Chronotherapy of hypertension: let's not throw the baby out with the bathwater!

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We read with interest the meta-analysis by Lee *et al.* [1] and the attached editorial by Reboldi *et al.* [2] addressing the unresolved issue of what the best timing is for antihypertensive medications to maximize their cardiovascular benefit. The controversy arises mainly as a consequence of clinical trials conducted in Spain [3,4]. They have been challenged with respect to the validity of the methods used and therefore the plausibility of their results [5], and they should be treated with caution. Likewise, studies from China included in the recent meta-analysis might have similar methodological inadequacies [1]. Nevertheless, the debate is far from settled.

We agree with Lee *et al.* and Reboldi *et al.* that the decision about the optimal antihypertensive administration time (morning vs. evening) is complicated. However, we believe an answer could be found once the question is clearly defined and the study is appropriately designed. Clearly, more and better designed randomized clinical trials (RCTs) are needed. However, the confusion arises from several factors.

First, there is ambivalence between the aim of answering clinically relevant questions pragmatically and that of establishing the underlying mechanisms of interventions via explanatory trials. For example, both TIME [6] and BedMed [7] were designed to answer a purely clinical question, not to elucidate mechanisms of action. Conversely, some small studies included in the latest meta-analysis [1] were focusing on the pharmacokinetics and pharmacodynamics of drug classes [8].

Second, there is ambivalence in focusing on blood pressure (BP) lowering effect (either daytime or nocturnal) vs. addressing the effectiveness of the treatment on fatal and nonfatal cardiovascular events. Hence, the choice of the clinical outcome can be a significant source of confusion. Elevated nocturnal BP is the strongest predictor of cardiovascular mortality and morbidity, however clinical guidelines do not take nighttime BP into account when setting BP targets, because it is not routinely measured and no properly designed RCTs have assessed the benefit of lowering night BP. Therefore, when debating the best dosing time of antihypertensive medications, a focus on fatal and nonfatal cardiovascular outcomes would be preferred, as indicated in the recent European Society of Cardiology (ESC) recommendations [9]. After all, both TIME and BedMed did not measure BP reliably. In sub-group analyses of self-reported home BP readings, TIME detected lower morning BP in the evening dosing group (1.8/0.4 mmHg) [6] and conversely lower evening BP in the morning dosing group (1.1/0.9 mmHg) [6]. BedMed on the other hand conducted 24 h ABPM in approximately 300 participants in the Alberta area [7]. They found lower nocturnal BP in the evening dosing group (BedMed 7 mmHg systolic [7]). Neither of these differences resulted in improved cardiovascular health outcomes.

Third, the current studies failed to consider or satisfactorily deal with likely mediators of the relationship between dosing time and outcomes, amongst them, treatment adherence and chronotype. For example, one limitation of the TIME study – as well as other smaller studies - was the reliance on self-reported adherence to dosing time without any measure of adherence to prescribed antihypertensive medications [3].

Moreover, recent evidence has suggested chronotype (a behavioural marker of personal circadian rhythm) as a possible effect modifier. In the TIME chronotype subgroup, 5358 participants returned the ultra-short version of the Munich ChronoType Questionnaire (μMCTQ). We estimated chronotype as midpoint of sleep on free days (MSF) corrected for sleep debt on workdays (MSFsc). Sleep midpoint (hours:minutes) was treated as a continuous variable, with later midpoints of sleep indicating a 'later chronotype' ($n = 1414$; 26%) and earlier midpoints of sleep an 'earlier chronotype' ($n = 1335$; 24%); the remaining participants being intermediate ($n = 2442$; 45%) [10]. They were equally allocated to morning and evening dosing of their usual antihypertensive medications. After a median follow-up of 5.1 years, we observed a lower rate of hospitalization for nonfatal myocardial infarction when dosing time was synchronized with the participant's chronotype, specifically in later chronotypes receiving evening dosing and in earlier chronotypes receiving morning doses (interaction $P < 0.001$). Although the detailed analysis has not yet been published, the BedMed researchers have reported that '*there were some trends in the direction that the TIME group were suggesting*' [11]. In line with the main TIME study results, we found no effect of dosing time on cardiovascular

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outcomes in the intermediate chronotypes. Additionally, we observed that later chronotypes showed a trend towards an increased risk of nonfatal stroke, independent of dosing time, in line with the evidence that a later chronotype is an independent predictor of cardiovascular events [12]. If confirmed in RCTs, these observations may suggest that simply establishing chronotype may identify individuals in whom a re-alignment of dosing time of antihypertensive medications with their circadian rhythm (personalized chronotherapy) might provide further cardiovascular clinical benefit.

The recent debate at the ESC Congress in London has indicated that with the results of TIME and BedMed the controversy has been put to rest as far as the concept of 'chronotherapy' of hypertension is concerned [4]. However, no hypertension clinical trial to date has been designed with a good methodological understanding of both cardiovascular disease [3,4] and chronobiology [6,7]. Therefore, we would recommend a more careful approach to the interpretation of the results so far. More crucial factors may have been missed, that conceal a clearer answer.

In the absence of clear evidence, let's not throw the baby out with the bathwater!

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Conflicts of interest

There are no conflicts of interest.

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