ONLINE EXCLUSIVE

Q/ Does taking BP medicine at night (vs morning) result in fewer cardiovascular events?

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EVIDENCE-BASED ANSWER

A/ **PROBABLY NOT.** In patients who have hypertension, the timing of administration of antihypertensive medications does not appear to impact cardiovascular outcomes (strength of recommendation: **B**; contradictory randomized controlled trials).

Evidence summary

Recent UK study shows no difference by timing

A 2022 UK prospective, randomized, multicenter trial assigned 21,104 predominantly White adults (58% men) with hypertension to take their usual antihypertensive medication either in the morning (6 AM to 10 AM) or evening (8 PM to midnight).[1] A computer algorithm randomized patients, but neither the patients nor the investigators were masked to allocation.

All patient baseline characteristics were equivalent between groups. If troubled by nocturia, patients in the evening group taking diuretics were told to take only the diuretic earlier (6 PM) and subsequently to change to morning if they experienced persistent bothersome symptoms. More patients in the evening administration group than in the morning administration group reported having to change the time of day that they took their diuretic (546 [5.2%] vs 71 [0.7%]; $P < .0001$).

The median follow-up was 5.2 years. Data were collected at regular intervals through patient completion of online questionnaires and researcher analysis of National Health Service data on hospitalization and death. The intention-to-treat analysis showed no difference in the primary outcome (a composite of vascular death, nonfatal myocardial infarction, or nonfatal stroke) between the evening and morning administration groups (0.69 events vs 0.72 events per 100 person-years; hazard ratio [HR] = 0.95; 95% CI, 0.83-1.10; $P = .53$).

The controversial Hygia Project favored evening

Prior to the UK study was the Hygia Chronotherapy Trial, a prospective, controlled, multicenter study conducted within the primary care setting in Spain. Caucasian Spanish adults (N = 19,168; mean age, 61 years; 56% men) with hypertension were randomly assigned to take all prescribed antihypertensive medication either at bedtime or upon waking.[2]

The Hygia Project initially sought to establish the value of ambulatory blood pressure monitoring (ABPM) compared to office blood pressure (BP) monitoring and to explore the prognostic value of sleeping BP.[3] The study objectives evolved over time. The randomization process was not clearly described,[2,3] but multiple randomizations were alluded to. The authors stated that "for any of these chronotherapy trials" randomizations were done separately for "each participating center" and "randomization of participants to treatment-time regimen is done separately

A 2022 UK multicenter trial found no difference between the evening and morning administration groups in a composite outcome of vascular death, nonfatal myocardial infarction, or nonfatal stroke.

for each hypertension medication or combination being tested."

The baseline characteristics of patients in the evening and morning administration groups were similar, but statistically significant differences existed in BMI (29.6 vs 29.7; $P = .030$) and sleep-time systolic BP percent decline (9.3 vs 9.0; $P < .001$). Mean baseline 48-hour BP was 132/77 mm Hg. Hypertension was defined as an awake systolic BP ≥ 135 mm Hg or diastolic BP ≥ 85 mm Hg, or asleep systolic BP ≥ 120 mm Hg or diastolic BP ≥ 70 mm Hg. BP readings were confirmed with 48-hour ABPM. Exclusion criteria included pregnancy, a history of substance use disorder, night-shift work, and cardiovascular disease (defined as unstable angina, heart failure, life-threatening arrhythmia, atrial fibrillation, kidney failure, and grade III-IV retinopathy).

Prescribers were free to prescribe medicines from 5 classes (diuretic, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or beta-blocker) as they thought appropriate, were encouraged to use fixed-dose combination pills, and were told not to use split (eg, twice per day) dosing. Annual 48-hour ABPM was completed, and patients' electronic health records were analyzed by blinded investigators. Median follow-up was 6.3 years, and only 84 participants failed to complete the minimum 1-year participation requirement.

The primary outcome—a composite of cardiovascular death, myocardial infarction, coronary revascularization, heart failure, or stroke—occurred in 1752 patients, favoring the bedtime group (HR = 0.55; 95% CI, 0.50-0.61; $P < .001$). The calculated number of events was 1130 in the morning administration group and 622 in the evening administration group; the authors did not explicitly report the event numbers in each group. Each component of the composite outcome also favored evening administration ($P < .001$ for all): cardiovascular death (HR = 0.44; 95% CI, 0.34-0.56), myocardial infarction (HR = 0.66; 95% CI, 0.52-0.84), coronary revascularization (HR = 0.60; 95% CI, 0.47-0.75), heart failure (HR = 0.58; 95% CI, 0.49-0.70), and stroke (HR = 0.51; 95% CI, 0.41-0.63).

The complicated, layered study design and randomization methods limit the ability to critically appraise the study.

Smaller Spanish study also supported evening administration

A prior, smaller, prospective randomized trial conducted by the same researchers as the Hygia Project found even greater benefits to evening BP medication administration.[4] The 2156 Spanish patients (52% men; average age, 55 years) from multiple primary care offices were randomized 1:1 to BP medication administration either upon awakening or at bedtime. Dozens of baseline characteristics were evenly distributed except for age (55.0 vs 56.3; $P = .021$) and creatinine (0.96 vs 0.98; $P = .028$), both of which were lower in the evening group.

After a median follow-up of 5.6 years, the bedtime group had significantly lower total events (187 events in the morning group vs 68 in the evening group; relative risk [RR] = 0.39; 95% CI, 0.29-0.51; $P < .001$). Individual cardiovascular outcomes also dramatically favored the evening group: total deaths (12 vs 28; $P = .008$), cardiovascular deaths (3 vs 14; $P = .006$), cardiovascular disease events (30 vs 74; $P < .001$), stroke (7 vs 24; $P = .001$), and heart failure (8 vs 33; $P < .001$).

Limits of both the UK trial and the Hygia Project trial included single countries of study with a lack of racial and ethnic diversity, and greater nonadherence to the evening administration of the medications.

Recommendations from others

A 2022 consensus statement from the International Society of Hypertension, published before the UK trial, recommended against bedtime dosing until more high-quality data became available. They pointed to evidence showing higher medication adherence with morning dosing, risk for asleep BP dropping, and worsening daytime BP control as reasons to continue morning administration.[5] Other reviewers have questioned the Hygia Project results due to their reported implausibly large effects on cardiovascular outcomes, noting that independent attempts to verify the methods and the data have proven challenging and are not completed.[6]

Editor's takeaway

I confess that I was swayed by the results of the Hygia Project; for a year or so, I advised my patients to take at least 1 BP pill at night. But after the UK study came out, I needed to reconsider. I began to worry that the great outcomes of nocturnal therapy may have been a mirage. I have returned to counseling patients to take their BP medications in whichever way fosters consistency while minimizing adverse effects for them. **JFP**

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