Hypertension

COMMENTARY

Missing Verification of Source Data in Hypertension Research: The HYGIA PROJECT in Perspective

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Several large randomized clinical trials of blockers of the renin-angiotensin system in patients with hypertension, including the JIKEI Heart Study, the KYOTO Heart study, and the NAGOYA Heart Study, were retracted between 2003 and 2012 due to insufficient verification of adjudication of events. In the following, we discuss recently retracted papers in hypertension research, emphasizing the reasons for retraction, and highlight similarities between the retracted articles and the recently published HYGIA PROJECT on bedtime administration of antihypertensive drugs.[1]

The PREDIMED study (Prevención con Dieta Mediterránea) was retracted and later republished in 2018.[2,3] Eighty percent of the participants in the PREDIMED study had hypertension, and a subgroup analysis showed that the beneficial effect of intervention in PREDIMED was limited to these 80% with hypertension.[2] The primary end point was a composite of myocardial infarction, stroke, and cardiovascular death, occurring in 96 (3.8%) participants assigned to a Mediterranean diet with extravirgin olive oil, in 83 (3.4%) participants assigned to a Mediterranean diet with nuts, and in 109 (4.4%) participants in the regular Mediterranean diet group. The authors described a series of misrepresentations following source data verification,[3] most importantly, departures from the randomization process.[3] Instead of individual random allocation, several hundred participants were allocated on a household basis or depending on which clinic they attended.

In 2020, a registry study showing a stronger relationship between ambulatory blood pressure measurement (ABPM)[4] than clinic blood pressure (BP) with mortality was retracted by the authors. They stated, "Because we have identified inaccuracies in the analytic database and data analyses underlying 'Relationship between Clinic and ABPM and Mortality', which was published in the April 19, 2018, issue of the Journal, we wish to retract the article."[5] One of the authors in a newsletter interview reported inconsistencies between the original database and a new one created from the original source data, in addition to problems with the statistical analyses.[6] The Universidad Autónoma de Madrid investigated the issue. The authors then retracted a subsequent article and HYPERTENSION/AHA published the following statement: "After review and consideration, the problems with data set and analysis could not be addressed and corrected; therefore, out of caution, the authors have requested to retract the article."[7]

While the results from PREDIMED and the ABPM registry may not be valid, adherence to a Mediterranean diet with or without supplement is probably not harmful, and the retraction of the ABPM analysis reduces its damage. In contrast, serious problems persist in relation to the HYGIA PROJECT's conclusion that bedtime administration of antihypertensive medications reduced the relative risk of composite cardiovascular events by 45% (95% CIs, 39%–50%), including a 56% (95% CIs, 44%–66%) reduction in cardiovascular mortality.[1] The

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article received extensive coverage in social and mass media, with an Altmetric score of 2124 in March 2021, and many of our patients have recently asked if they should take their antihypertensive drugs in the evening.

A lowering of BP during night can find some support from the argument that pharmacokinetically, bedtime administration of antihypertensive drugs may favor BP control during the early morning hours where a noticeable fraction of fatal and nonfatal cardiovascular events occur.[8] In addition, several studies have shown that nighttime BP values predict cardiovascular outcomes and mortality better than daytime ones.[9] However, no evidence has ever been obtained that treatment-induced reductions in nighttime BP have a protective effect, a possibility raised by trials such as Heart Outcomes Prevention Evaluation (HOPE) on a pure hypothetical basis.[10] Rather, the morning BP surge, which increases when night time BP reduction is more pronounced, has been associated with an increased cardiovascular risk, stroke risk in particular.[11]

It is clear that excessive lowering of BP during the night may also be hazardous for some specific patients, as recently reviewed.[12] Over-dipping (>20% fall in nighttime BP) has been associated with increased risk of myocardial ischemia and silent cerebral infarcts, especially in elderly patients. Low BP during the night may also increase the risk of falls in elderly patients with nocturia. Nocturnal BP fall is also a risk factor for progressive visual field loss in patients with glaucoma,[13] and adherence is lower for drugs taken in the evening compared with the morning.[14] Given the uncertainty of benefit versus harm and the problems with HYGIA reported below and summarized in the Figure, we advise against changing clinical practice based on the current evidence.

