2 (Hermida 2010), Article 3 (Hermida 2011)

DISCUSSION

There are questions about the validity of the Hygia trial and the randomization of the study participants. There are also concerns about the large patient population coming from the compilation of smaller studies going on concurrently with the Hermida research group and not a single, large study design.

Journal Ethics Committee of the European Society of Cardiology found no evidence of misconduct in December 2020 but not all dissenting parties are convinced by their investigation findings.

There are two RCTs (TIME & BedMed) underway in the UK and Canada, respectively, that have the potential to change the strength of recommendation.

REFERENCES

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- Hermida, Ramón C., et al. “Influence of Circadian Time of Hypertension Treatment on Cardiovascular Risk: Results of the MAPEC Study.” Chronobiology International, vol. 27, no. 8, 2010, pp. 1629–1651., <https://doi.org/10.3109/07420528.2010.510230>.
- Hermida, Ramón C., et al. “Influence of Time of Day of Blood Pressure—Lowering Treatment on Cardiovascular Risk in Hypertensive Patients with Type 2 Diabetes.” Diabetes Care, vol. 34, no. 6, 2011, pp. 1270–1276., <https://doi.org/10.2337/dc11-0297>.