Evidence-Based Medicine: Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes

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Our patient . . .

You are seeing a 67-year-old man for routine follow up in the office for hypertension. He has a history of a stroke five years ago. He is asymptomatic and has no residual neurologic deficits.

Medications:

- Lisinopril 20 mg po daily
- Atorvastatin 80 mg po qhs
- Clopidogrel 75 mg po daily

His vital signs today: bp 128/78 p 82 RR 14 afebrile. His exam is unremarkable.

He asks you if it is better to take his medications in the morning or in the evening?

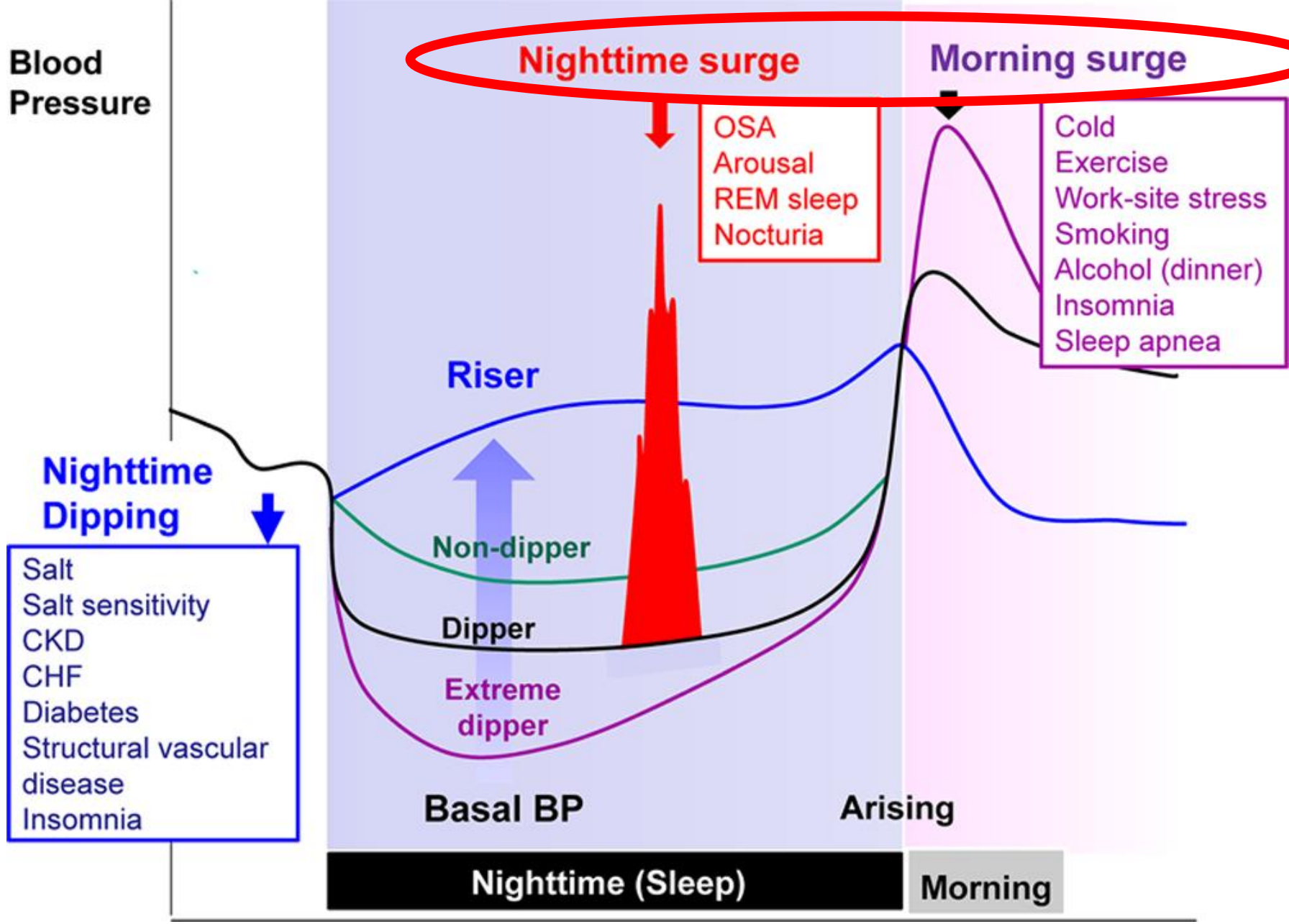
Clinical Question:
What is the effect of evening vs morning administration of antihypertensive medication on cardiovascular outcomes?

