Growth differentiation factor-15 and mortality in suspected or known coronary heart disease patients with diabetes: a subanalysis of the ANOX study

Authors:
T Unoki¹, M Suzuki², M Matsuda³, Y Ajiro⁴, T Shinozaki⁵, S Sakagami⁶, K Yonezawa⁷, M Shimizu⁸, J Funada⁹, T Takenaka¹⁰, Y Morita¹¹, M Abe¹, M Akao¹, K Hasegawa¹, H Wada¹, ¹National Hospital Organization Kyoto Medical Center - Kyoto - Japan, ²National Hospital Organization Saitama National Hospital - Saitama - Japan, ³National Hospital Organization Kure Medical Center - Kure - Japan, ⁴National Hospital Organization Yokohama Medical Center - Yokohama - Japan, ⁵National Hospital Organization Sendai Medical Center - Sendai - Japan, ⁶National Hospital Organization Kanazawa Medical Center - Kanazawa - Japan, ⁷National Hospital Organization Hakodate National Hospital - Hakodate - Japan, ⁸National Hospital Organization Kobe Medical Center - Kobe - Japan, ⁹National Hospital Organization Ehime Medical Center - Toon - Japan, ¹⁰National Hospital Organization Hokkaido Medical Center - Sapporo - Japan, ¹¹National Hospital Organization Sagamihara National Hospital - Sagamihara - Japan,

On behalf: the ANOX study investigators

Topic(s):
Coronary Artery Disease – Epidemiology, Prognosis, Outcome

Citation:
The ANOX study is supported by a Grant-in-Aid for Clinical Research from the National Hospital Organization.

Background: Diabetes is a risk factor for coronary heart disease (CHD), but further risk stratification in patients with diabetes is necessary to improve the prediction and prevention of cardiovascular events and deaths. Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine, which plays an important role in the regulation of the inflammatory response, growth and cell differentiation. Elevated GDF-15 was found in various diseases including diabetes and stable CHD, and was reported to predict mortality and cardiovascular events in general or established CHD population. However, the prognostic value of GDF-15 in suspected or known CHD patients with diabetes is unknown.

Methods: Serum GDF-15 levels were measured in 1,087 suspected or known CHD patients with diabetes undergoing elective coronary angiography, enrolled in the development of novel biomarkers related to angiogenesis or oxidative stress to predict cardiovascular events (ANOX) study, and followed up for 3 years. The primary outcome was all-cause death. The secondary outcomes were cardiovascular death, and major adverse cardiovascular events (MACE) defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Results: During the follow-up, 147 patients died from any cause, 47 died from cardiovascular disease, and 94 developed MACE. After adjustment for established risk factors, GDF-15 levels were significantly associated with all-cause death (hazard ratio [HR] for 1-SD increase, 1.66; 95% confidence interval [CI], 1.48–1.86), cardiovascular death (HR, 1.63; 95% CI, 1.34–1.99), and MACE (HR, 1.41; 95% CI, 1.20–1.65). 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 all-cause death (continuous net reclassification improvement [NRI], 0.344; 95% CI, 0.172–0.517; P<0.001; integrated discrimination improvement [IDI], 0.049; 95% CI, 0.026–0.072; P<0.001), but not that of cardiovascular death (NRI, -0.013; 95% CI, -0.300–0.274; P=0.931; IDI, 0.023; 95% CI, 0.003–0.043; P=0.026) or MACE (NRI, 0.059; 95% CI, -0.151–0.268; P=0.583; IDI, 0.005;
Conclusions: In suspected or known CHD patients with diabetes undergoing elective coronary angiography, elevated GDF-15 levels may predict all-cause mortality independent of established risk factors and cardiovascular biomarkers.