A problem with HYGIA is the large growth over time in the number of participants reported in Clinicaltrials.gov starting at 5000 participants in 2008, increasing to 15000 in 2014, 18000 in 2016, and ending at >19000 in the recent article.[1] According to the methods paper, 10700 participants would achieve 95% power to find a 20% reduction in the relative risk for cardiovascular disease at 5 years of follow-up, and an additional 3700 participants with diabetes and 3700 with chronic kidney disease would achieve 90% power to detect a 20% relative risk reduction in these subgroups, respectively.[15] First, designing a study with 90% to 95% power to detect differences in individual subgroups may be questioned from an ethical perspective. Second, when an excessive treatment effect is observed (as here 45% compared to 20% in the protocol), it is common practice and ethically recommended to stop recruitment and terminate the study. Thus, expansion of the study base, as reported on clinicaltrials.gov, seems inappropriate.

Modern trials have formal stopping rules, considered by their data safety and monitoring boards in interim analyses to guarantee the safety of study participants. The HYGIA methods paper[15] stated that interim analyses were planned every second year to identify the need for premature termination but did not specify who would perform such analyses and which criteria were to be used to terminate the trial. Surprisingly, an editorial[16] accompanying the HYGIA article[1] dismissed these issues, stating that HYGIA was pragmatic and underfunded, a peculiar conclusion when the number of participants increased 4-fold, and the study was continued for an extra year.

Although presented as a prospective randomized open-label blinded end point trial in the recent article,[1] the HYGIA methods article stated[15]: "Randomization of participants to treatment-time regimen was done separately for each hypertension medication or combination being tested. Specific trials to evaluate short-term (usually 3–6 months) chronotherapeutic effects on ABPM include, among many others, patients on ramipril, irbesartan, lercanidipine, nebivolol and aliskiren. Participants uncontrolled according to ABPM criteria on monotherapy are eligible to participate in prospective trials designed to evaluate the administration-time-dependent effects of combination therapy." Thus, it seems to us that HYGIA was in fact many small trials, not one large trial, as reported recently.[1] Furthermore, in a 2018 publication, HYGIA was described as a prospective evaluation of participants, without using the term randomization.[17] It is evident from the patient characteristics tables that both articles[1,17] reported data from the same study. If HYGIA were a randomized controlled trial, it is very unfortunate that randomization was not taken into account, or even mentioned, in the previous article.[17] These publications add to the confusion regarding the actual study design of HYGIA.

Examination of baseline characteristics of enrollees in prospective clinical trials revealed falsifications and led to retraction of several articles.[18] If properly randomized, it is unlikely that there would be differences in baseline characteristics between treatment groups in a study with >19000 participants. The HYGIA Project Table 1 showed numerically small, but statistically significant baseline differences in body mass index (P=0.030) and sleep-time relative systolic BP decline (P=0.000) between the 2 study arms.[1] In particular, the difference in sleep-time relative BP decline, of great importance to the study question, warrants further explanation. This could fit well with data from many smaller studies, as suggested in the methods paper,[15] or from a large observational study, as suggested in the 2018 report.[17]

The table of patient characteristics at the end of HYGIA shows multiple group differences, including that bedtime-dosed patients had significantly more favorable BP and blood chemistry data.[1] The authors ascribed this to benefits of bedtime dosing, but the differences also fit well with the assumption that due to lack of proper randomization, the 2 groups were not comparable. Lifestyle may differ between those preferring morning versus bedtime intake of drug, and given the open-label design, investigators may have treated participants differently depending on treatment group, resulting in performance

