JAMA | Original Investigation

Antihypertensive Medication Timing and Cardiovascular Events and Death
The BedMed Randomized Clinical Trial

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IMPORTANCE Whether administration of blood pressure medications at bedtime instead of in the morning reduces cardiovascular risk is unknown, as findings from large clinical trials have not been consistent. There is also concern that bedtime antihypertensive use could induce glaucoma-related visual loss or other hypotensive/ischemic adverse effects.

OBJECTIVE To determine the effect of bedtime vs morning administration of antihypertensive medications on major cardiovascular events and death.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, open-label, pragmatic randomized clinical trial with blinded end-point assessment and recruitment via 436 primary care clinicians across 5 Canadian provinces inviting their community-dwelling adult patients with hypertension taking at least 1 once-daily antihypertensive medication. Participants were recruited from March 31, 2017, to May 26, 2022, with final follow-up on December 22, 2023.

INTERVENTIONS Participants were randomized in a 1:1 ratio to using all once-daily antihypertensive medications either at bedtime (intervention group; n = 1677) or in the morning (control group; n = 1680).

MAIN OUTCOMES AND MEASURES The primary outcome was time to first occurrence of all-cause death or hospitalization/emergency department (ED) visit for stroke, acute coronary syndrome, or heart failure. All-cause unplanned hospitalizations/ED visits, and visual, cognitive, and fall- and/or fracture-related safety outcomes were also assessed.

RESULTS A total of 3357 adults (56.4% female; median age, 67 years; 53.7% taking monotherapy) were randomized and followed up for a median of 4.6 years in each treatment group. The composite primary outcome event occurred at a rate of 2.3 per 100 patient-years in the bedtime group and 2.4 per 100 patient-years in the morning group (adjusted hazard ratio, 0.96; 95% CI, 0.77-1.19; *P* = .70). Individual components of the primary outcome, all-cause hospitalizations/ED visits, and safety outcomes did not differ between groups. In particular, there was no difference in falls or fractures, new glaucoma diagnoses, or 18-month cognitive decline.

CONCLUSIONS AND RELEVANCE Among adults with hypertension in primary care, bedtime administration of antihypertensive medications was safe but did not reduce cardiovascular risk. Antihypertensive medication administration time did not affect the risks and benefits of blood pressure–lowering medication and instead should be guided by patient preferences.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02990663

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JAMA. doi:10.1001/jama.2025.4390
Published online May 12, 2025.

Normal blood pressure (BP) exhibits circadian modulation, being lower during sleep,[1,2] and sleep-time BP is a better predictor of adverse cardiovascular events than is BP measured during the day.[3-5] Conceivably, high BP might convey greater cardiovascular risk at night because daytime and sleep-time metabolic states are different.[6-8] Given that antihypertensive medications might preferentially lower overnight BP if administered at bedtime,[9] administration time might influence the degree of cardiovascular risk reduction these medications convey. Three large randomized clinical trials (RCTs) have compared bedtime vs morning antihypertensive use, but their findings have not been consistent.[10-12]

The MAPEC trial was conducted from 2000 to 2009, enrolling 2156 adults with hypertension referred to a specialty clinic for ambulatory BP monitoring (ABPM), and reported a 61% reduction in major adverse cardiovascular events favoring bedtime medication administration.[10] The same investigators later conducted the Hygia trial from 2008 to 2018, enrolling 19 084 adults with hypertension in primary care, and reported a 45% reduction in major adverse cardiovascular events favoring bedtime medication administration.[11] These results were controversial in the hypertension management community and motivated calls for independent confirmation before widespread adoption of bedtime medication administration.[13-18] A third study, the TIME trial, was conducted from 2011 to 2021, enrolling 21 104 adults with hypertension, and reported no benefit from bedtime medication administration,[12] null findings that were attributed to poor adherence and a low-risk population.[19]

To better understand whether administration of BP medications at bedtime instead of in the morning reduces cardiovascular risk, we conducted the BedMed antihypertensive timing trial.[20] BedMed randomized community-dwelling Canadian adults with hypertension in primary care to bedtime vs morning administration of all once-daily antihypertensive medications and examined differences in mortality and cardiovascular morbidity. The trial focused solely on the effect of antihypertensive administration time, not on BP control.

Key Points

Question Does bedtime administration of blood pressure–lowering medication, compared with conventional morning use, reduce a composite of death or major cardiovascular events?

Findings In this randomized trial of 3357 Canadian primary care patients with hypertension followed up for a median of 4.6 years, bedtime administration of antihypertensive medications had no effect on death or major cardiovascular events (2.3 per 100 patient-years vs 2.4 per 100 patient-years with morning antihypertensive use; adjusted hazard ratio, 0.96). There was no difference in visual, cognitive, or fall- and/or fracture-related safety outcomes.

Meaning Among adults with hypertension in primary care, bedtime administration of antihypertensive medications was safe but did not reduce cardiovascular risk.

Methods

Trial Design and Organization

BedMed used a parallel PROBE design (prospective, randomized, open, blinded end-point assessment),[21] with participants randomized to morning vs bedtime use of all once-daily antihypertensive medications. A detailed trial protocol and statistical analysis plan have been published.[20] The trial protocol is available in Supplement 1 and the statistical analysis plan in Supplement 2. The trial ran to completion, recruiting from March 31, 2017, to May 26, 2022, and observing until December 22, 2023. Participants were recruited through 436 primary care clinicians (429 family physicians and 7 nurse practitioners) in 5 Canadian provinces (eFigure 1 in Supplement 3). Funding was public via the Canadian Institutes of Health Research and Alberta Innovates. Ethical approval was obtained in each participating province, and all participants provided informed consent, either in writing or electronically (via 2-factor authenticated REDCap[22] email survey), after telephone discussion with a BedMed research assistant. Trial oversight was conducted by the Pragmatic Trials Collaborative at the University of Alberta in Edmonton (http://pragmatictrials.ca). The trial followed Consolidated Standards of Reporting Trials (CONSORT) guidelines.[23] BedMed has approval from 7 university ethics boards, including University of Alberta (Pro00045958), University of Calgary (REB17-1887), University of Manitoba (HS20852 [B2017:08]), University of British Columbia (H21-00523), University of Saskatchewan (1421), University of Toronto (00038892), and McMaster University (13092).

