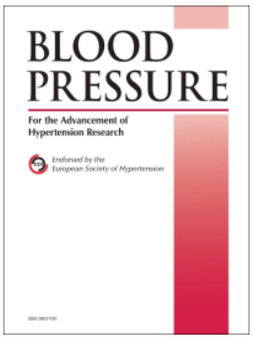

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TIME to face the reality about evening dosing of antihypertensive drugs in hypertension

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EDITORIAL

TIME to face the reality about evening dosing of antihypertensive drugs in hypertension

Should blood pressure (BP) medications be taken in the morning or in the evening? The TIME study results were presented at the ESC congress 2022 and published not too long after [1]. TIME was a large prospective, randomised clinical trial that investigated whether taking BP medications in the evening improves cardiovascular outcomes compared to taking the medications in the morning. A total of 21,104 participants from the United Kingdom were randomised in a 1:1 ratio to take their usual BP medications in the morning or in the evening. The average age of participants was 65 years, 58% were men and 98% were white, 14% had diabetes, 4% were smokers, 13% had prior cardiovascular disease, and mean BP at entry was 135/79 mmHg. The median follow-up duration was 5.2 years, but some patients were followed for over 9 years. The study was funded by the British Heart Foundation. The composite primary endpoint was hospitalisation for nonfatal myocardial infarction (MI) or nonfatal stroke, or vascular death. Secondary outcomes were non-fatal stroke, non-fatal MI, cardiovascular death, all-cause mortality, and heart failure hospitalisation. The primary endpoint occurred in 362 (3.4%) participants in the evening-dosing group (0.69 events per 100 patient-years) and 390 (3.7%) in the morning-dosing group (0.72 events per 100 patient-years), giving an unadjusted hazard ratio of 0.95 (95% CIs, 0.83–1.10; $p = 0.53$).

The results of this large randomised study clearly show that there was no difference in the primary outcome between the morning and the evening dosing groups. There were also no differences between groups for the secondary outcomes as well as between pre-specified subgroups. Thus, for the prevention of MI, stroke or vascular death taking BP medications in the evening is no better or worse than taking them in the morning; the key message being that patients can take their BP medications whenever it is convenient to them.

Taking the medication at night does not result in an increase in nocturnal hypotension that translates into more dizziness and injurious falls if patients who get up to use the bathroom during the night because the rate of fractures and hospitalisation for fractures were also identical between the two groups.

TIME was a pragmatic study, with participants recruited from primary and secondary care and registering on the internet, and information on hospitalisations and deaths obtained from participants by email and through record linkage to national databases. Further data were gathered from family doctors and hospitals, with an independent adjudication by a blinded committee.

The study did find some differences between the two dosing schedules in the BP profiles. When antihypertensive medication was taken in the morning, BP was higher in the morning and lower in the evening while the reverse was true with the evening dosing. The difference was not large, just 1–2 mmHg, and did not translate into any difference in outcomes. This indirectly speaks against a protective effect of a therapeutically-dependent enhancement of the physiological nocturnal BP reduction despite the evidence that attenuation of nocturnal BP fall (from dipping to non-dipping and reverse dipping) is accompanied by a progressive increase of cardiovascular risk [2]. This conclusion, however, may not hold for all patients. Studies with a limited number of participants have shown an apparent benefit of night-time dosing (and thus greater therapeutic BP falls) in certain patient groups, such as those with sleep apnoea, non-dippers, and patients with nocturnal hypertension. If the aim is to look at specific groups of patients then investigators will have to do larger studies in those particular groups, with a quality level as good as that of the TIME trial in which all events were adjudicated and adherence to treatment was measured and good, i.e. at 60%.

The TIME results are in direct contradiction with those of the HYGIA Chronotherapy Trial [3] published in 2020, which found an extremely large protective effect (>50% reduction of cardiovascular outcomes) of evening antihypertensive drug dosing. The study attracted an immediate large media attention, but also much criticism, including an 'expression of concern', and is raising several important methodological questions and perplexities [4,5]. Further, a systematic review from the International Society of Hypertension (ISH) published recently concluded that previous trials of bedtime antihypertensive dosing (Table 1) all had 'major flaws' [6] and that thus, bedtime drug dosing should not be routinely recommended in clinical practice. TIME adds to this conclusion, however, that in general bedtime dosing is not associated with any harm, which expands the dosing choice at disposal of the doctor and is preferable by the patient. This does not mean that patients can do as they wish or that morning and evening dosing can be changed at will. Also to be considered is that the vast majority of well-conducted outcomes studies that are used to guide the treatment of hypertension administered all drugs in the morning.

Table 1. Studies mentioned in the literature (detailed assessed in reference [6]) with our comments.

Study acronym	Design and comments
HYGIA	*Non-randomized observational data
MAPEC	*Non-randomized observational data
CONVINCE	**Randomised double-blinded clinical trial aborted by the sponsor
HOPE	***Randomised double-blinded clinical trial; ramipril *vs.* placebo in high risk patients. Blood pressure collected *post-hoc* from hospital charts
FACET	****Randomised open label
SYST-EUR	***Randomised double-blinded clinical trial; nitrendipine *vs.* placebo
Sobiczewski et al.	*****Single centre prospective observational study
SYST-CHINA	***Non-randomised prospective study; nitrendipine *vs.* placebo

Before the TIME study, there has never been a properly designed outcome trial investigating the question of morning *vs.* bedtime dosing of antihypertensive drugs on cardiovascular outcomes.
*See our comments detailed in references [4,5].
**No significant finding.
***Placebo-controlled and irrelevant for the research question discussed.
****Morning fosinopril is marginally better than bedtime amlodipine but data unadjusted.
*****Unclear design and results irrelevant to the research question discussed.

The TIME study was an important study, far more reliable than the observational HYGIA study as we have discussed in detail before [4,5]. From a scientific point of view, patients have a choice as to when to take their medication, but we strongly recommend taking blood pressure medication in the morning since adherence to antihypertensive medication is proven to be worse at bedtime [7]. However, providers may consider bedtime dosing in patients proven to have high night-time blood pressure. A possible alternative approach for patients taking more than one drug could be to take one in the morning and the remainder in the evening which may give better 24-h coverage similar to a higher smoothness index on combination treatment compared to monotherapy [8].

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