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

Chau Le Bao Ho* and Christopher M. Reid
Curtin University, Bentley 6102, Western Australia, Australia

*Correspondence: Chau Le Bao Ho, Curtin University, Bentley 6102, Western Australia, Australia. chau.ho@curtin.edu.au
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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

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

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](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 different 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](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 wrote 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.

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