Therapeutics

Should blood pressure medications be taken at bedtime?

10.1136/bmjebm-2019-111311

Check for updates

Carl Heneghan [1], Jack O'Sullivan [2], Kamal R Mahtani [1]

[1]Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK, [2]Stanford University, Stanford, California, USA

Correspondence to: Professor Carl Heneghan, Primary Care Health Sciences, University of Oxford, Oxford OX1 2JD, UK; carl.heneghan@phc.ox.ac.uk

EBM Verdict:

EBM Verdict on: Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. *Eur Heart J*. 2019: ehz754. doi: 10.1093/eurheartj/ehz754.

- Taking at least one hypertensive at bedtime appears to lead to reductions in night-time blood pressure and significant reductions in cardiovascular events.

Hypertension is a common problem that increases cardiovascular risk. A recent large trial suggests the timing of treatment can make a difference to outcomes.

Accumulating evidence shows that the time of day that antihypertensives are taken can impact their effectiveness: taking them at night reduces asleep blood pressure (BP), without compromising their effect on daytime BP.[1] Asleep BP is also a better predictor of cardiovascular risk than daytime measurements and non-dipping during sleep, defined as a decline of less than a 10% in systolic pressure, is associated with an increased cardiovascular risk.[2]

In 2010, a randomised trial including 2156 hypertensives, taking ≥1 BP-lowering medication at bedtime, reported significant reductions in night-time BP and cardiovascular events at a mean 5.6 years of follow-up.[3] However, the generalisability of the trial findings was limited by the single-centre design and the small sample size of the study. Replication of these findings in a much larger primary care population was therefore needed.

The Hygia Chronotherapy Trial sought to address this evidence gap. The study randomised 19 084 primary care patients, across a network of 40 primary care centres in northern Spain. Participants were allocated to take one or more hypertensive medications at bedtime or in the morning. The primary outcomes were any change in cardiovascular events.[4] During the 6.3 years of patient follow-up, 1752 participants experienced the primary CVD outcome (CVD death, myocardial infarction, coronary revascularisation, heart failure or stroke). Taking medications at bedtime led to significantly lower rates of the primary CVD outcome (CVD death, myocardial infarction, coronary revascularisation, heart failure or stroke), HR 0.55 (95% CI 0.50 to 0.61). Each of the single components of the primary outcome was also significantly reduced, including CVD death, HR 0.44 (95% CI 0.34 to 0.56), p<0.001. Data from the final ambulatory BP monitoring (ABPM) assessment showed lower asleep (p<0.001), but not awake systolic and diastolic BP in those taking hypertensives at bedtime. There were no differences in adverse effects with the timing of treatment during the follow-up.

One of the strengths of the study was its multicentre design and that it was embedded into routine primary care. Other strengths include the use of 48 hours ABPM, the independent blinded adjudication of the outcomes and the minimal losses to follow-up (99.6% of patients enrolled were included in the final evaluated population). The study had some weaknesses, including the lack of generalisability to ethnic groups: the trial included only Spanish people of a white ethnic background. The class effects of different medications on night-time BP could also not be determined as participants were free to choose which hypertensive agent they took at night and not assigned to specific classes of drugs. The open-label trial meant patients could not be blinded to the timing of their treatments, and researchers were also made aware of the timings. The blinded adjudication of endpoints was, therefore, essential.

While many news outlets were clear in their headlines: hypertensive 'work better at bedtime,'[5] the National Health Service 'Behind the Headlines service was more cautious in its recommendations: 'Further conclusive findings may in future lead to changes in how BP medicines are prescribed.'[6]

Current guidelines on the management of hypertension do not mention the timing of treatments. The UK's National Institute for Health and Care Excellence (NICE), for example, has no recommendations on the timing of treatments. Having just updated its guidance in August 2019, the timing of hypertensives was also not in NICE's research recommendations.[7] Similarly, the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines makes no specific recommendations on timing, but do state 'the dosing of multidrug regimens, occasionally including night-time dosing, maybe best optimised by hypertension specialists.'[8]

The Hygia trial recruitment took 10 years, and further evidence on the timing of hypertensive is forthcoming: the Canadian-based 'BedMed' randomised controlled trial (RCT) is currently recruiting 8750 participants to assess the timing of antihypertensive effect on morbidity and mortality. The trial is due to complete in February 2022 (ClinicalTrials.gov Identifier: NCT02990663)[9]

A large, well-conducted, multicentre RCT reported a large decrease in CVD events in patients who took their antihypertensive medications at night. Prescribing medications for night-time consumption is a relatively straightforward intervention, and relevant guidelines should consider reflecting this new evidence in their updates.

Twitter Carl Heneghan @carlheneghan, Jack O'Sullivan @@DrJackOSullivan and Kamal R Mahtani @krmahtani

Contributors CH wrote the first draft, JO and KRM contributed to further drafts and all authors approved the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests CH is supported by the NIHR School for Primary Care Research. Evidence Synthesis Working group (NIHR SPCR ESWG project 390). CH isalso supported by the NIHR

Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, an NIHR senior investigator and editor-in-chief of BMJ Evidence-Based Medicine. JO is an NIH Postdoctoral Fellow at Stanford University. He is an associate editor at BMJ Evidence-Based Medicine. KRM is supported by the NIHR School for Primary Care ResearchEvidence Synthesis Working group (NIHR SPCR ESWG project 390).

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite: Heneghan C, O'Sullivan J, Mahtani KR. *BMJ Evidence-Based Medicine* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bmjebm-2019-111311

ORCID iDs
Carl Heneghan http://orcid.org/0000-0002-1009-1992
Jack O'Sullivan http://orcid.org/0000-0003-3629-2546
Kamal R Mahtani http://orcid.org/0000-0002-7791-8552

References

1 **Roush GC**, Fagard RH, Salles GF, *et al*. Prognostic impact from clinic, daytime, and night-time systolic blood pressure in nine cohorts of 13844 patients with hypertension. *J Hypertens* 2014;**32**:2332–40.
2 **Verdecchia P**, Porcellati C, Schillaci G, *et al*. Ambulatory blood pressure. an independent predictor of prognosis in essential hypertension. *Hypertension* 1994;**24**:793–801.
3 **Hermida RC**, Ayala DE, Mojón A, *et al*. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. *Chronobiol Int* 2010;**27**:1629–51.
4 **Hermida RC**, Crespo JJ, Domínguez-Sardiña M, *et al*. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia chronotherapy trial. *Eur Heart J*;39.
5 **Roberts M**. Blood pressure pills 'work better at bedtime'. BBC News, 2019. Available: https://www.bbc.com/news/health-50122964 [Accessed 26 Nov 2019].
6 **Website NHS**. Could blood pressure tablets be more effective if taken at bedtime? nhs.uk. Available: https://www.nhs.uk/news/medication/could-blood-pressure-tablets-be-more-effective-if-taken-bedtime/ [Accessed 26 Nov 2019].
7 **NICE**. Overview | hypertension in adults: diagnosis and management | guidance. Available: https://www.nice.org.uk/guidance/ng136 [Accessed 28 Nov 2019].
8 **American College of Cardiology**. Guideline for High Blood Pressure in Adults - American College of Cardiology, 2017. Available: http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2ften-points-to-remember%2f2017%2f11%2f09%2f11%2f41%2f2017-guideline-for-high-blood-pressure-in-adults [Accessed 26 Nov 2019].
9 **ClinicalTrials.gov**. The Effect of Antihypertensive Medication Timing on Morbidity and Mortality - Full Text View. Available: https://clinicaltrials.gov/ct2/show/NCT02990663 [Accessed 26 Nov 2019].