Participants

We included adults (≥18 years) diagnosed with hypertension and taking 1 or more once-daily BP-lowering medication. Additional BP medications used more than once daily were allowed to avoid excluding more medically complex individuals (eg, those with heart disease). All antihypertensive medications were eligible, including diuretics, despite initial concern that bedtime diuretic-induced nocturia might worsen adherence. While we did carry out a predefined interim assessment of 6-month adherence to bedtime diuretic use in participants taking monotherapy in order to exclude future enrollment of those using diuretics if adherence was inadequate,[20] no changes were thought to be necessary (three-fourths of participants being adherent to bedtime use).[24] We excluded only those with sleep-disrupting shift work, those with glaucoma (given that nocturnal hypotension is associated with optic neuropathy/worsening vision in patients with glaucoma),[25-27] and those living in continuing care facilities. To improve generalizability, we gathered self-reported race and ethnicity according to fixed categories.

Setting

Most recruitment (76.5%) occurred via primary care clinicians mailing letters of invitation to all of their patients with

hypertension. A social media campaign augmented recruitment (see video at https://www.youtube.com/watch?v=uhuyxErXkYY), and some participants heard about the trial through word of mouth or media reporting (for recruitment breakdown, see eTable 1 in Supplement 3).

Intervention

Participants were centrally randomized 1:1 to taking all once-daily antihypertensives at bedtime, vs morning, using permuted blocks (random block sizes of 10 or 12, stratified by province of residence). Allocation was received directly from a research assistant with no preceding clinical interactions, ensuring irreversible and concealed allocation.

Either primary care clinicians or research assistants (participant's choice) talked participants through timing changes, with research assistants recommending 1 timing change per week until all once-daily antihypertensives were per allocation. The bedtime group took BP medication when readying for bed; the morning group took BP medication on arising. If participants proved intolerant of bedtime use, dinnertime use was encouraged, rather than reverting back to morning use. Similarly, for participants intolerant of morning use, lunchtime use was requested. Follow-up telephone interviews at 1 week, 6 weeks, 6 months, and every 6 months encouraged and assessed adherence to allocation time. Excepting the 18-month Short Blessed Test (an assessment of cognitive function),[28-30] participants could instead opt for 6-monthly email surveys (for follow-up breakdown, see eTable 2 in Supplement 3). If participants reported a new glaucoma diagnosis, morning antihypertensive use was advised, regardless of allocation (n = 43 in the bedtime group).

Outcomes

Primary Outcome

The primary outcome was time to occurrence of a composite of death and major cardiovascular events, defined as first occurrence of either all-cause death or a hospitalization/emergency department visit for acute coronary syndrome, stroke, or heart failure. All-cause mortality was chosen over cardiovascular mortality given difficulty in clearly distinguishing cardiovascular and noncardiovascular death and given that MAPEC and Hygia both reported large reductions in all-cause death.

Secondary Outcomes

Secondary outcomes were cognitive decline at 18 months (≥2-point worsening from baseline on the Short Blessed Test) and time to occurrence of (1) each primary outcome component, (2) all-cause unplanned hospitalization/emergency department visit, (3) nursing home admission, (4) nonvertebral fracture, and (5) new glaucoma diagnosis.

Other safety outcomes included self-reported worsening of vision ("much worse" than last follow-up at any point or "slightly worse" than last follow-up on ≥2 occasions), new impairment consistent with dementia (18-month Short Blessed Test score newly ≥10 or new dementia diagnosis in administrative health data), self-reported light-headedness (prior month), self-reported fainting (prior month), self-reported falling (prior month), time to hip fracture, and nocturia (already reported[24]). We also examined 12-month EuroQol 5-Level 5-Dimension (EQ-5D-5L) overall health scores. Some secondary outcomes were altered from their initial protocol/trial registry descriptions. This occurred while investigators were fully blinded to all outcomes (see rationale in eAppendix Section 5 in Supplement 3).

Finally, adherence to allocation time was self-reported and measured at the medication level. It reflects the stated time medications were ingested, not an assessment of missed/forgotten doses. Participants could be adherent for one antihypertensive and not adherent for another.

Outcomes were collected in duplicate, via both self-report and linked administrative health data available for 92.6% of participants (*International Classification of Diseases, Ninth Revision/International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes) (eAppendix Section 2 in Supplement 3). Of the 7.4% without administrative data, 90.3% resided in Ontario or Saskatchewan, whose privacy laws prevented patient-level data crossing provincial borders. A blinded 3-physician adjudication committee reviewed outcomes from both sources and requested information from primary care clinicians when data were discordant (eg, differing diagnoses or reporting from only 1 data source). Adjudication rules and proportions of outcomes disallowed are provided in eAppendix Section 3 in Supplement 3.

