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A terminal metabolite of niacin promotes vascular inflammation and contributes to cardiovascular disease risk

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Despite intensive preventive cardiovascular disease (CVD) efforts, substantial residual CVD risk remains even for individuals receiving all guideline-recommended interventions. Niacin is an essential micronutrient fortified in food staples, but its role in CVD is not well understood. In this study, untargeted metabolomics analysis of fasting plasma from stable cardiac patients in a prospective discovery cohort (n = 1,162 total, n = 422 females) suggested that niacin metabolism was associated with incident major adverse cardiovascular events (MACE). Serum levels of the terminal metabolites of excess niacin, N1-methyl-2-pyridone-5-carboxamide (2PY) and N1-methyl-4-pyridone-3-carboxamide (4PY), were associated with increased 3-year MACE risk in two validation cohorts (US n = 2,331 total, n = 774 females; European n = 832 total, n = 249 females) (adjusted hazard ratio (HR) (95% confidence interval) for 2PY: 1.64 (1.10–2.42) and 2.02 (1.29–3.18), respectively; for 4PY: 1.89 (1.26–2.84) and 1.99 (1.26–3.14), respectively). Phenome-wide association analysis of the genetic variant rs10496731, which was significantly associated with both 2PY and 4PY levels, revealed an association of this variant with levels of soluble vascular adhesion molecule 1 (sVCAM-1). Further meta-analysis confirmed association of rs10496731 with sVCAM-1 (n = 106,000 total, n = 53,075 females, $P = 3.6 \times 10^{-18}$). Moreover, sVCAM-1 levels were significantly correlated with both 2PY and 4PY in a validation cohort (n = 974 total, n = 333 females) (2PY: rho = 0.13, $P = 7.7 \times 10^{-5}$; 4PY: rho = 0.18, $P = 1.1 \times 10^{-8}$). Lastly, treatment with physiological levels of 4PY, but not its structural isomer 2PY, induced expression of VCAM-1 and leukocyte adherence to vascular endothelium in mice. Collectively, these results indicate that the terminal breakdown products of excess niacin, 2PY and 4PY, are both associated with residual CVD risk. They also suggest an inflammation-dependent mechanism underlying the clinical association between 4PY and MACE.

"cardiac" patients, approx 60/40 men/women
definition of "cardiac"
on other meds?
specific genetic subtype at risk?
nicotinic acid (niacin) is NOT the same as nicotinamide (niacinamide) in humans.

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide[1], but only a portion of attributable risk is accounted for by established risk factors[2]. Despite substantial advances in therapies, residual CVD risk remains high, suggesting that additional, yet unrecognized factors are involved in CVD. In randomized clinical trials of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, treatment groups achieved mean low-density lipoprotein (LDL) levels well below 50 mg dl^{-1} but still had substantial cardiovascular event

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