Source:

Mackenzie IS, et al. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomized, open-label, blinded endpoint trial. **Lancet** 2022; 400: 1417-1425

A Rationale for evening antihypertensive dosing . . .

Could evening antihypertensive medication treat the nighttime and morning bp surges better than morning dosing?



Karoi, K, *Hypertension* 2018; 71(6): 997-1009.

Critical Appraisal of a Single Therapeutic Trial: Is the Trial Valid?

Sackett, Richardson,Rosenberg and Haynes: Evidence-Based Medicine; How to Practice and Teach EBM, London: Churchill Livingstone, 1997

1. Was the assignment of patients to treatment randomized? And was the randomization list concealed?

2. Were all patients who entered the trial accounted for at its conclusion? And were they analyzed in the groups to which they were randomized?

Critical Appraisal of a Single Therapeutic Trial: Is the Trial Valid?

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1. Were the patients and clinicians kept “blind” to which treatment was being received?

2. Aside from the experimental treatment, were the groups treated equally?

3. Were the groups similar at the start of the trial?

If the study satisfies these criteria, then it has *internal validity.*

Critical Appraisal of a Single Therapeutic Trial: Can you apply the evidence in this trial to your patient?

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Do these results apply to your patient?

(ie. Do the results have *external validity*?)

- Are the patients in the study similar enough to your patient such that the study results can help you?
- How great would the potential benefit of therapy actually be for your individual patient?

Critical Appraisal of a Single Therapeutic Trial: Can you apply the evidence in this trial to your patient?

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- Are your patient's values and preferences satisfied by the regimen and its consequences?
  - Do your patient and you have a clear assessment of their values and preferences?
  - Are they met by this regimen and its consequences?

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes

Design: Prospective, randomized, controlled, open-label, blinded endpoint trial

Setting: United Kingdom

Was the assignment of patients treatment randomized?
And was the randomization list concealed?

Endpoint Assessors Yes
Patients No

Were the patients and clinicians kept “blind” to which treatment was being received?

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Patients included

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Patients included

- UK residents ≥ 18 years old
- Diagnosed HTN
- Taking at least one antihypertensive medication daily
- Email contact
- Registered with a general practitioner through the National Health Service (NHS)

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Patients excluded

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Patients excluded

- Regular overnight shift work
- More than one dosing time daily

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Interventions

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Interventions

- Patients randomized in 1:1 fashion with no stratification to take their usual antihypertensive medication
    - Morning: between 6 and 10 am

    OR
    - Evening: between 8 pm and MN

- Patients and study investigators were not blinded to group allocation

- Endpoint assessors were blinded to group allocation

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Interventions

- All screening, consent, randomization and follow up were done online via a study portal plus through email.

- If patients were randomized to evening dosing and were taking diurectics, they were instructed to attempt an early evening diuretic dose at 6 pm. If patients could not tolerate an evening dose, then patients could move the diuretic dose to the morning.

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Interventions

- Patients completed online questionnaires 1 month after randomization and every 3 months afterward to assess:
  - Compliance with bp medication
  - Any cardiovascular event
  - Any medication side effects
  - If patients had a home bp monitor, they were asked if they could provide home bp readings in the morning and the evening every three months
  - Other adverse events

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes : Interventions

- Intention-to-treat analysis: every subject included in data analysis once randomization has occurred.

Were all patients who entered the trial accounted for at its conclusion? And were they analyzed in the groups to which they were randomized?