Sample Size

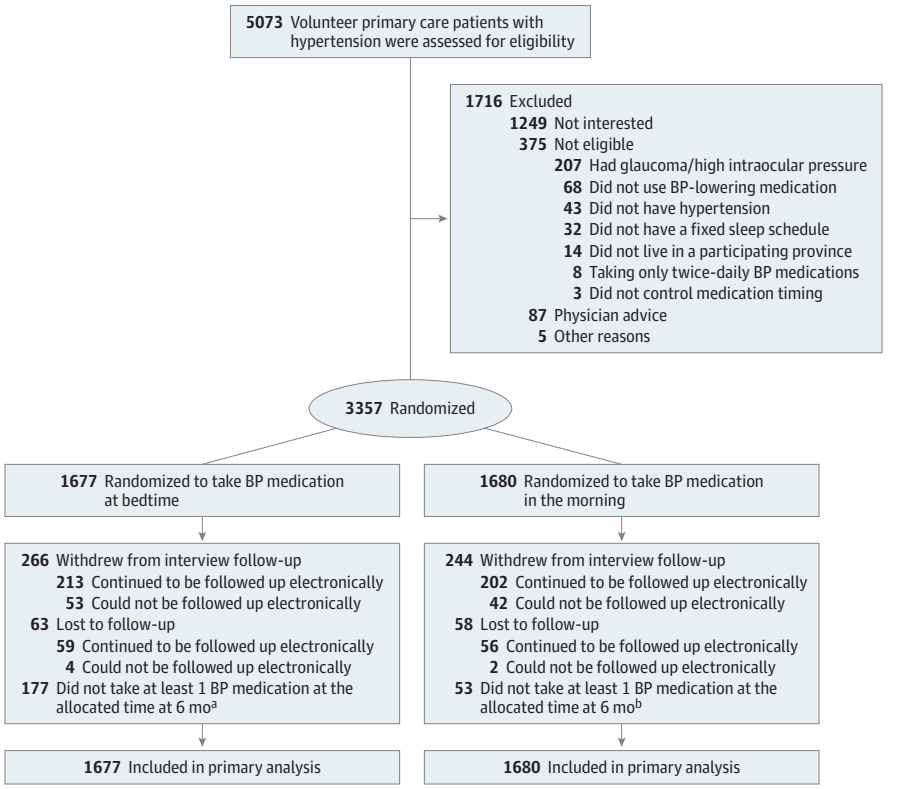
BedMed was designed to be event driven and to detect or exclude a 25% reduction (hazard ratio ≤0.75) in the primary outcome with a probability (power) of 0.8. For a time-to-event survival analysis with 1:1 allocation and type I error probability of .05, this required 379 events. We increased this by 7% to a target of 406 primary outcome events to account for withdrawals and loss to follow-up, projected to be 5%. We powered for differences we believed feasible to detect, not for a minimum clinically important difference, given that even small differences in death and major cardiovascular events are likely important to patients.

Interim Analysis

A 5-member independent data and safety monitoring board reviewed the only interim analysis on May 18, 2022 (n = 155 primary outcomes; all outcomes analyzed). They met again on October 28, 2022, to discuss the newly published TIME trial[12] and whether the TIME findings would change their previous recommendation. The committee was directed to consider a recommendation for early stopping if $P \leq .001$ in support of a primary outcome benefit or if $P \leq .05$ in the direction of harm for any outcome. Recommendations to continue the trial were made on each occasion.

Investigators were fully blinded to all but aggregated data throughout the trial, excepting adherence to allocation and 24-hour ambulatory BP, knowledge of which helped ensure adequate implementation of the timing intervention. The trial stopped early solely due to funding constraints.

Figure 1. Participant Flow in the BedMed Trial



BP indicates blood pressure.
[a]Among 1518 respondents.
[b]Among 1567 respondents.

Statistical Analysis

The primary outcome was analyzed in the intention-to-treat (as-randomized) population using Cox proportional hazards survival analysis. Most other outcomes used Cox proportional hazards or Poisson regression. Secondary survival analyses were also by intention to treat, while other analyses included only individuals with available data. We did not impute missing values. Hypothesis testing was 2-sided with a $P < .05$ significance threshold.

If participants were lost to all follow-up, survival analyses were censored on the last date of telephone/email contact. If participants were dropped from active follow-up but remained trackable through administrative health data, they were censored on the last date of health care contact according to administrative health records (ie, last date among hospitalizations, emergency department visits, physician visits, prescription dispensations, continuing care admissions, or laboratory blood tests).

Post hoc, we carried out a per-protocol sensitivity analysis of participants with higher adherence to allocation timing by excluding those with a β-blocker or diuretic at baseline (the medication classes with poorest adherence); participants with diuretic-nondiuretic combination agents, whose adherence was higher, were not excluded.

Analysis was done using SAS version 9.4 (SAS Institute Inc) and R version 4.3.2 (R Foundation).

Results

Trial Participants

Of 5073 screened individuals, 3357 were randomized to bedtime (n = 1677) vs morning (n = 1680) antihypertensive use (**Figure 1**). Baseline characteristics were well balanced (**Table 1**; see expanded baseline characteristics in eTable 3 in Supplement 3). Overall, participants were 56% female and a median of 67 years old; 18% had diabetes, 11% had known coronary artery disease, and 7% had chronic kidney disease. Roughly half of participants were taking monotherapy, and antihypertensive medications included angiotensin-converting enzyme inhibitors (36%), angiotensin receptor blockers (30%), calcium channel blockers (29%), diuretics (27%), combination pills (18%), β-blockers (17%), and other agents (1%). Specific drugs are listed in eFigure 2 in Supplement 3.

Among 3357 participants, over a median of 4.6 years, 101 (3.0%) withdrew or were lost to all follow-up, including 57 of 1677 (3.4%) in the bedtime group vs 44 of 1680 (2.6%) in the morning group. An additional 530 of 3357 (15.8%) withdrew or were lost to active follow-up but continued to be tracked using administrative health data, including 272 of 1677 (16.2%) in the bedtime group and 258 of 1680 (15.4%) in the morning group (for dropouts over time, see

