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Niacin, food intake and cardiovascular effects

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Ferrell et al.[1] report a surprisingly strong association between terminal metabolites of niacin and major adverse cardiovascular events (MACE), amounting to roughly a doubling of MACE risk in the 4th quartile of circulating levels of the 4PY (*N*[1]-methyl-4-pyridone-3-carboxamide) metabolite. The results presented by Ferrell et al.[1] are impressive and deserve further attention. Here we would like to suggest alternative interpretations for these results; in particular, we discuss how two aspects of food intake—first, consumption of foods with high niacin content and, second, a historical shift from mealtime to bedtime administration of pharmacological niacin doses—could help explain cardiovascular effects ascribed to niacin.

The authors raise a concern regarding the degree of niacin fortification of wheat flour and cereals that is mandated by public health authorities for pellagra prevention. However, these same refined carbohydrates, along with beef, pork and chicken, which naturally supply abundant niacin, closely match the current notion of an unhealthy fast-food diet (see table 4 in ref. 2). We suggest that overall diet quality rather than micronutrient supply may account for the striking association between 4PY and MACE that was observed by Ferrell et al.[1]

The randomized controlled trial (RCT) data cited by Ferrell et al.[1] need to be further clarified. While the authors describe a 'modest reduction' of cardiovascular events among the niacin treatment group in the Coronary Drug Project, significant relative risk reductions of 26% for myocardial infarction and 24% for stroke, but not for mortality, were observed in comparison to the group receiving placebo[3]. These results are similar to or greater than the degree to which MACE were reduced in pivotal anti-PCSK9 monoclonal antibody trials. Follow-up of Coronary Drug Project participants approximately 9 years after the randomized treatment period revealed that 47.5% of all niacin-assigned participants were still alive, as compared to 41.5% of placebo-assigned participants (6% absolute reduction and 11% relative reduction of total mortality; $P = 0.0004$)[4]. This extraordinary result was echoed in the Stockholm Ischemic Heart Disease RCT. Over a follow-up of 5 years after acute Imyocardial infarction, the group of participants randomized to receive a niacin formulation experienced 22% total mortality, versus 30% ($P < 0.05$) for the control group of participants who received no drug[5]. Notably, these benefits of niacin for preventing death, myocardial infarction or stroke were observed in the pre-statin era, when standard advice specified mealtime niacin dosing to reduce flushing.

By contrast, Ferrell et al.[1] cite a meta-analysis by Jenkins et al.[6] as showing that niacin "was observed to increase total mortality" in recent RCTs among participants receiving first-line statin therapy. The risk ratio for mortality in the three included RCTs was 1.10, which was a statistically marginal effect ($P = 0.05$, not corrected for multiple comparisons). Among six other outcomes more closely related to atherosclerotic cardiovascular disease, trends in either direction occurred and did not approach significance.

Finally, we offer a testable hypothesis to account for the failure of niacin, when taken at bedtime, to improve cardiovascular outcomes, as observed in recent RCTs[7,8]. A major effect of pharmacological niacin doses, known since the 1960s but often ignored, is a profound reduction of adipocyte lipolysis, leading to >60% reduction of circulating non-esterified fatty acids (NEFAs) in the fasting state, followed by NEFA rebound[9]. When fasting, but not at mealtime, this effect could be expected to impair overall fuel supply as NEFA levels fall, leading to a counterregulatory hormone response that includes a surge in catecholamine levels[10]. Consistent with this hypothesis, bedtime dosing of niacin has been shown to result in a fall in NEFA levels and a subsequent rebound[11]. We suggest that counterregulatory sympathetic stimulation may elevate the risk of MACE, in accord with evidence that increased sympathetic activity may contribute to the increased frequency of myocardial infarction and sudden cardiac death in the morning after assuming upright posture[12,13]. In the current era of RCTs in which niacin is co-administered with statins, niacin dosing has shifted from mealtime to bedtime, raising a concern that niacin intake may trigger NEFA insufficiency and a counterregulatory catecholamine response. This hypothesis has not yet been investigated in detail, but might explain the lack of benefit for niacin that has been observed in RCTs in which participants received niacin at bedtime.

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Author contributions

J.R.G. wrote the initial draft. W.E.B. and J.R.G. together formulated arguments, interpreted available evidence and revised the manuscript.

Competing interests

J.R.G. declares no competing interests. W.E.B. served on the executive steering committee for the TRAVERSE trial, funded by AbbVie, and has received research grant support from AbbVie. In the past, both authors received institutional support from the AIM-HIGH trial funded by the US National Institutes of Health (NIH), and W.E.B. served as principal investigator of AIM-HIGH.

Additional information

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