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Outcomes

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Primary Outcome

Composite endpoint of

- Vascular death
- Hospitalization for non-fatal MI
- Hospitalization for non-fatal stroke

- Analyzed as time to first event

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Secondary Outcomes---Individual endpoints

- Hospitalization for non-fatal MI
- Hospitalization for non-fatal stroke
- Vascular death
- All-cause mortality
- Hospitalization or death from congestive heart failure
- Participant-reported adherence to randomized antihypertensive regimen
- Prespecified adverse event (ex: falls, fractures)

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes : Study Power

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes : Study Power

- Assuming a 20% superiority in primary outcome with evening dosing compared to morning dosing
- With an 80% chance (ie. power) of detecting a difference
- With a risk of *type 1 error* of 5%
- THEN at least 631 patients would be needed

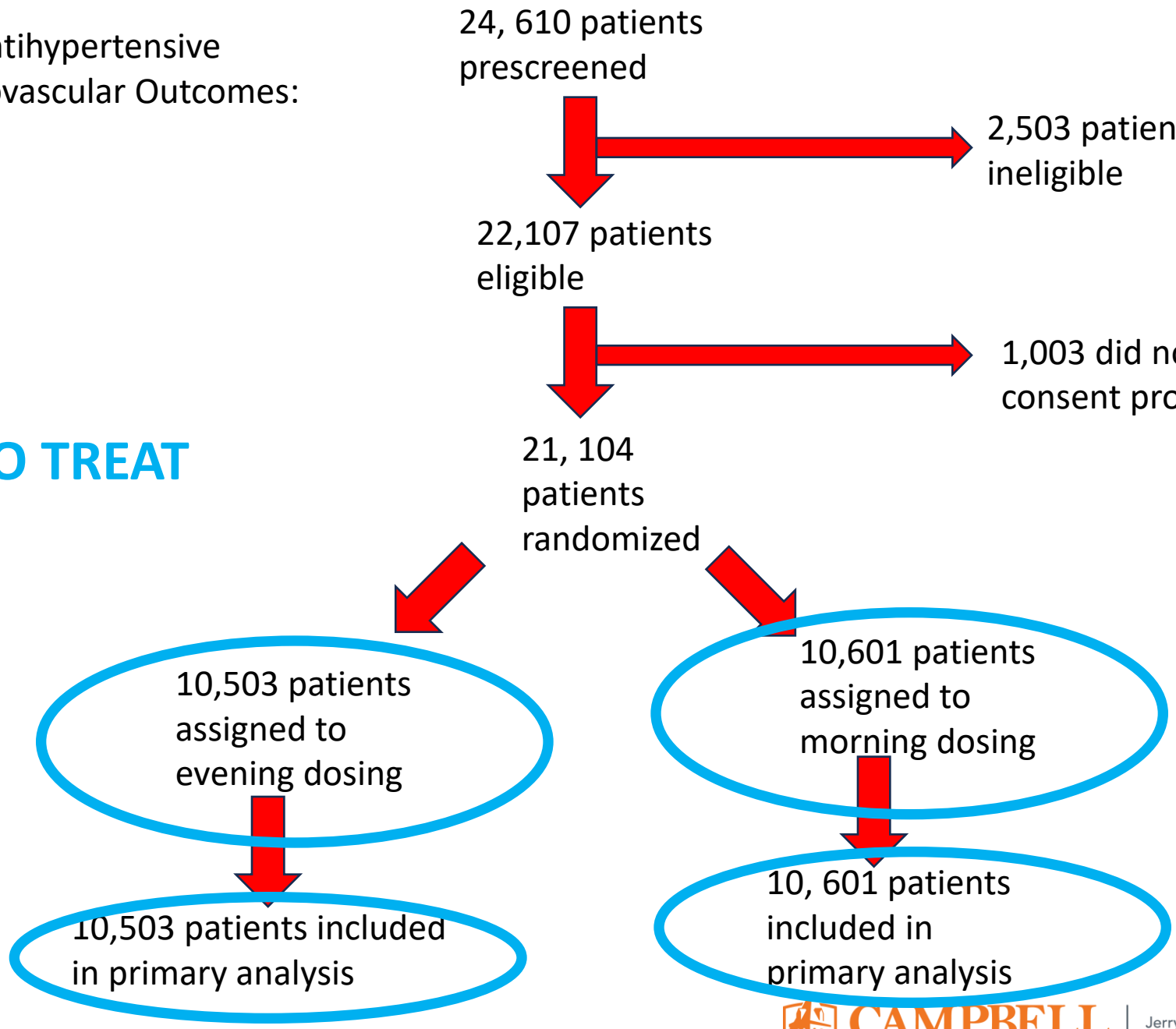
Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes : Study Power