Table 1. Baseline Participant Characteristics

Characteristics	Antihypertensive medication timing	
	Bedtime (n = 1677)	Morning (n = 1680)
Age, median (IQR), y	67 (60-73)	67 (61-73)
Aged ≥75 y, No. (%)	370 (22.1)	369 (22.0)
Sex, No. (%)		
Female	950 (56.6)	943 (56.1)
Male	727 (43.4)	737 (43.9)
Race and ethnicity, No. (%)[a]		
Asian	42 (2.5)	34 (2.0)
Black	7 (0.4)	7 (0.4)
Hispanic or Latino	5 (0.3)	4 (0.2)
Indigenous	29 (1.7)	22 (1.3)
Southeast Asian/Indian	17 (1.0)	20 (1.2)
White	1565 (93.3)	1587 (94.5)
More than 1 race	9 (0.5)	5 (0.3)
Declined to answer	3 (0.2)	1 (<0.1)
Province, No. (%)		
Alberta	1200 (71.5)	1200 (71.4)
British Columbia	235 (14.0)	236 (14.0)
Manitoba	130 (7.8)	131 (7.8)
Ontario	74 (4.4)	75 (4.5)
Saskatchewan	38 (2.3)	38 (2.3)
Chronotype, No. (%)[b]		
Early bird	881 (52.5)	859 (51.1)
Night owl	477 (28.5)	495 (29.5)
Neither	319 (19.0)	326 (19.4)
Current smoking, No. (%)	122 (7.3)	121 (7.2)
No. of exercise days per week, median (IQR)[c]	3 (0-5)	3 (0-5)
Never exercises, No. (%)[c]	434 (25.9)	458 (27.3)
Body mass index, median (IQR)[d]	28.8 (25.7-33.0)	28.9 (25.7-32.9)
Physically frail, No. (%)[e]	299 (17.8)	307 (18.3)
EQ-5D-5L overall health score, median (IQR)[f]	80 (70-90)	80 (75-90)
Short Blessed Test score (degree of cognitive impairment), No. (%)[g]		
≤3	1376 (82.1)	1403 (83.5)
4-6	248 (14.8)	224 (13.3)
7-9	33 (2)	29 (1.7)
≥10	19 (1.1)	23 (1.4)
Declined to answer	1 (<0.1)	1 (<0.1)
Comorbidities, No. (%)		
Sleep apnea	377 (22.5)	341 (20.3)
Diabetes	289 (17.2)	311 (18.5)
Coronary artery disease	172 (10.3)	188 (11.2)

(continued)

Table 1. Baseline Participant Characteristics (continued)

Characteristics	Antihypertensive medication timing	
	Bedtime (n = 1677)	Morning (n = 1680)
Chronic kidney disease	119 (7.1)	129 (7.7)
Chronic obstructive pulmonary disease	86 (5.1)	80 (4.8)
Stroke	75 (4.5)	75 (4.5)
Heart failure	28 (1.7)	32 (1.9)
Hip fracture	22 (1.3)	27 (1.6)
None of the above	876 (52.2)	877 (52.2)
No. of blood pressure medications, No. (%)		
1	895 (53.4)	908 (54.0)
2	588 (35.1)	577 (34.3)
3	155 (9.2)	170 (10.1)
≥4	39 (2.3)	25 (1.5)
Type of blood pressure medications, No. (%)		
Angiotensin-converting enzyme inhibitor	584 (34.8)	631 (37.6)
Angiotensin receptor blocker	536 (32)	471 (28)
Calcium channel blocker	479 (28.2)	489 (29.1)
Diuretic	446 (26.6)	472 (28.1)
Combination pill	315 (18.8)	300 (17.9)
β-Blocker	289 (17.2)	278 (16.5)
Other class	26 (1.6)	21 (1.3)

[a] Race and ethnicity were self-selected by participants from the list provided in this table.

[b] Chronotype is the time of day that people are more alert and/or active. Participants were asked "Would you say you are naturally a night owl or an early bird?"

[c] Participants were asked "How many days in the past week have you exercised for 30 minutes or more, vigorously enough to raise your breathing rate?" Participants were considered to never exercise if they answered 0 minutes.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] Determined by the physical frailty subscale of the Tilburg Frailty Indicator. Potential scores range from 0 (least physically frail) to 8 (most physically frail). Subscale scores ≥3 indicate physically frail.

[f] Self-reported quality of life via the EuroQol 5-Level 5-Dimension (EQ-5D-5L) measure. Higher scores indicate higher quality of life (score range, 0-100).

[g] The Short Blessed Test is a weighted 6-item test of cognitive impairment. Scores range from 0 to 28; scores of 5 to 9 suggest questionable impairment and scores ≥10 suggest impairment consistent with dementia.

eFigure 3 in Supplement 3). Dropouts had lower EQ-5D-5L overall health scoresand were more likely to be aged 80 years or older, physically frail, and cognitively impaired (eTable 4 in Supplement 3). Dropouts who could vs could not be followed up electronically appeared no different (eTable 5 in Supplement 3).

Primary Outcome

Prior to interim analysis, recognizing slower than projected recruitment, we reduced our event target to match the event total in MAPEC (ie, reduced from 406 to 255 target events). This correspondingly advanced the interim analysis, intended to take place on observing half the targeted events. However, subsequent to the interim analysis, we obtained a no-cost grant extension to continue observing until the limits of funding led the trial to conclude, at which point 336 primary outcomes had been observed.

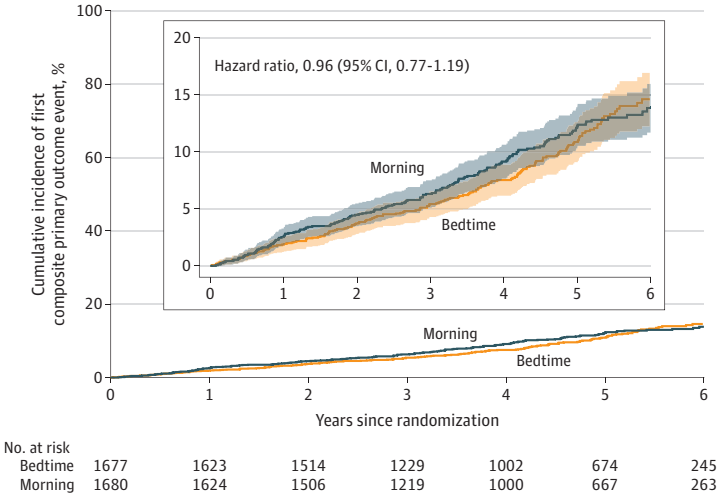
Death or major cardiovascular events (the primary outcome) did not differ significantly between groups (**Figure 2**). Over a median 4.6 years in each treatment group, the primary outcome event rate was 2.3 per 100 patient-years in the bedtime group and 2.4 per 100 patient-years in the morning group (adjusted hazard ratio, 0.96; 95% CI, 0.77-1.19; P = .70). The same was true for all individual components of the primary outcome (**Table 2**) and for all predefined subgroups (**Figure 3**). Adjusted and unadjusted analyses for the primary outcome were nearly identical (unadjusted hazard ratio, 0.94; 95% CI, 0.76-1.17), and we confirmed no violations of the proportional hazards assumption (eAppendix Section 5 in Supplement 3).

