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Update on trials examining effects of night-time blood pressure lowering drug treatment on prevention of cardiovascular disease

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Abstract

Current evidence on benefits of night-time blood pressure (BP) lowering drug treatment on cardiovascular disease (CVD) prevention attributable to the Ambulatory Blood Pressure Monitoring in the Prediction of Cardiovascular Events and Effects of Chronotherapy (MAPEC) trial and Bedtime hypertension treatment improves cardiovascular risk reduction (Hygia) trials has raised concern on their validity and methodology. In this commentary, the authors have updated the progress of the ongoing trials that were planned to examine the effect of night-time BP lowering drug treatment on CVD prevention. As compared to MAPEC and Hygia trials, three pragmatic trials the Blood Pressure Medication Timing (BPMedtime) trial (US), the Treatment In Morning *versus* Evening (TIME) trial (UK), Bedmed and Bedmed-frail (Canada) were planned without ambulatory BP monitoring. The BPMedtime trial was stopped after the pilot phase due to underestimated sample size and insufficient funds. TIME trial (UK) had a similar issue when changing the sample size from 10,269 to more than 20,000 participants. The TIME trial was completed and the initial results showing that protection against heart attack, stroke and vascular death is not affected by whether antihypertensive medications are taken in the morning or evening. The full study of the TIME trial is published in December 2022. Bedmed and Bedmed-frail trials are ongoing and will be completed in 2023. Time of taking BP lowering drug should be determined by patients at their convenience to improve the adherence. There was no difference in adverse effects of taking BP lowering drugs at night or morning. Evidence on the effect of night-time treatment on CVD events is inconsistent. The results from ongoing trials in Canada will contribute evidence to the use of BP lowering drug treatment for the prevention of CVD.

Keywords

Night-time, hypertension, antihypertensive treatment

Introduction

An increase of 20 mmHg in night-time blood pressure (BP) and riser pattern was independently associated with increased risks of 21% and 48% cardiovascular disease (CVD) respectively [1]. As compared with normal dippers, non-dippers were more likely to have an increased risk of major CVD event and all-cause mortality

with a hazard ratio (HR) 1.40 [95% confidence interval (CI), 1.20–1.63] and an HR 1.33 (95% CI, 1.07–1.65) respectively [2]. Switching the time of taking BP lowering drugs from morning to night may be a reasonable approach to improve BP control and CVD prevention.

The Ambulatory Blood Pressure Monitoring in the Prediction of Cardiovascular Events and Effects of Chronotherapy (MAPEC) [3] and Bedtime hypertension treatment improves cardiovascular risk reduction (Hygia) trials by Hermida et al. [4] were conducted in hypertensive patients and had a median follow-up of five years to compare the effect of taking at least one BP lowering drug treatment at night time in comparison to taking all BP lowering drug treatments in the morning. Both studies reported a reduction of approximately 50% in major CVD events and all-cause mortality with night-time dosing and a reduction of 60% in CVD mortality. However, only a difference of less than 5 mmHg in night-time systolic BP between two randomised groups was observed in both studies. The Heart Outcomes Prevention Evaluation (HOPE) trial in high CVD risk population that compared a night-time Ramipril 10 mg and placebo reported smaller effect size with an HR 0.78 (95% CI, 0.70–0.86) for major CVD events although a small difference of 2 mmHg in office systolic BP between groups was observed [4]. Participants in the HOPE trial had low mean BP at entry of 139/79 mmHg. The validity and methodology of the MAPEC and Hygia trials have raised an ongoing discussion and thus the results should be interpreted carefully [5–9]. As for information about the randomization process, recruitment process, and the assessment of endpoints, monitoring throughout the trials was not adequately reported in the main articles [10, 11] and the protocols [12, 13]. Provided information was unclear to determine whether these trials were properly conducted randomised controlled trials. Carlberg and Brunstrom [5] raised an ethical issue of whether these trials should have stopped earlier due to the very large observed benefit of a 50% reduction in all-cause mortality in the night-time treatment group recorded in both the Hygia and MAPEC trials. Both trials were based on ambulatory BP that has recently been recommended for the diagnosis of hypertension [14–16]. However, ambulatory BP monitoring has not been widely adopted in current practice particularly for the management of hypertension treatment. Pragmatic trials are required to determine whether night-time dosing can be readily translated to improve BP control at a population level.