- Original plan was to recruit 10,269 patients and follow them for five years.
- But, based on lower than expected rates of cardiovascular events in trials involving patient similar to this trial, the sample size was expanded to 20,000 patients
- Primary and secondary outcomes were analyzed by intention-to-treat

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes : Main Results

Morning vs Evening Antihypertensive Medication and Cardiovascular Outcomes: Study Design

INTENTION TO TREAT



Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Baseline Patient Characteristics

Characteristic	**Evening Dosing Group (n=10,503)**	**Morning Dosing Group (n =10,601)**
Mean age, years	65.0	65.2
Male (%)	57.5	57.5
Female (%)	42.5	42.5

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Baseline Patient Characteristics

Ethnicity (%)	**Evening Dosing Group (n=10,503)**	**Morning Dosing Group (n =10,601)**
White	90.2	90.8
Black, African, Caribbean or Black British	0.4	0.5
Asian or Asian British	0.7	0.8

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Baseline Patient Characteristics

Ethnicity (%)	**Evening Dosing Group (n=10,503)**	**Morning Dosing Group (n =10,601)**
Mixed or multiple	0.3	0.5
Other	0.1	0.1
Not reported	8.2	7.3

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Baseline Patient Characteristics

Characteristic	**Evening Dosing Group (n=9,713)**	**Morning Dosing Group (n =9,791)**
Mean BMI (kg/m2)	28.4	28.4

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Baseline Patient Characteristics

Smoking history (%)	**Evening Dosing Group (n=10,503)**	**Morning Dosing Group (n =10,601)**
Never	57.8	56.7
Former	37.6	38.3
Current	4.1	4.3
Missing	0.6	0.7

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Baseline Patient Characteristics

Characteristic	**Evening Dosing Group (n=5052)**	**Morning Dosing Group (n =5026)**
Mean systolic bp (mm Hg)	135.0	134.8

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Baseline Patient Characteristics

Characteristic	**Evening Dosing Group (n=5044)**	**Morning Dosing Group (n =5023)**
Mean diastolic bp (mm Hg)	79.1	78.8

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Baseline Patient Characteristics

Cardiovascular history (%)	**Evening Dosing Group (n=10,503)**	**Morning Dosing Group (n =10,601)**
Evidence of cardiovascular disease (self-reported)	13.0	12.8
Previous MI	4.9	4.4
Angina, requiring medical treatment	2.9	3.2

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Baseline Patient Characteristics

Cardiovascular history (%)	**Evening Dosing Group (n=10,503)**	**Morning Dosing Group (n =10,601)**
Previous stroke	2.5	2.2
Previous TIA	4.1	4.2
Peripheral vascular disease	1.6	1.5

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Baseline Patient Characteristics

Other medical history (%)	**Evening Dosing Group (n=10,503)**	**Morning Dosing Group (n =10,601)**
Any diabetes	12.9	13.3
Diabetes requiring medical treatment	9.5	10.1
Asthma	10.0	9.8
Arthritis requiring medical treatment	6.5	6.9

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Baseline Patient Characteristics

Other medical history (%)	**Evening Dosing Group (n=10,503)**	**Morning Dosing Group (n =10,601)**
Impaired kidney function	3.1	3.3
COPD	3.0	2.8
Number of anti-HTN medications at study entry	1.49	1.50

✓ Aside from the experimental treatment, were the groups treated equally?

✓ Were the groups similar at the start of the trial?

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Results

- Median follow up 5.2 years

- Prior to study, 85.4% of patients had taken their antihypertensive medications in the morning

- *Complete* adherence to assigned antihypertensive dosing schedule over the study
  - Evening dosing: 61%
  - Morning dosing: 77.5%

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Primary Outcome

Composite endpoint of

- Vascular death
- Hospitalization for non-fatal MI
- Hospitalization for non-fatal stroke