Post hoc per-protocol sensitivity analysis of 1042 participants in the bedtime group and 1023 participants in the morning group not using a β-blocker or diuretic at baseline found that over a median of 4.7 years, the primary outcome event rate was 1.7 per 100 patient-years in the bedtime group vs 1.8 per 100 patient-years in the morning group (unadjusted hazard ratio, 0.94; 95% CI, 0.68-1.28; adjusted hazard ratio, 0.90; 95% CI, 0.65-1.23; P = .50).

Adherence and BP

At 6 months, 83% of once-daily bedtime group antihypertensives and 95% of once-daily morning group antihypertensives were self-reported to be taken as allocated (eFigure 4 and eTable 6 in Supplement 3). One or more once-daily antihypertensive was taken at the allocated time by 88% of bedtime and 97% of morning participants. Of medications considered to be per allocation, 1% of morning group medications were taken at lunchtime and 5% of bedtime group medications were taken at dinnertime. Adherence to allocation decreased gradually with time, but at 72 months, when at its lowest, 1 or more once-daily antihypertensive was still taken per allocation by 70% of bedtime and 88% of morning participants (eTable 7 in Supplement 3). Reasons for nonadherence varied by medication class (eTable 8 in Supplement 3), with twice-daily β-blockers typically remaining unchanged and participants using diuretics at bedtime more likely to experience nocturia.

Figure 2. Effect of Medication Timing on Cardiovascular Events and Death



Cumulative incidence of a first composite primary outcome event (all-cause death or hospitalization/emergency department visit for stroke, acute coronary syndrome, or heart failure) for the comparison of bedtime vs morning antihypertensive use. Median follow-up time was 4.6 (IQR, 2.9-5.4) patient-years in the bedtime group and 4.6 (IQR, 2.8-5.4) patient-years in the morning group. Baseline characteristics used as covariates to produce the adjusted hazard ratio shown were predefined at the protocol stage and included age, sex, physical frailty (physical frailty subscale of the Tilburg Frailty Indicator), current smoking, number of non–blood pressure medications, EuroQol 5-Level 5-Dimension overall health score, hospitalization during prior 6 months, heart failure, diabetes, coronary artery disease, stroke or transient ischemic attack, chronic kidney disease, dialysis, body mass index >35, body mass index <20, sleep apnea, number of exercise days, and province of residence. The unadjusted hazard ratio was 0.94 (95% CI, 0.76-1.17).

We arranged 24-hour ABPM in a prespecified[20] consecutive sample of 151 bedtime group and 151 morning group volunteers a median of 9.6 months into the trial (90% power to detect the difference in overnight systolic BP observed in MAPEC) (see details in eAppendix Section 4 in Supplement 3). Comparing bedtime vs morning participants (eTable 9 in Supplement 3), neither mean daytime systolic BP (133.8 mm Hg vs 136.2 mm Hg; $P = .15$) nor mean daytime diastolic BP (75.2 mm Hg vs 75.6 mm Hg; $P = .72$) were statistically different. Overnight mean systolic BP was lower in the bedtime group (116.5 mm Hg vs 123.9 mm Hg; difference, −7.4 mm Hg; 95% CI, −11.2 to −3.7 mm Hg; $P < .001$), as was overnight mean diastolic BP (62.9 mm Hg vs 65.5 mm Hg; difference, −2.7 mm Hg; 95% CI, −4.9 to −0.4 mm Hg; $P = .02$). Daytime BP was controlled according to American College of Cardiology/American Heart Association 2017 guideline recommendations (ie, systolic and diastolic BP were <130/80 mm Hg)[31] for 41.1% of bedtime participants vs 32.5% of morning participants ($P = .12$).

Secondary and Safety Outcomes

Secondary and safety outcomes were no different between groups (Table 2), nor was the 1-year self-reported EQ-5D-5L overall health score (range, 0-100; bedtime group mean score, 78.9 [SD, 15.2]; morning group mean score, 79.5 [SD, 14.6]; absolute difference, −0.75; 95% CI, −1.69 to 0.19; $P = .12$).

Discussion

In this pragmatic RCT of antihypertensive medication timing, we observed no difference in all-cause deaths or major cardiovascular events or in potential hypotensive, visual, or cognition-related adverse events between adults with hypertension in primary care randomized to medication administration at bedtime vs in the morning. In particular, there was no difference in falls or fractures, new glaucoma diagnoses, or cognitive decline. Administration time affected neither the benefits nor the risks of BP-lowering medication.

Our findings align closely with the TIME trial, which similarly reported neither benefit nor harm from bedtime antihypertensive use.[12] They also align closely with observational evidence from the Spanish Ambulatory Blood Pressure Monitoring Registry, which monitored 35 129 people with morning use and 6723 people with evening/bedtime use of antihypertensives for a median of 9.7 years and reported no difference in all-cause or cardiovascular mortality in an adjusted analysis.[32] However, our findings differ markedly from 2 RCTs (MAPEC[10] and Hygia[11]) reporting 61% and 45% reductions in major adverse cardiovascular events and 57% and 45% reductions in all-cause death attributed to bedtime use. Of note, the 2024 Cochrane review on this topic excluded the MAPEC, Hygia, and TIME trials for enrolling participants taking more than 1 antihypertensive medication.[33] Consequently, that review addressed short-term tolerability and 24-hour mean BP differences but could draw no conclusions regarding cardiovascular outcomes (given only 3 deaths and 24 serious adverse events from included trials). The Cochrane review did not report on falls/fractures or visual or cognitive adverse events.

