



## Blood pressure medication should not be routinely dosed at bedtime. We must disregard the data from the HYGIA project

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## Blood pressure medication should not be routinely dosed at bedtime. We must disregard the data from the HYGIA project

Because they were intrigued by the results, many colleagues and journalists have made us aware of the paper “Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial” by Hermida et al. which was published in the European Heart Journal [1]. The publication and the accompanying editorial [2] have received a great deal of attention in Europe, the UK and the USA (<https://www.jwatch.org/na51128/2020/03/17/taking-antihypertension-medications-night-interview>). We continue to be concerned by several aspects of the study.

First, we find it strange that a large randomised clinical trial (RCT) with 19,084 enrolled patients conducted in Europe over many years could have escaped our attention with very little reporting on it at meetings or in preliminary publications. The 2019 publication cited above, to our surprise, reported essentially the same data previously reported in 2018 in the same journal [3], again with an accompanying editorial [4]. While in the current paper the authors stated in the Abstract “In this multicentre, controlled, prospective endpoint trial, 19,084 hypertensive patients were assigned (1:1),” they stated in the former 2018 paper “We prospectively evaluated 18,078 individuals with baseline ambulatory BP ranging from normal blood pressure to hypertension.” However, when reading the 2018 paper, including its Table S1, it became evident that the 2018 European Heart Journal paper was a preliminary report of the current “endpoint trial.” In the current article [1] we were surprised by the lack of Supplementary material showing more details of the protocol and data analysis, including assessment of endpoints using a prospective randomised open blinded endpoint (PROBE) design. Our reading of the protocol paper [5] suggested to us that no properly randomised RCT had been performed.

The study protocol published in 2008 on ClinicalTrials.gov initially anticipated the recruitment of 5000 patients. Actual recruitment began in 2007 and, without evident justification, intended enrolment increased to 15,000 in 2014 and 18,000 in 2016. This marked increase is surprising, as in the published protocol [5], 10,700 individuals would have been sufficient for the detection of a reduction in morbidity/mortality of >20% after a median follow-up of 5 years. Of note, the primary endpoint included 15 items. The randomisation described is an unclear process. The database appears as a summary database of multiple smaller studies already completed and published, such as the MAPEC study [6],

which included 2156 hypertensive patients in an identical protocol. There is no evidence that the strict rules that apply to RCTs were implemented, no indication of how the conduct of the study was monitored and no documentation of the membership of the event adjudication committee or of audit by independent investigators. For example, it is unclear how the investigators assessed and dealt with potential adverse events occurring during the night.

We are very concerned about this approach; consequently, we contacted some key opinion leaders in US and in some European countries to gather their positions on the paper. The responses received in November 2019 were shocking. The email responses were included in a claim package that we submitted to the Editor-in-Chief of the European Heart Journal, who forwarded them for further scrutiny to the journal’s ethical committee. Original email texts and other materials are on file.

When evaluating the patient characteristics and their changes over the period of follow-up multiple issues arose. Further detailed discussion questioning the plausibility of the reported data from a clinical point of view is beyond the scope of this paper.

According to the initial protocol (ClinicalTrials.gov NCT00741585) the authors engaged 20 centres to perform the study, but this grew to 40 centres and 292 physicians doing yearly 48 h ABPM on 19,000 patients. On this background, only 607 patients dropped out because of inappropriate 48 h measurements – this seems impossible if one takes into account the known difficulties that one encounters when using ABPM devices. Moreover, from a methodological point of view, one of our colleagues carried out a technical assessment of the HYGIA project. Ambulatory blood pressure measurements (ABPM) were made with Spacelabs instruments that barely last 48 h in clinical use even when rechargeable batteries were used. Performing 48 h measurements on more than 19,000 patients annually would result in an enormous battery consumption. At last, in total, the HYGIA study should have produced over 150,000 long-term blood pressure measurements with a failure rate of less than 10% – which we cannot achieve in clinical use – not even with Spacelabs devices. Another point is data consolidation. The solution offered by Spacelabs appears not suitable for handling such a large potential set of data.

The impact of a paper published in European Heart Journal is large. Journalists in good faith will continue writing about the study in newspapers and other venues, and patients may start following this untoward advice, namely taking some of their BP lowering medication at bedtime. Our opinion is that this is undocumented and can be dangerous for many patients who experience very low BP in the middle of the night. Excessive night-time lowering of blood pressure, including over-dipping or extreme-dipping, has been associated with an increased risk of ischaemia in patients with coronary heart disease [7] and an increased risk of developing silent cerebral infarcts [8]. These risks are especially great in older patients [9,10].

Further, it has been shown using the Medication Event Monitoring System (MEMS) that drug adherence is significantly lower when drugs are taken in the evening when compared to taking medication in the morning [11].

We consider the situation very serious. As editors of journals endorsed by the European Society of Hypertension and/or present or past members of the European or US Hypertension Guidelines Committee, we feel responsible to send out this message:

The reported data from the HYGIA project must be interpreted with great caution. In our opinion, there Is No Reliable Evidence That Blood Pressure Lowering Medications Should Be Routinely Dosed At Bedtime, Unless There Is A Specific Evidence-Supported Indication.

## Disclosure statement

RK is president of the European Society of Hypertension. SEK, MB, KN and SO are editors of Blood Pressure. GM is co-chair of the 2018 European Hypertension Guidelines. RK, SEK, MB, KN, SO and GM report no relevant conflicts of interest to disclose related to this editorial.

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