Update on the process of trials examining effects of night-time BP lowering drug treatment on CVD prevention

After MAPEC, three pragmatic trials without ambulatory BP monitoring (ABPM) were planned to examine the effect of taking BP lowering drugs at night and CVD prevention in the UK (TIME), Canada (Bedmed and Bedmed-frail) and the US (BPMedtime) [17–19]. However, these trials do not comply with the quality requirements listed in the guidelines by the International Society for Chronobiology for conducting chronotherapy trials in hypertension [20]. The pragmatic trials use clock-time (mainly TIME) instead of biological one (awakening/bedtime) for treatment. As summarised in Table 1, all trials randomised patients with all once-daily antihypertensive drugs to either night-time or morning except for the US study that was restricted to a non-diuretic regimen. Not many details were recorded for the US study as it was stopped at the pilot phase and did not proceed to the main trial phase according to an update in June 2015 [21]. BPMedtime trial substantially underestimated the sample size to detect the main effect that was lower than expected. The study needed 5,000 participants rather than the original sample size of 1,000 which was unachievable within the funded budget. At the same time, the TIME trial was piloted in 2011 and 2014 to validate the feasibility of an online study with online recruitment, consent and follow-up. Similar to BPMedtime, the TIME trial adjusted the sample size from 10,269 to more than 20,000 participants in order to "achieve the necessary number of events needed" and actually 21,104 participants were enrolled and randomised after five years of recruitment in 2016 [17, 22, 23]. No calculation for the updated sample size, no information on the expected event rate, and no data on the actual event rates were observed since the trial start date has been reported. The TIME investigators also extended the completion time of the study from 2016 to 2022 (https://www.isrctn.com/ISRCTN18157641). In a hot line session on 26th August at the European Society of Cardiology (ESC) Congress 2022 (Barcelona, Spain), the principal investigator Professor Thomas

MacDonald of the TIME trial presented that protection against heart attack, stroke and vascular death is not affected by whether antihypertensive medications are taken in the morning or evening with an unadjusted HR 0.95 (95% CI, 0.83–1.10) [24]. Taking medication in the evening was not harmful. Results from the TIME study on CVD events are opposite to what were observed in the MAPEC and Hygia trials. More discussion is needed once the full study of the TIME trial is published in December 2022.

Table 1. Summary of the ongoing trials examining effect of night-time BP lowering drugs on CVD

Study characteristics	TIME (UK) [17]	BPMedtime (US) [18]	Bedmed (Canada) [19]	Bedmed-frail (Canada)
Study design	PROBE ("All endpoint adjudication will be blinded to dosing time")	Unclear	PROBE (primary and secondary outcomes: "will be reviewed by a panel of three physicians blinded to allocation")	PROBE
Population	Hypertensive patients using antihypertensives	Hypertensive patients with > 1 other significant increased CVD risks in university health care systems	Hypertensive patients in primary care using antihypertensives and free from glaucoma	Hypertensive patients in long term care facilities using antihypertensives and free from glaucoma
Intervention	Evening use of all antihypertensives (20:00–midnight)	Night-time use of all once-daily non-diuretic antihypertensives	Bedtime use of all antihypertensives	
Comparator	Morning use of all antihypertensives (6:00–10:00)	Morning use of all antihypertensives	Morning use of all antihypertensives	
Main outcomes	Composite of CVD death or hospitalisation for CVD	Composite of CVD death or hospitalisation for CVD	Composite of all-cause death or hospitalisation for CVD	
Follow-up	4 years	36–42 months	3 years	2 years
Sample size	Estimated 10,269 participants (randomised 21,104 participants)	1,000	254 main outcome events as in MAPEC (recruited 3,357 participants)	368 main outcome events (estimated 775 participants)
Recruitment duration	8/2011–7/2016	No information	12/2016–6/2022	5/2020–ongoing
Study duration	8/2011–6/2022	2013–2015 (stopped at pilot phase)	12/2016–12/2023	5/2020–10/2023
Trial registration	ISRCTN18157641 (https://www.isrctn.com/ISRCTN18157641)	No information	ClinicalTrials.gov Identifier: NCT02990663	ClinicalTrials.gov Identifier: NCT04054648