Participation in BedMed and TIME involved only telephone or email follow-up for most participants. In contrast, for MAPEC and Hygia, all participants were asked to undergo fasting bloodwork, urine collection, and 48-hour ABPM

Table 2. Primary and Secondary Outcomes

Outcomes	Antihypertensive medication timing						Difference[b]	Hazard ratio or relative risk (95% CI)[c]	*P* value
	Bedtime (n = 1677)			Morning (n = 1680)					
	No. (%)[a]	Patient-years of follow-up, median (IQR)	Rate per 100 patient-years	No. (%)[a]	Patient-years of follow-up, median (IQR)	Rate per 100 patient-years			
Primary outcome									
Composite of all-cause death and major cardiovascular events	163	4.6 (2.9-5.4)	2.30	173	4.6 (2.8-5.4)	2.44	−0.14	0.96 (0.77-1.19)	.70
Secondary outcomes for efficacy									
Primary outcome components									
All-cause mortality	81	4.7 (3.1-5.5)	1.11	94	4.7 (3.1-5.5)	1.28	−0.18	0.90 (0.67-1.22)	.50
Hospitalization/ED visit for stroke	27	4.7 (3.0-5.5)	0.37	32	4.7 (3.0-5.5)	0.44	−0.07	0.86 (0.52-1.44)	.57
Hospitalization/ED visit for MI/ACS	48	4.7 (3.0-5.5)	0.67	39	4.6 (2.9-5.5)	0.54	0.13	1.25 (0.82-1.91)	.30
Hospitalization/ED visit for heart failure	30	4.7 (3.0-5.5)	0.41	43	4.7 (2.9-5.5)	0.59	−0.18	0.72 (0.45-1.15)	.17
All-cause unplanned hospitalization/ED visit	993	2.2 (1.0-4.0)	23.26	1047	2.2 (0.9-3.9)	25.15	−1.89	0.93 (0.85-1.02)	.10
Secondary outcomes for safety									
Postural hypotension related									
Nonvertebral fracture	152	4.5 (2.8-5.4)	2.18	166	4.5 (2.8-5.4)	2.40	−0.22	0.92 (0.74-1.14)	.44
Hip fracture	20	4.7 (3.0-5.5)	0.27	31	4.6 (2.9-5.5)	0.43	−0.15	0.65 (0.37-1.15)	.14
Falling, mean (SD)[a]	4.9 (11.7)			5.0 (11.2)				0.96 (0.86-1.07)	.47
Syncope, mean (SD)[a]	0.6 (3.8)			0.6 (4.1)				1.28 (0.93-1.75)	.12
Lightheadedness, mean (SD)[a]	18.8 (25.2)			20.3 (26.2)				0.95 (0.90-1.00)	.06
Vision related									
New glaucoma diagnosis	43	4.7 (3.0-5.5)	0.60	39	4.6 (2.9-5.5)	0.54	0.06	1.13 (0.73-1.74)	.58
Subjective worsening of vision[d]	420 (25.0)			411 (24.5)			0.5	1.02 (0.89-1.17)	.74
Cognition related									
Cognitive decline at 18 mo[e]	376/1446 (26.0)			395/1493 (26.5)			−0.5	0.98 (0.85-1.13)	.82
New impairment consistent with dementia[f]	89 (5.3)			83 (4.9)			0.4	1.12 (0.83-1.51)	.48
Nursing home admission[g]	38	4.7 (3.0-5.5)	0.52	26	4.7 (3.0-5.5)	0.36	0.17	1.38 (0.83-2.27)	.21

Abbreviations: ACS, acute coronary syndrome; ED, emergency department; MI, myocardial infarction.

[a] Data are number (when analyzed via survival analysis) or number and percentage of participants with the outcome of interest (when a dichotomous outcome was analyzed via Poisson regression), with the exception of falling, syncope, and lightheadedness, for which data are the mean (SD) percentage of interviews reporting the outcome as occurring at least once in the prior 30 days. For cognitive decline at 18 months, a separate denominator is provided because not all participants took the 18-month Short Blessed Test.

[b] Data are the absolute difference in event rate (per 100 patient-years) or the absolute difference in the percentage of participants experiencing the outcome.

[c] Point estimates are hazard ratios except for falling, syncope, lightheadedness, subjective worsening of vision, cognitive decline at 18 months, and new impairment consistent with dementia, all of which are relative risks.

[d] Vision described as "much worse" compared with the last follow-up at any point or "slightly worse" than the last follow-up on 2 or more occasions.

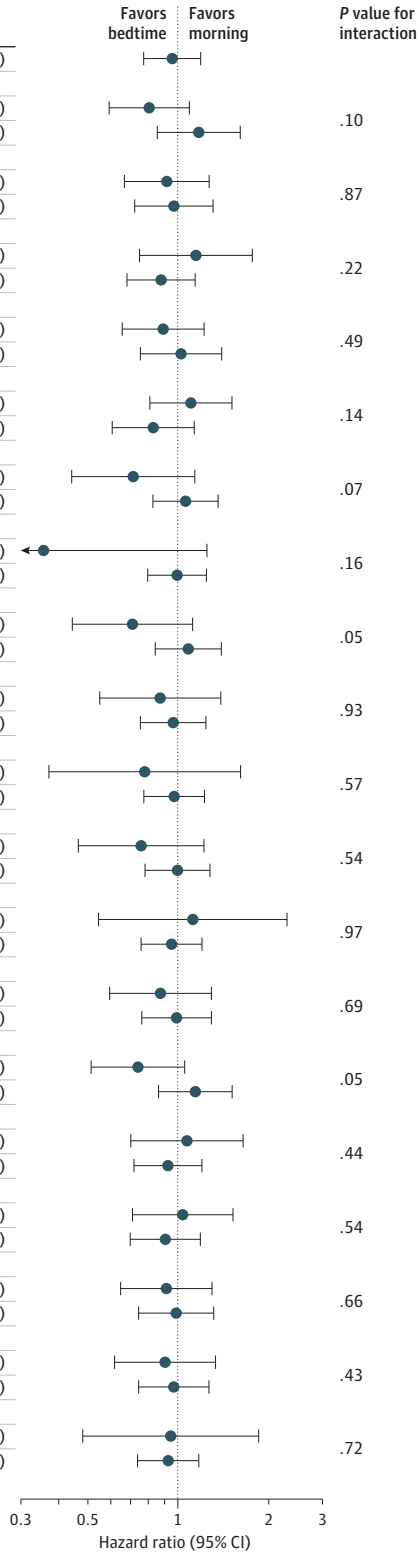
[e] Two-point or greater worsening in cognitive performance compared with baseline, as measured by the Short Blessed Test at 18 months. The Short Blessed Test is a weighted, 6-item test of cognitive impairment. Scores range from 0 to 28; scores of 5 to 9 suggest questionable impairment and scores ≥10 suggest impairment consistent with dementia.