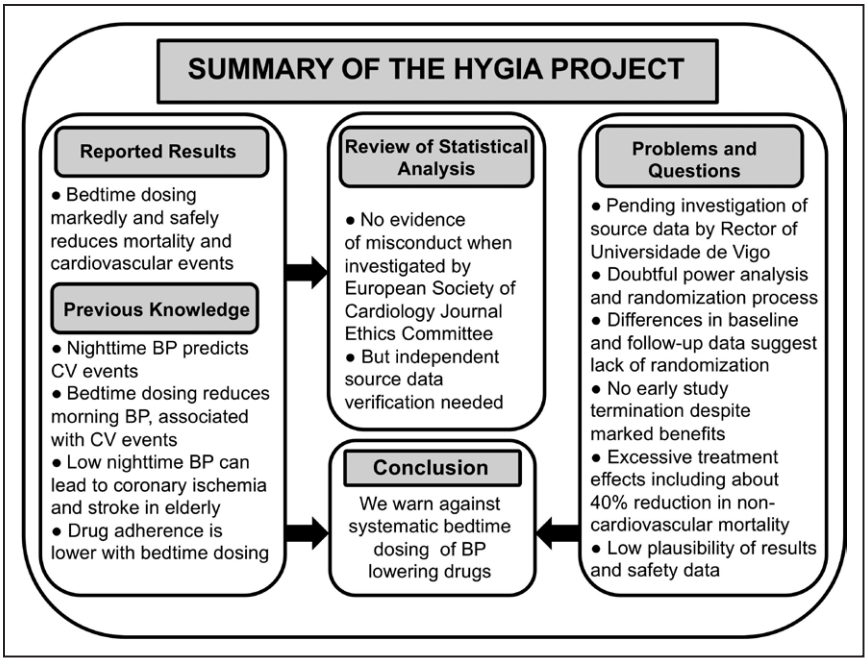

Figure. Schematic summary of the HYGIA Project; reported results of bedtime dosing of ≥1 antihypertensive drugs, previous knowledge regarding bedtime dosing, review of the outcome by the European Society of Cardiology Journal Ethics Committee, problems and questions related to the project, and the conclusion of this commentary.
BP indicates blood pressure; and CV, cardiovascular.

bias. Furthermore, the bedtime group received more calcium-channel blockers and fewer diuretics and β-blockers compared with the morning group, possibly contributing to fewer cardiovascular events, independent of the timing of drug intake.[19]

One of the most important factors to consider when interpreting scientific studies is the plausibility of the observed results. This has been conceptualized in different ways in different contexts, such as Bradford-Hills criteria for causal inference from observational research or the use of priors in Bayesian statistics. Unlike the editors[16] of the HYGIA article,[1] we think that the unexpected large effect of bedtime dosing of antihypertensive drugs on cardiovascular protection is an important reason to question the validity of HYGIA.[1] The observed beneficial effect on noncardiovascular mortality, which, by hand counting from all-cause and cardiovascular mortality is ≈40%, adds to the concerns. In the absence of an explanatory mechanism and previous data supporting such effects, the most likely explanation is some form of bias.

Due to the above concerns, raised soon after HYGIA appeared online, the Journal Ethics Committee of the European Society of Cardiology started an investigation. In the editorial published alongside the main article in December 2020, they report that "no evidence of fraud was found.[16] However, the European Society of Cardiology Journal Ethics Committee cannot verify the source data, as this would require enormous resources that would be well beyond the expectations of the peer-review process. However, the editors have recommended to the Rector of the Universidade de Vigo to perform such an investigation in the near future and to report on its outcome."[16]

In our opinion, the efforts made thus far are not sufficient to accept the results of HYGIA. Lack of source verification was the key reason for retraction of the other articles discussed above. We find both the randomization process and the data presentation of HYGIA questionable and think that it is premature to conclude that there is no evidence of misconduct, given these major concerns. Although we certainly welcome further investigation by the Universidade de Vigo, previous experience shows that investigation by the responsible university may not be enough.[20] This setting is particularly delicate as the Universidade de Vigo holds a patent for an ABPM system, developed by 3 of the HYGIA investigators.[21]

Misconduct accounts for the majority of retracted scientific publications.[18] Our impression is that the problem is growing in clinical research, as shown by the number of recently retracted articles on the treatment of coronavirus disease 2019 (COVID-19) infection. Misconduct may result in harmful treatment of patients, disturb ongoing high-quality research, discredit journals, and weaken the public's respect for scientific work. Unfortunately, some articles are quoted even for years after their retraction.[22] We conclude that independent source data verification (preferably not by the host university) is urgently needed before applying the HYGIA findings to clinical practice. Furthermore, results from 2 ongoing randomized cardiovascular outcome trials, the TIME study from the United Kingdom[23] and Bed-Med from Canada,[24] should be awaited before one can conclude whether bedtime dosing of antihypertensive medication may lower cardiovascular events better than dosing of medication in the morning.

ARTICLE INFORMATION

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