Two trials in Canada, the Bedmed and Bedmed-frail trials were started later in 2016 and 2020. These two trials are event-driven in which Bedmed trial [19] expected to observe 254 primary outcome events and risk ratio differences of 17% as reported in MAPEC trial and Bedmed-frail trial (https://clinicaltrials.gov/ct2/show/NCT04054648) expected to observe 368 primary outcome events. The Bedmed trial has just completed recruitment in June 2022 with 3,357 participants whereas the Bedmed-frail trial is aimed to recruit 775 participants as Bedmed-frail includes higher risk population. Both are expected to be completed in 2023. Given the substantially smaller sample size and shorter follow-up as compared to the TIME and Hygia trials, how these trials may show a significantly difference on CVD outcomes between the night-time and morning treatment groups is questionable. In addition to the main composite outcome of CVD mortality and morbidity, the TIME trial examined home BP and cognitive function in substudies. The Bedmed and Bedmed-frail trials have collected further data on new glaucoma diagnoses in the main studies; 24-ABMP and adherence to bedtime diuretics in substudies.

In 2019, Hermida et al. [25] team started a new trial Treatment of Hypertension During Sleep "THADEUS" (https://clinicaltrials.gov/ct2/show/NCT03457168) in participants with sleep-time hypertension to examine if intensive control of asleep systolic BP measured by 48-h ABPM less than 110 mmHg is better than the conventional control of less than 120 mmHg on CVD morbidity and mortality, new onset type 2 diabetes and new-onset chronic kidney disease (CKD). Sleep-time hypertension was

defined by mean sleep-time BP ≥ 110/65 mmHg as per the American ACC/AHA guideline [15] whereas the European ESC guideline [14] used a slightly different threshold of mean sleep-time BP ≥ 120/70 mmHg. The study is recruiting participants and plans to complete in March 2031 (median follow-up of 5 years). Based on the information provided in the trial registration (https://clinicaltrials.gov/ct2/show/NCT03457168), the BP treatment strategy to achieve the asleep BP target is unclear and the intensive control of asleep systolic BP lower than 110 mmHg may cause non-arteritic ischemic optic neuropathy due to low night-time BP or excessive dipping, worsening of several different forms of glaucoma or the development of glaucoma damage in susceptible individuals [26–32]. No information on the exclusion of people at risk of glaucoma or the outcomes of glaucoma diagnosis was considered in the trial registration. As suggested by Pillunat et al. [28], given that intraocular pressure is well controlled, glaucoma progression of patients with mean night-time BP ranging from 65 to 90 mmHg may be slower than those with mean night-time BP out of the above range.

Given the current uncertainty of night-time BP lowering drugs, once daily dose of antihypertensive drug treatment is recommended to take at the most convenient time for patients. In a cross-sectional study by Perry et al. [33], only 25% out of 139 participants were taking at least one antihypertensive drugs at night in which angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (ACEI/ARB), beta-blockers and calcium channel blockers (CCBs) were the most common drugs. Self-reported adherence to night-time dose was lower than those with morning dose but a promising adherence rate of 70% was reported in this exploratory analysis. A longitudinal study by Vrijens et al. [34] recorded only 7% of patients taking BP lowering drugs at night. Morning drug takers were less likely to miss the dose [34]. Results from studies by Perry et al. [33] and Vrijens et al. [34] should be interpreted carefully due to a lack of formal tools to assess drug adherence although they reflected adherence rate in usual practice. In a recent meta-analysis by Hermida et al. [35], no significant difference in adherence rate between morning and night-time doses was reported in included randomised controlled trials with an average adherence rate of more than 90% for both groups. However, adherence rates recorded in a randomised controlled trial tend to be higher than figures recorded in usual care [36]. The TIME and Bedmed trials are likely to contribute more data on drug adherence. Future trials could consider examining the effect of night-time BP lowering drug treatment on CKD progression in CKD and diabetes patients that was missing in the planned outcomes of TIME and Bedmed trials [17, 19].

Conclusions

Time of taking BP lowering drug should be determined by patients at their convenience to improve the adherence. There was no difference in adverse effects of taking BP lowering at night or morning. Evidence on the effect of night-time treatment on CVD events is inconsistent. The results from ongoing trials in Canada will contribute evidence to the timing of BP lowering drug treatment for the prevention of CVD.

