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Perspective

Can We Mend the Broken Clock by Timing Antihypertensive Therapy Sensibly?

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In 2017, the Nobel Prize in Physiology or Medicine was awarded to Hall, Rosbash, and Young for their discovery of molecular mechanisms that regulate circadian rhythms (1). The central clock is located in the suprachiasmatic nucleus in the hypothalamus and modulates the circadian expression of clock genes in each tissue/organ constituting the peripheral clock (1). Physiologic function and organ homeostasis is maintained when the central and peripheral clocks are in phase. It is now widely recognized that dyssynchrony between the central and peripheral clocks, or disharmonization among peripheral clocks, triggers the development of cardiovascular disease (1).

BP follows a normal circadian variation under the master regulation of the sleep activity cycle (2). BP values exhibit a peak in parallel with physical activity during daytime and fall to a substantial degree with sleep during nighttime (2). Disruption of this normal diurnal BP variation, termed "nondipping," is seen in several disease states, but is perhaps most common in CKD (2). Nondipping—over and above the 24-hour BP load—has been associated with accelerated target organ damage, and with an excess future risk of cardiovascular morbidity and mortality (3). If these risk associations are causal, then restoration of a normal circadian BP pattern with bedtime dosing of antihypertensive therapy may improve clinical outcomes. Thus, if we can mend the clock simply by timing the administration of antihypertensive therapy, great cardiovascular benefit may emerge. In this Perspective, we discuss the promises and the pitfalls of randomized trials in this area.

The BP-lowering effect of bedtime chronotherapy was quantified in a 2011 Cochrane meta-analysis of 21 randomized trials incorporating data from 1993 participants with hypertension (4). The difference in ambulatory BP between the bedtime and morning administration of antihypertensive therapy was −1.71 mm Hg [95% confidence interval (95% CI), −2.78 to −0.65 mm Hg] for 24-hour systolic BP (SBP) and −1.38 mm Hg (95% CI, −2.13 to −0.62 mm Hg) for 24-hour diastolic BP, respectively (4). However, this meta-analysis observed substantial statistical heterogeneity across eligible trials. Furthermore, none of the included studies reported treatment effects on cardiovascular outcomes; thus, the net clinical benefit of bedtime dosing could not be quantified.

After the publication of this meta-analysis, two randomized trials were strongly supportive of the notion that the clock can be mended and cardiovascular protection can be afforded, both conducted in Spain. In the Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares (MAPEC) trial (5), 2156 patients with hypertension confirmed by 48-hour ambulatory BP monitoring (ABPM) were randomized to bedtime treatment with ≥1 BP-lowering medications versus morning dosing of all antihypertensives for a median follow-up of 5.6 years. ABPM was performed at baseline and at least annually thereafter. At the study's end, compared with morning dosing, bedtime chronotherapy provoked an average reduction of −5.2 mm Hg in nighttime SBP, cut the proportion of nondippers by about one half, and lowered the risk of fatal and nonfatal cardiovascular events by 67% (5).

In the Hygia Chronotherapy Trial (6), 19,084 patients with uncontrolled hypertension confirmed by ABPM were randomized to receive the entire daily dose of ≥1 BP-lowering medication at bedtime or to take all their antihypertensives upon awaking. Antihypertensive therapy was guided by periodic 48-hour ABPM evaluation performed at baseline and at each scheduled visit (at least annually) over a median 6.3-year-long follow-up. At study end, compared with morning dosing, nighttime SBP was 3.3 mm Hg lower in the bedtime arm and a 45% reduction in the primary composite cardiovascular outcome of the trial was noted (6).

The question that arises is whether this impressive clinical trial evidence provides a robust scientific basis to change our practice to bedtime dosing of antihypertensive drugs. The cardioprotection afforded by bedtime chronotherapy should be interpreted within the context of the methodological limitations of these studies. Both MAPEC and the Hygia Chronotherapy Trial followed the prospective, randomized, open-label, blinded-end point (PROBE) design (5,6). In the PROBE design, investigators who adjudicate outcomes (*e.g.*, stroke) are blinded to treatment allocation but treating physicians, and study participants, are aware of the group assignment and ABPM recordings; this creates a potential source of bias. Furthermore, treating physicians did not follow a prespecified therapeutic algorithm regardless of the timing of therapy. In fact, the protocol of the Hygia Chronotherapy Trial allowed

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treating physicians to prescribe, "without restriction," any medication of the major antihypertensive drug classes. Review of the medications used suggests that it is possible that the benefit of bedtime chronotherapy may not be attributable to this intervention *per se* but to between-arm differences in treatment.

