May We Die Twice?

To the Editor:

The re-analysis of the INSIGHT trial presented by Mancia and associates recently in Hypertension1 is questionable in some aspects and may not have internal validity. Any conclusion based on analysis of subgroups with a small proportion of the participants of the entire trial should be taken as hypothesis generating and may invalidate it if not established a priori.2 This report does not comply with these rules, since the conclusions were based on a secondary analysis of an outcome not defined a priori, in a subgroup of 1/5 of the whole participants of the original trial. Differently from that stated in the present manuscript, the original publication of the INSIGHT trial3 did not include total mortality, cardiovascular mortality and death from a nonvascular cause as a primary or secondary prespecified outcome. Any subgroup analysis should also be limited in view of the nonsignificant 10% higher incidence of the primary endpoint in patients treated with nifedipine GITS in the original trial.3 Independently of these shortcomings, it is difficult to follow the definition of the secondary outcome employed in this re-analysis, the composite of all-cause death, death from a vascular cause, and death from a nonvascular cause (literal). Looking at Table 4, we see that 103 individuals in the diabetic subgroup died during the study (total mortality). In the figure on the same page, however, we may see that 214 individuals with diabetes presented the secondary outcome. In the original report of this trial,3 the sum of partial causes of deaths was 305 (all deaths, first event, Table 4). In the current report, the sum of all deaths, in diabetics and nondiabetic patients (Figure) was 780. In the absence of an alternative explanation, it seems that the secondary outcome employed in this report was the sum of all-cause death, death from cardiovascular cause and death from a nonvascular cause; ie, some participants may have died twice during the trial.

In addition, the advantage of nifedipine GITS over diuretic in terms of effect on hard outcomes was restricted to this unusual outcome. The higher incidence of coronary heart disease and heart failure in diabetics was similar to that observed in the original trial, despite not being formally significant in view of the small sample size. Based on the findings of this re-analysis, the authors state that nifedipine could be considered as first-line therapy for hypertensive diabetics. Moreover, they state that nifedipine has direct organ-protective properties in addition to the protection provided by the blood pressure lowering effect per se. In view of the recent findings of the ALLHAT trial,4 it is evident that we need to lower blood pressure in order to get cardiovascular protection, and that this may be better accomplished starting treatment with a diuretic, in patients with or without diabetes. It is certainly time to stop fooling us.5

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Response

We thank Dr Flávio Fuchs for his interest in our study.1 First, there was no question of double-counting in INSIGHT. Unlike some other trials, we were careful to count only one event per person for our analyses, so that our analyses were not compromised by some patients having multiple nonfatal events. This is in contrast to information supplied to the Blood Pressure Lowering Treatment Trialists’ Collaboration whose meta-analyses count individual outcomes, acknowledging that trials and meta-analyses serve different purposes.

Dr Fuchs confused 780 secondary outcomes in INSIGHT as though such was the total number of deaths. This misunderstanding was perhaps due to our paper inadvertently containing two definitions of secondary outcomes—the correct one being a composite of primary endpoint plus all-cause mortality and nonfatal vascular events (transient ischemic attacks, renal failure, and new or worsening angina). Onset of new diabetes was a predefined subgroup of interest and not a post hoc analysis. As a further point of clarification, our article reported results consistent with the intention-to-treat analyses of the original publication, based on 6321 patients.2 Use of at-risk denominators, ie, nondiabetics at baseline, changes the percentages of incident diabetes to 5.4% for nifedipine versus 7.0% for the diuretic combination, with odds ratio (95% CI) 1.315 (1.044, 1.656), P=0.02, a difference very slightly more significant than previously stated. In the longer term, beyond the scope of clinical trials with typical 4- to 6-years’ follow-up, consequences of newly-diagnosed diabetes remain unknown, although there is suggestive evidence that in-treatment diabetes confers a risk similar to that of diabetes at baseline.3,4 INSIGHT, uncommonly for outcome trials, regarded heart failure as a primary endpoint. To allow a more direct comparison with ALLHAT, any re-analysis considering heart failure as a secondary endpoint brings nifedipine and co-amizolide regimens even closer to equivalence,2 further strengthening the argument that blood pressure, not particular treatment choice, is what matters.

We agree with Dr Fuchs that the results derived from subgroup analysis (widely explored in all trials) should be viewed with caution, but we acknowledged this in our paper. We disagree, on the other hand, with his interpretation of ALLHAT data. There is no evidence in ALLHAT that diuretic is superior to the other agents tested. Because (1) the study did not include a placebo group and (2) previous studies with diuretic treatment involve patients with higher initial blood pressures, there is also no evidence that, within the blood pressure ranges explored in the trial (from about 145/85 to about 135/75 mm Hg), lower blood pressure is more protective.

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