Impact of smoking status on the relationships of growth differentiation factor 15 with mortality and cardiovascular events in patients with suspected or known coronary artery disease: the ANOX study

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Background: Growth differentiation factor 15 (GDF-15) is a stress-responsive cytokine that plays an important role in the regulation of the inflammatory response, growth and cell differentiation. An elevated GDF-15 was found in various conditions including cigarette smoking and stable coronary artery disease (CAD), and it was reported to predict mortality and cardiovascular (CV) events in general population and in patients with established CAD. However, the impact of smoking status on the relationships of GDF-15 with mortality and CV events in patients with suspected or known CAD is unclear.

Methods: Serum GDF-15 levels were measured in 2,418 patients with suspected or known CAD undergoing elective coronary angiography, enrolled in the development of novel biomarkers related to angiogenesis or oxidative stress to predict CV events (ANOX) study, and followed up for 3 years. Patients were divided into 3 groups according to the smoking status: current (n=428), past (n=1,035), and never smokers (n=955). The outcomes were total death, CV death, and major adverse CV events (MACE) defined as a composite of CV death, nonfatal myocardial infarction, and nonfatal stroke.

Results: During the follow-up, 48 current, 120 past, and 86 never smokers died from any cause, 17 current, 47 past, and 24 never smokers died from CV disease, and 35 current, 80 past, and 50 never smokers developed MACE. After adjustment for established risk factors, GDF-15 levels were significantly associated with total death (hazard ratio [HR] for 1-SD increase, 1.30; 95% confidence interval [CI], 1.03–1.65), but not with CV death (HR, 1.09; 95% CI, 0.69–1.62) or MACE (HR, 0.95; 95% CI, 0.64–1.34) in current smokers; GDF-15 levels were significantly associated with total death (HR, 1.73; 95% CI, 1.46–2.05) and CV death (HR, 1.41; 95% CI, 1.09–1.85), but not with MACE (HR, 1.20; 95% CI, 0.96–1.48) in past smokers; GDF-15 levels were significantly associated with total death (HR, 1.62; 95% CI, 1.32–1.95), CV death (HR, 1.76; 95% CI, 1.22–2.46), and MACE (HR, 1.64; 95% CI, 1.27–2.07) in never smokers. Even after incorporation of N-terminal pro-brain natriuretic peptide, contemporary sensitive cardiac troponin I, and high-sensitivity C-reactive protein into a model with established risk factors, the addition of GDF-15 levels further improved the prediction of total death ($P<0.001$ for continuous net reclassification improvement [NRI], $P=0.001$ for integrated discrimination improvement [IDI]) and MACE ($P<0.001$ for NRI, $P=0.045$ for IDI), but not that of CV death, in never smokers, while it did not significantly improved the prediction of total death, CV death, or MACE either in current or in past smokers.

Conclusions: The GDF-15 level was independently associated with total death and MACE in never, but not in current or past smokers with suspected or known CAD. The relationships of GDF-15 with mortality and CV events seem to be attenuated by the presence of current and past smoking.