Several other trials have found little to no benefit on nocturnal BP and restoration of dipping pattern. In a 2013 crossover trial (7), 147 black patients with hypertensive nephrosclerosis, who were former participants of the African American Study of Kidney Disease and had adequately controlled clinic BP, were assigned to three different dosing schedules of antihypertensive therapy in a randomized order: (*1*) taking all antihypertensives once daily in the morning; (*2*) taking all antihypertensives once daily at bedtime; or (*3*) taking all antihypertensives once daily in the morning plus one dose of diltiazem (60–120 mg), hydralazine (25 mg), or ramipril (5 mg) administered at bedtime as add-on therapy. The follow-up duration of each study phase was 6 weeks and the efficacy of each dosing regimen was evaluated by ABPM (7). The difference in nighttime SBP between the bedtime and morning dosing regimen was −1.70 mm Hg, and this difference was NS (95% CI, −4.05 to 0.65 mm Hg). Similarly, there was no significant difference in nighttime SBP between the add-on and the morning dosing regimen (between-group difference: −2.07 mm Hg; 95% CI, −4.40 to 0.26 mm Hg) (7). This absence of benefit either with the bedtime or with the add-on regimen was consistent across subgroups stratified by the dipping status of participants. Therefore, in a population of black patients with CKD and a high burden of nocturnal hypertension (approximately 75% of participants were nondippers or reverse dippers at baseline), bedtime chronotherapy was ineffective in improving nighttime BP.

The effect of timing of antihypertensive therapy on ambulatory BP profile was explored in the 2018 Hellenic-Anglo Research into Morning or Night Antihypertensive Drug Delivery (HARMONY) trial (8). This trial enrolled 103 patients with hypertension with clinic BP ≤150/90 mm Hg under stable therapy for at least 3 months from 2 centers in London and Thessaloniki. After the completion of a baseline ABPM evaluation, participants were randomized to morning (6–11 AM) or evening (6–11 PM) administration of all their antihypertensives for 12 weeks. At this time point, participants were crossed over to the other dosing regimen for another 12-week period. ABPM was repeated at the end of each phase (8). Of the 103 patients with hypertension originally enrolled, 95 participants completed the three prespecified ABPM recordings and were included in the analysis. Compared with baseline, there was no difference in nighttime SBP with 12-week-long dosing of all BP-lowering medications either in the morning or at bedtime. After adjustment for center, carry over, and period effects, nighttime SBP did not differ between the bedtime and the morning dosing regimen (between-group difference: −1.62 mm Hg; 95% CI, −5.38 to 2.15 mm Hg) (8).

Taken together, the above-described inconsistency in the available clinical trial evidence raises uncertainties on whether bedtime dosing of antihypertensive therapy can effectively lower nocturnal BP and normalize diurnal BP variation. Moreover, evidence to confirm or refute the impressive cardioprotective benefits documented in MAPEC and the Hygia Chronotherapy Trial is currently missing.

The Treatment In Morning versus Evening (TIME) trial (9) follows the PROBE design, incorporates an online portal, and plans to randomize 10,269 patients with hypertension with a valid email address in the United Kingdom to receive all their BP-lowering medications either in the morning or in the evening. Over an average follow-up of 4 years, TIME is anticipated to provide evidence on clinical outcomes, but in the absence of ABPM data, this trial is also unlikely to clarify the underlying mechanisms mediating the treatment effects of bedtime chronotherapy.

In the Effect of Antihypertensive Medication Timing on Morbidity and Mortality (BedMed: NCT02990663) trial, 8750 patients with hypertension in Canada are being randomized to use their BP-lowering medications either in the morning or at bedtime for an average of 2.5 years. Apart from the anticipated evidence on major adverse cardiovascular events, BedMed will also evaluate between-arm differences in nighttime BP in a subset of 302 participants who will undergo ABPM at 6 months of follow-up. The evaluation of worsening of vision, hip fractures, cognitive dysfunction, and nocturia burden as prespecified secondary end points may elucidate several areas of uncertainty on the safety of this intervention.