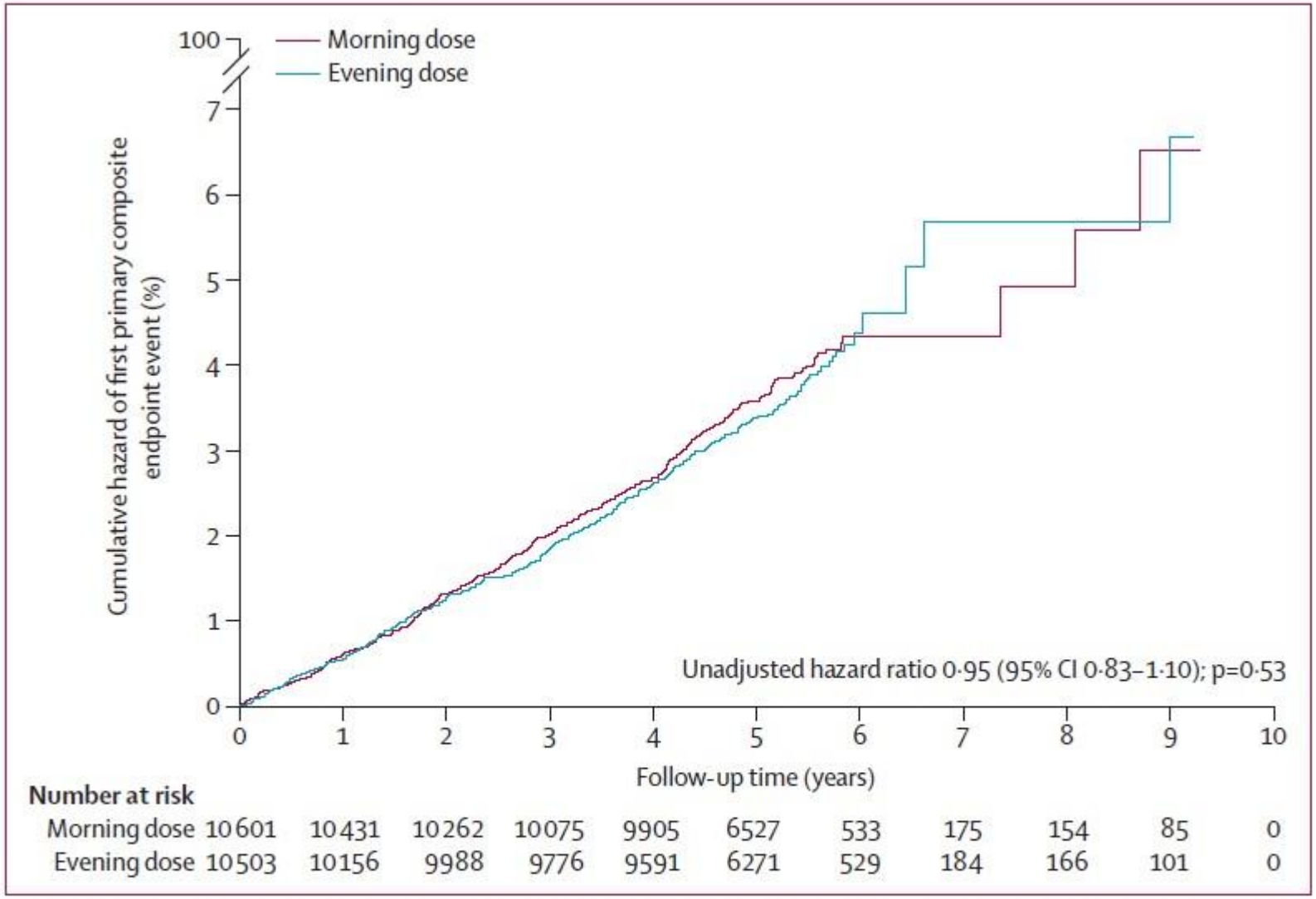


Figure 2: **Cumulative hazard of the first primary composite endpoint event, accounting for the competing risk of deaths not included in the endpoint (intention-to-treat population; n=21104)**
The primary composite endpoint was vascular death or hospitalisation for non-fatal myocardial infarction or non-fatal stroke.

