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Cardiovascular safety of vitamin B_3 administration

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Ferrell et al.[1] recently reported associations between serum levels of the terminal niacin metabolites *N*1-methyl-2-pyridone-5-carboxamide (2PY) and *N*1-methyl-4-pyridone-3-carboxamide (4PY) with an increased 3-year incident risk of major adverse cardiovascular events. The association of 4PY with cardiovascular risk was linked to increased endothelial VCAM-1 expression and increased leukocyte adherence to the vascular endothelium as a potential causal mechanism. The study suggests that niacin supplementation may be harmful by increasing cardiovascular morbidity and mortality. Strikingly, the exact mechanism identified as a potential adverse outcome by Ferrell et al.[1] has been noted to be suppressed with niacin supplementation[2], arguing for a more complex interpretation of the findings. Here, we would like to briefly put the study of Ferrell et al.[1] into the perspective of decades of clinical trial experience and pharmacovigilance with nicotinic acid (niacin) and nicotinamide, the two forms of vitamin B_3.

The meta-analysis cited by Ferrell et al.[1] to support their view regarding the potential adverse effects of niacin supplementation only states that 'niacin showed a marginally significant increase in all-cause mortality', at a significance of $P = 0.05$ (ref. 3). Moreover, niacin exposure in the general population investigated by Ferrell et al.[1] is much lower than in cohorts treated with high-dose niacin, where to our knowledge no such safety signals have been picked up. Unfortunately, Ferrell et al.[1] also did not address relevant methodological concerns related to the HPS2-THRIVE and AIM-HIGH trials they mention, especially concerning their distinct patient characteristics and trial design. There have already been diligent efforts to correct misinterpretations of these trials[4].

In the Coronary Drug Project[5], a long-term trial of lipid-influencing drugs in male survivors of myocardial infarction, 1,119 patients received 3 g per day of niacin and 2,789 patients received placebo, with a mean in-trial follow-up of 6.2 years. At a mean follow-up of about 15 years, all-cause mortality was 11% lower in the niacin group compared to placebo ($P = 0.0004$), and the authors reported that "the survival benefit in the niacin group is primarily evident for death caused by coronary heart disease"[5]. In another study, the long-term safety results of the sustained-release niacin Niaspan in 517 patients receiving ≤3.000 mg per day of niacin without concomitant lipid-lowering medications for ≤96 weeks showed that "although serious adverse events occurred in about 10% of patients, none were considered probably or definitively related to Niaspan"[6]. A meta-analysis of 11 randomized controlled trials with a total of 3,394 control patients and 2,682 patients receiving niacin alone or in combination concluded: "Although the studies were conducted before statin therapy became standard care, and mostly in patients in secondary prevention, with various dosages of nicotinic acid 1–3 g per day, this meta-analysis found positive effects of niacin alone or in combination on all cardiovascular events and on atherosclerosis evolution"[7]. A systematic review of 11 trials (8 double-blind) involving a total of 9,959 patients demonstrated a significant reduction in the occurrence of any cardiovascular disease (CVD) event (odds ratio (OR): 0.66; 95% confidence interval (CI): 0.49 to 0.89; $P = 0.007$) and of a major coronary heart disease event (OR: 0.75; 95% CI: 0.59 to 0.96; $P = 0.02$)[8]. Cardioprotective properties of niacin were also identified in a meta-analysis of studies reporting the effects of niacin on flow-mediated dilation in a total of 441 patients, of whom 228 received niacin and the remaining 213 received control treatment. Niacin increased flow-mediated dilation most strongly and significantly at daily doses of ≥2,000 mg or more, with a weighted mean difference of 4.40 (95% CI: 2.75 to 6.05; $P < 0.00001$) compared to controls[9]. The most recent meta-analysis on niacin and CVD outcomes, published in 2019, included 35,760 patients with CVD or dyslipidemia and "found no preventive association of niacin with cardiovascular outcomes in secondary prevention" and showed limited beneficial effects of niacin in a stratified meta-analysis[10]. Collectively, these findings indicate that niacin is either harmless or even effective in reducing cardiovascular risk in select populations.

In line with the high tolerable upper intake level of 900 mg per day[11] (the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population) and its 'generally recognized as safe' status, the safety of nicotinamide has not been as extensively studied as that of niacin.

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The most recent large review of the safety of high-dose nicotinamide was published in 2000, when nicotinamide was under clinical evaluation for prevention of type 1 diabetes[12]. The authors of this review concluded that "nicotinamide is a safe therapy to use when given at adult doses of no more than 3 g per day". In a recent publication from 2021, higher nutritional intake of niacin equivalents was associated with lower blood pressure and a reduced risk of cardiac mortality during a 20-year follow-up in a prospective community-based study enrolling an age-stratified and sex-stratified random sample of 1,000 men and women[13].

