We read with great interest the recent article by Professor Hermida and colleagues in the European Heart Journal(1), which appears to show a striking reduction in cardiovascular events in patients assigned to taking their antihypertensive medications in the evening.

We would be interested in how the safe and ethical conduct of the Hygia trial was overseen. A 45% relative risk reduction in cardiovascular disease outcome would have been apparent before the median follow-up duration of 6.3 years. This begs the question, why was the trial allowed to continue for more than 6 years despite a significant difference in event rates that must have been evident earlier in the study?

Only adjusted hazard ratios were reported for the primary outcome, with adjustment made for various baseline characteristics that were not pre-specified. What was the reason for not pre-specifying factors for adjustment?

We would be fascinated to learn how the Hygia study achieved their incredible patient retention rate. It is remarkable that, in a study with 19,084 participants, no patients were recorded as lost to follow-up despite annual visits requiring 48-hour ambulatory monitoring, and only 84 patients had <1-year follow-up.

It is also not clear to us how allocation was managed. Was this a single, prospective randomised trial? The title of the paper gives the impression it was, but other published information suggests it was not. The published rationale and design paper(2) states that patients were randomized using a computerised random number generator, but then goes on to state that patients were randomized separately to different antihypertensive medications regimens as part of 3-6 month trials. The protocol also refers to further trials of combination therapy for patients who were improperly controlled according to ABPM criteria. Despite the description of these sub-studies, the protocol states that medication choice was at the discretion of the treating physician. We would be interested to find out how many patients took part in one or more of these sub-studies and how they were incorporated into the final study results, particularly given the significant difference reported between the groups in terms of medication choice.

Finally, we were surprised by the implausibly large effect size of night-time blood pressure treatment dosing which (by a long way) is the biggest difference in mortality between treatment groups ever reported in a blood pressure lowering trial, and even more striking for a primary prevention study that is not placebo-controlled. The HOPE trial(3) and the Syst-Eur trial(4) (cited in the main Hygia paper) were both trials comparing a single antihypertensive drug to a placebo. Interestingly both trials demonstrated a much smaller effect size than the Hygia study despite larger BP differences, and both were terminated early on safety grounds. As a group conducting a clinical trial comparing morning versus evening dosing of medication for hypertension treatment in over 20,000 patients(5), we look forward to learning more about how this fascinating study result came about, particularly as our independent data monitoring committee has not seen any reason to terminate our study early.

Yours sincerely,

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