Abbreviations

BP: blood pressure

CI: confidence interval

CKD: chronic kidney disease

CVD: cardiovascular disease

HR: hazard ratio

MAPEC: Ambulatory Blood Pressure Monitoring in the Prediction of Cardiovascular Events and Effects of Chronotherapy

Declarations

Author contributions

CH and CR contributed conception of the review. CH wroted the first draft of the manuscript. CR contributed to manuscript revision, read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

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References

1. Kario K, Hoshide S, Mizuno H, Kabutoya T, Nishizawa M, Yoshida T, et al.; JAMP Study Group. Nighttime blood pressure phenotype and cardiovascular prognosis: practitioner-based nationwide JAMP study. Circulation. 2020;142:1810–20.
2. Salles GF, Reboldi G, Fagard RH, Cardoso CR, Pierdomenico SD, Verdecchia P, et al.; ABC-H Investigators. Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: the ambulatory blood pressure collaboration in patients with hypertension (ABC-H) meta-analysis. Hypertension. 2016;67:693–700.
3. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. Diabetes Care. 2011;34:1270–6.
4. Hermida RC, Crespo JJ, Domínguez-Sardiña M, Otero A, Moyá A, Ríos MT, et al.; Hygia Project Investigators. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia chronotherapy trial. Eur Heart J. 2020;41:4565–76.
5. Heart Outcomes Prevention Evaluation Study Investigators; Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342:145–53.
6. Carlberg B, Brunstrom M. Is Bedtime the best time of the day? 2020 [cited 2020 Jul 1]. Available from: https://ish-world.com/data/uploads/2003-9.pdf
7. Kreutz R, Kjeldsen SE, Burnier M, Narkiewicz K, Oparil S, Mancia G. Blood pressure medication should not be routinely dosed at bedtime. We must disregard the data from the HYGIA project. Blood Press. 2020;29:135–6.
8. Lemmer B, Middeke M. A commentary on the Spanish hypertension studies MAPEC and HYGIA. Chronobiol Int. 2020;37:728–30.

9. Brunström M, Kjeldsen SE, Kreutz R, Gjesdal K, Narkiewicz K, Burnier M, et al. Missing verification of source data in hypertension research: the HYGIA PROJECT in perspective. Hypertension. 2021;78:555–8.
10. Turgeon RD, Althouse AD, Cohen JB, Enache B, Hogenesch JB, Johansen ME, et al. Lowering nighttime blood pressure with bedtime dosing of antihypertensive medications: controversies in hypertension-con side of the argument. Hypertension. 2021;78:871–8.
11. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. Chronobiol Int. 2010;27:1629–51.
12. Hermida RC. Sleep-time ambulatory blood pressure as a prognostic marker of vascular and other risks and therapeutic target for prevention by hypertension chronotherapy: rationale and design of the Hygia project. Chronobiol Int. 2016;33:906–36.
13. Hermida RC. Ambulatory blood pressure monitoring in the prediction of cardiovascular events and effects of chronotherapy: rationale and design of the MAPEC study. Chronobiol Int. 2007;24:749–75.
14. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al.; Authors/Task Force Members. 2018 ESC/ESH Guidelines for the management of arterial hypertension. The task force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36:1953–2041.
15. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2018;71:e127–248. Erratum in: J Am Coll Cardiol. 2018;71:2275–9.
16. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020;75:1334–57.
17. Rorie DA, Rogers A, Mackenzie IS, Ford I, Webb DJ, Willams B, et al. Methods of a large prospective, randomised, open-label, blinded end-point study comparing morning *versus* evening dosing in hypertensive patients: the treatment in morning *versus* evening (TIME) study. BMJ Open. 2016;6:e010313.
18. Carter BL, Chrischilles EA, Rosenthal G, Gryzlak BM, Eisenstein EL, Vander Weg MW. Efficacy and safety of nighttime dosing of antihypertensives: review of the literature and design of a pragmatic clinical trial. J Clin Hypertens (Greenwich). 2014;16:115–21.
19. Garrison SR, Kolber MR, Allan GM, Bakal J, Green L, Singer A, et al. Bedtime *versus* morning use of antihypertensives for cardiovascular risk reduction (BedMed): protocol for a prospective, randomised, open-label, blinded end-point pragmatic trial. BMJ Open. 2022;12:e059711.
20. Hermida RC, Smolensky MH, Balan H, Castriotta RJ, Crespo JJ, Dagan Y, et al. Guidelines for the design and conduct of human clinical trials on ingestion-time differences-chronopharmacology and chronotherapy-of hypertension medications. Chronobiol Int. 2021;38:1–26.
21. Weinfurt KP, Hernandez AF, Coronado GD, DeBar LL, Dember LM, Green BB, et al. Pragmatic clinical trials embedded in healthcare systems: generalizable lessons from the NIH Collaboratory. BMC Med Res Methodol. 2017;17:144.
22. Anbarasan T, Rogers A, Rorie DA, Grieve JWK, Flynn RWV, MacDonald TM, et al. Factors influencing home blood pressure monitor ownership in a large clinical trial. J Hum Hypertens. 2022;36:325–32.
23. Rorie DA, Flynn RWV, Mackenzie IS, MacDonald TM, Rogers A. The treatment in morning *versus* evening (TIME) study: analysis of recruitment, follow-up and retention rates post-recruitment. Trials. 2017;18:557.
24. Evening dosing of blood pressure medication not better than morning dosing. TIME trial presented in a Hot Line Session today at ESC Congress 2022 [Internet]. Sophia Antipolis Cedex: European Society