Beneficial effects of niacin (and, to a lesser degree, of nicotinamide) have traditionally been attributed to its potential lipid-lowering activity and action on the vessel wall. Additionally, we and others have shown that systemic and local anti-inflammatory activities can be attributed to niacin/nicotinamide therapy in a tryptophan-low state, for example, in intestinal inflammation as studied in preclinical models. This anti-inflammatory effect appears to be conveyed partially by a direct interaction between tryptophan metabolites like nicotinamide and nicotinic acid with the gut microbiome, particularly if such metabolites are delivered through a pH-targeted delayed-release formulation[14]. In our view, the involvement of the gut microbiome not only in CVD pathogenesis but also in modulating the metabolism of drugs used to treat CVD, adds another layer of complexity. Understanding the role of the microbiome in the context of the findings by Ferrell et al.[1] could thus provide important insights regarding the targeted use of these agents in the setting of CVD.

In summary, and as already suggested by Ferrell et al.[1] when discussing the limitations of their study, we feel that their findings likely indicate correlative rather than causal relationships. A plausible explanation for the findings could be that an increased consumption of niacin-fortified and highly processed food not only leads to higher 2PY and 4PY levels, but also is a marker for nutritional and lifestyle habits predisposing to major adverse cardiovascular events. Further, increased levels of tryptophan degradation have been described in atherosclerosis[15], such that higher 2PY and 4PY levels could merely be markers of chronic inflammatory vascular processes, rather than causally responsible.

References

1. Ferrell, M. et al. A terminal metabolite of niacin promotes vascular inflammation and contributes to cardiovascular disease risk. *Nat. Med.* **30**, 424–434 (2024).
2. Wu, B. J. et al. Evidence that niacin inhibits acute vascular inflammation and improves endothelial dysfunction independent of changes in plasma lipids. *Arterioscler. Thromb. Vasc. Biol.* **30**, 968–975 (2010).
3. Jenkins, D. J. A. et al. Supplemental vitamins and minerals for CVD prevention and treatment. *J. Am. Coll. Cardiol.* **71**, 2570–2584 (2018).
4. Superko, H. R., Zhao, X. Q., Hodis, H. N. & Guyton, J. R. Niacin and heart disease prevention: engraving its tombstone is a mistake. *J. Clin. Lipidol.* **11**, 1309–1317 (2017).
5. Canner, P. L. et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J. Am. Coll. Cardiol.* **8**, 1245–1255 (1986).
6. Capuzzi, D. M. et al. Efficacy and safety of an extended-release niacin (Niaspan): a long-term study. *Am. J. Cardiol.* **82**, 74U–81U (1998).
7. Bruckert, E., Labreuche, J. & Amarenco, P. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. *Atherosclerosis* **210**, 353–361 (2010).
8. Lavigne, P. M. & Karas, R. H. The current state of niacin in cardiovascular disease prevention: a systematic review and meta-regression. *J. Am. Coll. Cardiol.* **61**, 440–446 (2013).
9. Sahebkar, A. Effect of niacin on endothelial function: a systematic review and meta-analysis of randomized controlled trials. *Vasc. Med.* **19**, 54–66 (2014).
10. D'Andrea, E., Hey, S. P., Ramirez, C. L. & Kesselheim, A. S. Assessment of the role of niacin in managing cardiovascular disease outcomes: a systematic review and meta-analysis. *JAMA Netw. Open* **2**, e192224 (2019).
11. EFSA NDA Panel. Scientific Opinion on Dietary Reference Values for niacin (EFSA Panel on Dietetic Products, Nutrition and Allergies). *EFSA J.* **12**, 3759 (2014).
12. Knip, M. et al. Safety of high-dose nicotinamide: a review. *Diabetologia* **43**, 1337–1345 (2000).
13. Abdellatif, M. et al. Nicotinamide for the treatment of heart failure with preserved ejection fraction. *Sci. Transl. Med.* **13**, eabd7064 (2021).
14. Hashimoto, T. et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature* **487**, 477–481 (2012).
15. Sudar-Milovanovic, E., Gluvic, Z., Obradovic, M., Zaric, B. & Isenovic, E. R. Tryptophan metabolism in atherosclerosis and diabetes. *Curr. Med. Chem.* **29**, 99–113 (2022).

Author contributions

S.S., G.H.W., M.L. and P.R. contributed to drafting and reviewing the paper.

Competing interests

S.S. reports indirect stock ownership in Gerion Biotech as well as consulting and personal fees from AbbVie, Allergosan, Amgen, Arena, BMS, Biogen, Celltrion, Celgene, Falk, Ferring, Fresenius, Galapagos/Gilead, HIKMA, I-Mab, Janssen, Lilly, Morphic, MSD, Mylan, Pfizer, Prometheus, Protagonist, Provention Bio, Sandoz/Hexal, Takeda and Theravance. G.H.W. is in part-time employment by CONARIS Research Institute AG (Kiel, Germany). M.L. reports lecture fees from Amarin, AstraZeneca, Boehringer Ingelheim, Chiesi, HRA Pharma, Lilly, Novo Nordisk, Roche and Sanofi. P.R. reports stock ownership in Gerion Biotech and consulting fees from Takeda.

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