Given all we know, should we prescribe all antihypertensive drugs at night? The answer appears to be no at the moment, pending further substantiating evidence from clinical trials. Excessive SBP lowering has been associated with anterior ischemic optic neuropathy and silent cerebral infarcts (10). Bedtime dosing of diuretics may not be acceptable to our patients. In our view, in the absence of "hard" evidence to mandate a change in our practice, and while awaiting the completion of the TIME and BedMed trials, choice of antihypertensive agents with long half-lives and persistent 24-hour BP-lowering action should continue to be the standard-of-care in pharmacotherapy of hypertension.

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Disclosures

Dr. Agarwal serves on member data safety monitoring committees for AstraZeneca and Ironwood Pharmaceuticals; member steering committees of randomized trials for Akebia, Bayer, Janssen, GlaxoSmithKline, Relypsa, Sanofi, and Genzyme US Companies; member adjudication committees for Bayer, Boehringer Ingelheim, and Janssen; and on member scientific advisory boards or as a consultant for Celgene, Daiichi Sankyo, Inc., Eli Lilly, Relypsa, Reata, Takeda Pharmaceuticals USA, and ZS Pharma. Dr. Georgianos has nothing to disclose.

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References

1. Takeda N, Maemura K: The role of clock genes and circadian rhythm in the development of cardiovascular diseases. *Cell Mol Life Sci* 72: 3225–3234, 2015
2. Agarwal R: Regulation of circadian blood pressure: From mice to astronauts. *Curr Opin Nephrol Hypertens* 19: 51–58, 2010
3. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, Clement D, de la Sierra A, de Leeuw P, Dolan E, Fagard R, Graves J, Head GA, Imai Y, Kario K, Lurbe E, Mallion JM, Mancia G, Mengden T, Myers M, Ogedegbe G, Ohkubo T, Omboni S, Palatini P, Redon J, Ruilope LM, Shennan A, Staessen JA, vanMontfrans G, Verdecchia P, Waeber B, Wang J, Zanchetti A, Zhang Y; European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability: European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 32: 1359–1366, 2014
4. Zhao P, Xu P, Wan C, Wang Z: Evening versus morning dosing regimen drug therapy for hypertension. *Cochrane Database Syst Rev* 10: CD004184, 2011
5. 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* 27: 1629–1651, 2010
6. Hermida RC, Crespo JJ, Domínguez-Sardiña M, Otero A, Moyá A, Ríos MT, Sineiro E, Castiñeira MC, Callejas PA, Pousa L, Salgado JL, Durán C, Sánchez JJ, Fernández JR, Mojón A, Ayala DE; Hygia Project Investigators: Bedtime hypertension treatment improves cardiovascular risk reduction: The Hygia Chronotherapy Trial [published online ahead of print Oct 22, 2019]. *Eur Heart J* doi: 10.1093/eurheartj/ehz754
7. Rahman M, Greene T, Phillips RA, Agodoa LY, Bakris GL, Charleston J, Contreras G, Gabbai F, Hiremath L, Jamerson K, Kendrick C, Kusek JW, Lash JP, Lea J, Miller ER 3rd, Rostand S, Toto R, Wang X, Wright JT Jr., Appel LJ: A trial of 2 strategies to reduce nocturnal blood pressure in blacks with chronic kidney disease. *Hypertension* 61: 82–88, 2013
8. Poulter NR, Savopoulos C, Anjum A, Apostolopoulou M, Chapman N, Cross M, Falaschetti E, Fotiadis S, James RM, Kanellos I, Szigeti M, Thom S, Sever P, Thompson D, Hatzitolios AI: Randomized crossover trial of the impact of morning or evening dosing of antihypertensive agents on 24-hour ambulatory blood pressure. *Hypertension* 72: 870–873, 2018
9. Rorie DA, Rogers A, Mackenzie IS, Ford I, Webb DJ, Willams B, Brown M, Poulter N, Findlay E, Saywood W, MacDonald TM: 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* 6: e010313, 2016
10. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K: Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: A prospective study. *Circulation* 107: 1401–1406, 2003

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