[f] New diagnosis of dementia from any physician in the electronic health data at any point during follow-up or 18-month Short Blessed Test score newly ≥10.

[g] Admission to a group living facility where participants no longer have control of their own medication timing.

Figure 3. Subgroup Analysis of the Composite Primary Outcome of All-Cause Death or Hospitalization/Emergency Department Visit for Stroke, Acute Coronary Syndrome, or Heart Failure

Subgroup	Bedtime No. of events	Bedtime Rate per 100 patient-years	Morning No. of events	Morning Rate per 100 patient-years	Hazard ratio (95% CI)	*P* value for interaction
All patients	163	71.0	173	71.0	0.96 (0.77-1.19)	
Sex						
Male	80	30.5	94	30.4	0.81 (0.59-1.09)	.10
Female	83	40.5	79	40.6	1.17 (0.86-1.61)	
Age ≥75 y						
Yes	77	14.9	81	14.5	0.92 (0.67-1.27)	.87
No	86	56.1	92	56.5	0.97 (0.72-1.31)	
Physically frail						
Yes	47	12.4	50	12.7	1.15 (0.75-1.76)	.22
No	116	58.6	123	58.3	0.88 (0.68-1.14)	
Polypharmacy						
Yes	80	23.0	91	22.4	0.90 (0.66-1.22)	.49
No	83	48.0	82	48.6	1.03 (0.75-1.40)	
Overall health score ≤75						
Yes	91	28.5	77	25.1	1.11 (0.81-1.51)	.14
No	72	42.5	96	45.9	0.83 (0.61-1.13)	
Resistant hypertension						
Yes	33	7.7	46	7.0	0.71 (0.45-1.14)	.07
No	130	63.3	127	64.0	1.06 (0.83-1.36)	
Heart failure						
Yes	6	1.1	15	1.1	0.36 (0.10-1.25)	.16
No	157	69.8	158	69.9	1.00 (0.80-1.24)	
Diabetes						
Yes	37	12.5	50	12.5	0.71 (0.45-1.12)	.05
No	126	58.5	123	58.5	1.08 (0.84-1.39)	
Coronary artery disease						
Yes	38	7.0	46	7.3	0.88 (0.55-1.39)	.93
No	125	63.9	127	63.7	0.97 (0.75-1.24)	
Stroke or transient ischemic attack						
Yes	16	4.6	25	4.8	0.78 (0.38-1.61)	.57
No	147	66.4	148	66.2	0.97 (0.77-1.23)	
Sleep apnea						
Yes	37	16.0	38	14.4	0.76 (0.47-1.22)	.54
No	126	55.0	135	56.6	1.00 (0.78-1.28)	
Chronic kidney disease						
Yes	19	4.8	25	4.8	1.12 (0.55-2.29)	.97
No	144	66.2	148	66.2	0.95 (0.76-1.20)	
Sedentary						
Yes	50	17.7	60	18.3	0.88 (0.60-1.29)	.69
No	113	53.2	113	52.7	0.99 (0.76-1.29)	
Angiotensin-converting enzyme inhibitor use						
Yes	54	24.4	78	25.8	0.74 (0.52-1.05)	.05
No	109	46.6	95	45.2	1.14 (0.86-1.51)	
Angiotensin receptor blocker use						
Yes	56	22.8	39	19.7	1.07 (0.70-1.64)	.44
No	107	48.2	134	51.3	0.93 (0.72-1.20)	
β-Blocker use						
Yes	59	11.6	55	10.9	1.04 (0.71-1.52)	.54
No	104	59.4	118	60.1	0.91 (0.70-1.19)	
Calcium channel blocker use						
Yes	64	19.2	75	19.8	0.92 (0.65-1.30)	.66
No	99	51.7	98	51.2	0.99 (0.74-1.31)	
Diuretic use						
Yes	50	18.6	63	19.6	0.91 (0.62-1.33)	.43
No	113	52.4	110	51.4	0.97 (0.74-1.27)	
Combination blood pressure medications						
Yes	20	14.1	23	13.4	0.95 (0.49-1.85)	.72
No	143	56.9	150	57.6	0.93 (0.74-1.17)	



Interaction *P* values for prespecified subgroup analyses were obtained from a Cox model using the same covariates as the primary analysis and including both the characteristic of interest and an interaction term between that characteristic and the randomization group. Overall health scores were by EuroQol 5-Level 5-Dimension measure. All confidence intervals are unadjusted.

annually over the 9 years of the MAPEC study and 10 years of Hygia. In our experience, primary care patients are often reluctant to repeat 24-hour ABPM, let alone 48-hour ABPM, due to inconvenience and sleep disruption. Our BedMed experience supports this, with 57% of 24-hour ABPM invitees declining participation. Unfortunately, MAPEC and Hygia did not report withdrawals and loss to follow-up as conventionally defined—with no description regarding whose data were censored and how censoring dates were chosen. If attrition was high and nonrandom or unbalanced, it might explain some of the discrepancy between MAPEC and Hygia vs BedMed and TIME.

To our knowledge, BedMed is the first RCT to examine the effect of bedtime antihypertensive use on cognition, new glaucoma diagnosis, and subjective visual deterioration. It complements TIME by studying cardiovascular outcomes in a higher-risk population, given that BedMed did not exclude individuals taking twice-daily antihypertensives (twice-daily β-blockers being common in patients with heart failure and coronary artery disease, and twice-daily antihypertensives being more common in those with difficult-to-control hypertension). Although most BedMed and TIME outcomes were defined differently and cannot be directly compared, all-cause mortality was 0.80 per 100 patient-years in TIME vs 1.20 per 100 patient-years in BedMed (ie, BedMed participants had 50% higher all-cause mortality).