of Cardiology; c2022 [cited 2022 Aug 5]. Available from: https://www.escardio.org/The-ESC/Press-Office/Press-releases/Evening-dosing-of-blood-pressure-medication-not-better-than-morning-dosing

25. Treatment of Hypertension During Sleep (THADEUS) [Internet]. Bethesda: National Library of Medicine; [cited 2022 Sep 30]. Available from: https://clinicaltrials.gov/ct2/show/NCT03457168
26. Melgarejo JD, Lee JH, Petitto M, Yépez JB, Murati FA, Jin Z, et al. Glaucomatous optic neuropathy associated with nocturnal dip in blood pressure: findings from the Maracaibo aging study. Ophthalmology. 2018;125:807–14.
27. Bowe A, Grünig M, Schubert J, Demir M, Hoffmann V, Kütting F, et al. Circadian variation in arterial blood pressure and glaucomatous optic neuropathy--a systematic review and meta-analysis. Am J Hypertens. 2015;28:1077–82.
28. Pillunat KR, Spoerl E, Jasper C, Furashova O, Hermann C, Borrmann A, et al. Nocturnal blood pressure in primary open-angle glaucoma. Acta Ophthalmol. 2015;93:e621–6.
29. Jin SW, Noh SY. Long-term clinical course of normal-tension glaucoma: 20 years of experience. J Ophthalmol. 2017;2017:2651645.
30. Kwon J, Lee J, Choi J, Jeong D, Kook MS. Association between nocturnal blood pressure dips and optic disc hemorrhage in patients with normal-tension glaucoma. Am J Ophthalmol. 2017;176:87–101.
31. Charlson ME, de Moraes CG, Link A, Wells MT, Harmon G, Peterson JC, et al. Nocturnal systemic hypotension increases the risk of glaucoma progression. Ophthalmology. 2014;121:2004–12.
32. Krasińska B, Karolczak-Kulesza M, Krasiński Z, Pawlaczyk-Gabriel K, Lopatka P, Głuszek J, et al. Effects of the time of antihypertensive drugs administration on the stage of primary open-angle glaucoma in patients with arterial hypertension. Blood Press. 2012;21:240–8.
33. Perry LA, Surowiec SM, Danso DA, Kerobo OI, Anugwom AA, Couvertier KP. Evaluation of administration time and adherence rates of morning vs. bedtime dosing of antihypertensive medications. J Contemp Pharm Pract. 2019;66:11–6.
34. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336:1114–7.
35. Hermida RC, Hermida-Ayala RG, Smolensky MH, Mojón A, Fernández JR. Ingestion-time differences in the pharmacodynamics of hypertension medications: systematic review of human chronopharmacology trials. Adv Drug Deliv Rev. 2021;170:200–13.
36. van Onzenoort HA, Menger FE, Neef C, Verberk WJ, Kroon AA, de Leeuw PW, et al. Participation in a clinical trial enhances adherence and persistence to treatment: a retrospective cohort study. Hypertension. 2011;58:573–8.