Letter by Nguyen Regarding Article, “Acetaminophen Increases Blood Pressure in Patients With Coronary Artery Disease”

To the Editor:

I read with interest the article by Sudano et al.1 In this double-blind, randomized, placebo-controlled crossover study involving 33 patients, the authors found a small increase over 24 hours in systolic and diastolic blood pressure (3/2 mm Hg) in favor of acetaminophen, this without any significant changes in oxidative stress, inflammatory markers, and endothelium-related vasodilatation. On the basis of this blood pressure effect, the authors call for more caution and for larger, well-designed, confirmatory trials.

The results of this trial are important, both because they may change clinical practice and because of their potentially major public health implications due to the widespread use of acetaminophen, particularly among patients with high cardiovascular risk. Therefore, concerns about the robustness of the results are justified and should be completely dissipated for physicians confronted with their translation into clinical practice. The authors can do this easily by clarifying the following points:

Validity of the Results

First, the Bonferroni correction, taken into account for the measured end points, was, in contrast, not mentioned for interim analyses. This is important because correction might statistically invalidate the results. In fact, the given P values are marginal for statistical significance. Second, several significant modifications to the original protocol, carefully documented by the authors at the Web site http://www.clinicaltrials.gov (unique identifier NCT00534651) may have altered the methodological strength of the initially intended standard design of the trial and therefore rendered the obtained results particularly vulnerable to biases. Furthermore, even if valid per se, one may wonder if the results of this trial might not be due to chance because of the small number of participants and especially considering other contradictory results from previous trials.2–4 Finally, there is presently, in contrast to other nonsteroidal antiinflammatory drugs, no sound biological and mechanistic basis to explain the blood pressure effect of acetaminophen.

Clinical Utility of the Results

Even in case of perfect validity of the obtained results, I wonder if the limited hypertensive effect of acetaminophen as a surrogate marker may actually imply a significant increase in clinical cardiovascular outcomes. The authors are invited to comment on this point, particularly in light of the recently published Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP) trial5 in which no difference in cardiovascular events was found in high-risk diabetic patients with systolic blood pressure <120 mm Hg and those with blood pressure of 120 to 140 mm Hg.

Clearly, the results provided by Sudano et al are adding more complexity to the cardiovascular safety issue of nonsteroidal antiinflammatory drugs and complicating clinical pain management. More high-quality data are therefore badly needed to resolve a part of this puzzle and to reestablish the confidence of the public, especially of those patients receiving long-term treatment with acetaminophen. To this purpose, I agree with the authors that other larger, flawlessly designed, and carefully executed double-blind, randomized, controlled trials should be conducted; these could probably be completed more rapidly and with less effort by renouncing the time-consuming expensive laboratory parameters and by resorting to other more easily recruitable populations (eg, hypertensive patients) with a unique goal to confirm or discard the blood pressure effect of acetaminophen. In case of negative results, everything else would not need to be done, and the public would be definitely reassured. On the other hand, positive results would, besides opening new research perspectives, teach us once again to be more critical of our own handling of so-called certainties.

In the meantime, even when confronted with the absence of any conﬁrmably safer alternatives for pain management, the concerned clinician can, in my personal opinion, still continue to prescribe acetaminophen with little risk by monitoring blood pressure more closely and by adapting antihypertensive treatment if necessary.

Disclosures

None.

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References

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