Limitations

There are limitations to our findings. First, the 24-hour ABPM assessments came from a small cohort of 302 volunteers; there was a high refusal rate. Selection bias might account for the large difference (−7.4 mm Hg) in sleep-time systolic BP, given that differences reported from a systematic review (−2.3 mm Hg)[34] and a randomized crossover trial (a nonsignificant −1.7 mm Hg)[35] were much smaller. However, we did not use ABPM to guide BP management, and neither do most Canadian primary care clinicians, who, in our experience, use ABPM mainly for diagnosing hypertension rather than for ongoing BP management.

Second, adherence to allocation time was self-reported and was lower in the bedtime group. However, our medication timing adherence appears comparable with that achieved in TIME, and adherence to allocation time was not reported in MAPEC or Hygia—those trials reported only the likelihood of missed/forgotten doses via the Morisky Green Levine measure.[36] Although we chose not to exclude people taking diuretics, whose adherence to bedtime allocation was lower, those taking diuretics were similarly included in the TIME, MAPEC, and Hygia trials. Additionally, we found similar results for the primary outcome in a post hoc per-protocol analysis that excluded participants taking medications with poorer adherence (diuretics and β-blockers).

Third, the BedMed trial stopped early, with fewer primary outcomes than Hygia and TIME. However, BedMed's primary outcome confidence interval rules out the 25% reduction that our study was powered to detect or exclude (BedMed excluded a hazard ratio ≤0.76; TIME excluded a hazard ratio ≤0.82), and this confidence interval has no overlap with the corresponding primary outcome confidence intervals in MAPEC and Hygia, suggesting sufficient power to conclude that the findings of BedMed vs MAPEC and Hygia are not congruent. BedMed is simultaneously strengthened by broad generalizability to primary care settings, having recruited from 436 widely distributed primary care practices, and a low 3% overall withdrawal/loss to follow-up.

Conclusions

Among adults with hypertension in primary care, bedtime administration of antihypertensive medications was safe but did not reduce cardiovascular risk. Antihypertensive medication administration time did not affect the risks and benefits of BP-lowering medication and instead should be guided by patient preferences.

ARTICLE INFORMATION

Accepted for Publication: March 15, 2025.

Published Online: May 12, 2025. doi:10.1001/jama.2025.4390

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Obtained funding: Garrison, Green, Gayayan.
Administrative, technical, or material support: Bakal, Kolber, Korownyk, Green, Kirkwood, McAlister, Lewanczuk, Hill, Katz, Kelmer, Gayayan, Campbell, Vucenovic, McGrail, O'Neill, Greiver, MacLean, Wong, Norris, Allan.
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Conflict of Interest Disclosures: Dr Padwal reported being past chief executive officer of mmHg, a digital health company. Dr Hill reported receipt of grants from Boehringer Ingelheim and Medtronic to the University of Calgary and being president of the not-for-profit Canadian Neurological Sciences Federation. Dr Singer reported being paid by the University of Manitoba for academic work; receiving honoraria for advisory work by the College of Physicians and Surgeons of Manitoba (2024), Canadian Cardiovascular Society (2024), Manitoba's Southern Chiefs Organization (2021-2023), and Canadian Association of Drugs and Technology for Health (2024); participating on teams with grant funding from the Canadian Institutes of Health Research, Research Manitoba, Public Health Agency of Canada, Bayer (administered by Research Manitoba), Children's Hospital Research Foundation, Health Science Centre Foundation, and Pfizer; being the principal investigator on a grant funded by IBM and Calian administered by the Canadian Institute for Military and Veterans Health Research; and participating in advocacy committees for the College of Family Physicians of Canada, Canadian Cardiovascular Society, and Choosing Wisely Canada. No other disclosures were reported.

Funding/Support: BedMed was funded by a Support for Patient Oriented Research Innovative Clinical Trial multi-year grant (151212) from the Canadian Institutes of Health Research and by a Partnership for Research and Innovation in the Health System grant from Alberta Innovates (201500912G2019000450). BedMed also received in-kind research assistance from the Enhancing Alberta Primary Care Research Networks (EnACt), which itself is funded entirely by Alberta Innovates, and received pilot funding from the Northern Alberta Family Medicine Fund (University of Alberta Department of Family Medicine).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Disclaimer: The interpretation and conclusions contained herein are those of the researchers, and neither the government of Alberta nor Alberta Health Services expressed any opinion in relation to this study.

Meeting Presentation: The results described in this report were presented at the European Society of Cardiology Congress; August 31, 2024; London, United Kingdom.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank Jim Wright, MD, PhD, of the Cochrane Hypertension Working Group, for chairing and selecting members for the independent data and safety monitoring board: Tom Perry, MD, Marco Perez, MD, PhD, Benji Heran, PhD, and Mohamed Ben-Eltriki, PhD. Neither Dr Wright nor the other members of the data and safety monitoring board received compensation, financial or otherwise, for their participation. We also thank Armen Gayayan, BSc (independent contractor; financial compensation received), for writing R computer code that facilitated the extraction and organization of self-reported follow-up data from the REDCap database. We thank the research assistants/coordinators from the University of Alberta Department of Family Medicine (financial compensation received) who supported the trial over multiple years, including Nicole Olivier, AHT, Janis Cole, BSc (research coordinators), Dorna Sadeghi, BSc, Jeffrey Cheng, BSc, Kaylin Bechard, MD, Yvonne Marcoux, BSc, and Aanchal Saran, MD (research assistants). We also thank the Advanced Respiratory Care Network for providing 24-hour ambulatory blood pressure monitoring services (financial compensation received). Finally, we thank the Alberta Strategy for Patient Oriented Research Support Unit (AbSPORU) for assistance with data collation and analyses.

Additional Information: Data were extracted from the Alberta Health Services Enterprise Data Warehouse with support provided by AbSPORU, which is funded by the Canadian Institutes of Health Research, Alberta Innovates, University Hospital Foundation, University of Alberta, University of Calgary, and Alberta Health Services. This study is based in part on data provided by Alberta Health and Alberta Health Services.

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