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Primary Composite Endpoint

Outcome	Evening Dosing Group (n=10,503)	Morning Dosing Group (n =10,601)	Hazard Ratio (95% CI)	P value
Composite primary endpoint: • Vascular death or • Hospitalization for non-fatal MI or non-fatal stroke	3.4%	3.7%	0.95 (0.83 to 1.10)	0.53

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Secondary Outcomes

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Secondary Outcomes

Outcome	Evening Dosing Group (n=10,503)	Morning Dosing Group (n =10,601)	Hazard Ratio (95% CI)	P value
Hospitalization for non-fatal myocardial infarction	1.3%	1.4%	0.92 (0.73-1.16)	0.48
Hospitalization for non-fatal stroke	1.2%	1.3%	0.93 (0.73-1.18)	0.54
Vascular death	1.1%	1.0%	1.10 (0.84-1.43)	0.49

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Secondary Outcomes

Outcome	Evening Dosing Group (n=10,503)	Morning Dosing Group (n =10,601)	Hazard Ratio (95% CI)	P value
All-cause death	4.2%	4.1%	1.04 (0.91-1.18)	0.59
Hospitalization or death from congestive heart failure	0.7%	0.9%	0.79 (0.59-1.07)	0.12

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Adverse Events

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment : Adverse Events

Adverse Event (%)	**Evening Dosing Group (n=9,574)**	**Morning Dosing Group (n=10,054)**	**Between Group Differences (95% CI)**
Dizziness or lightheadedness	36.7	**39.9**	-3.2 (-4.6 to -1.8)
Excessive visits to toilet	**40.0**	36.4	3.6 (2.2 to 4.9)
Sleep problems	42.0	41.0	0.9 (-0.5 to 2.3)

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment : Adverse Events

Adverse Event	**Evening Dosing Group (n=9,574)**	**Morning Dosing Group (n=10,054)**	**Between Group Differences (95% CI)**
Indigestion	27.6	**30.3**	-2.8 (-4.1 to -1.5)
Diarrhea	18.8	**21.6**	-2.8(-3.9 to -1.6)
Muscle aches	38.9	**43.3**	-4.4(-5.8 to -3.0)

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment : Main Conclusions

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment : Main Conclusions

- Among patients taking antihypertensive medications once per day, taking the medications in the evening compared to the morning led to no significant difference over about five years in a composite endpoint of:
  - Vascular death or
  - Hospitalization for non-fatal MI or
  - Hospitalization for non-fatal stroke

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment : Main Conclusions

- Among patients taking antihypertensive medications once per day, taking the medications in the evening compared to the morning led to no significant difference over about five years in individual endpoints of:
  - Hospitalization for non-fatal MI
  - Hospitalization for non-fatal stroke
  - Vascular death
  - All-cause death
  - Hospitalization or death from congestive heart failure

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment : Main Conclusions

- Patients taking antihypertensive meds in the morning compared to evening dosing had higher rates of:
  - Dizziness or lightheadedness
  - Indigestion
  - Diarrhea
  - Muscle aches

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment : Main Conclusions

- Patients taking antihypertensive meds in the evening compared to morning dosing had more frequent visits to the bathroom

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Study Strengths

- Large-scale study
- Used commonly prescribed antihypertensive medications
- Good long-term follow up over a median of five years
- Used clinically important endpoints

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Study Limitations

- Open-label study in which all patients were all aware of their assigned medication dosing time which can introduce bias.
- Patients reported adverse events via an online portal which can introduce recall and reporting bias.
- More patients in the evening dosing group withdrew from follow up online questionnaires which may result in under reporting of adverse events.

Cardiovascular Outcomes with Evening vs Morning Antihypertensive Treatment: Study Limitations

- Not a very diverse patient population: 90% white
- External validity (applying the study to many of your patients): this study excluded patients who had to take antihypertensive medications more than once per day. Many patients with hypertension take antihypertensive medications several times per day.
- Also, the study excluded patient working regular night shifts which may impact blood pressure.

Back to our patient. . .

Is the patient similar enough to those in the trial that its results can help you?

YES

You are seeing a 67-year-old man for routine follow up in the office for hypertension. He has a history of a stroke five years ago. He is asymptomatic and has no residual neurologic deficits.

Medications:

- Lisinopril 20 mg po daily
- Atorvastatin 80 mg po qhs
- Clopidogrel 75 mg po daily

His vital signs today: bp 128/78 p 82 RR 14 afebrile. His exam is unremarkable.

He asks you if it is better to take his medications in the morning or in the evening?

You advise your patient that there is no clear evidence of any advantage of evening vs morning medications from a large randomized trial and that the important thing is to pick a time which is *convenient* when he will *remembe*r to take them!

Questions?

Thank you!

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