Impact of chronic kidney disease on the relationship between vascular endothelial growth factor C and mortality in patients with suspected coronary artery disease: a subanalysis of the ANOX study

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Background: The lymphatic system has been suggested to play an important role in cholesterol metabolism and cardiovascular (CV) disease. Recently, we demonstrated that serum levels of vascular endothelial growth factor C (VEGF-C), a central player of lymphangiogenesis, are inversely and independently associated with the risk of all-cause mortality in patients with suspected or known coronary artery disease (CAD). However, the impact of chronic kidney disease (CKD) on the relationship between VEGF-C and mortality in patients with suspected CAD is unclear.

Methods: Serum VEGF-C levels were measured in 1,717 patients with suspected but no history of 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 2 groups according to the presence (CKD, n=674) or absence (non-CKD, n=1,043) of CKD. The primary outcome was all-cause death. The secondary outcomes were 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, 95 CKD and 66 non-CKD patients died from any cause, 37 CKD and 13 non-CKD died from CV disease, and 61 CKD and 43 non-CKD developed MACE. After adjustment for established risk factors, VEGF-C levels were significantly and inversely associated with all-cause death (hazard ratio [HR] for 1-SD increase, 0.72; 95% confidence interval [CI], 0.57–0.90) and CV death (HR, 0.69; 95% CI, 0.48–0.97), but not with MACE (HR, 0.78; 95% CI, 0.60–1.03) in CKD, while VEGF-C levels were significantly and inversely associated with all-cause death (HR, 0.69; 95% CI, 0.52–0.91), but not with CV death (HR, 0.91; 95% CI, 0.50–1.66) or MACE (HR, 1.09; 95% CI, 0.81–1.44) in non-CKD. 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 VEGF-C levels further improved the prediction of all-cause death (P=0.047 for continuous net reclassification improvement [NRI], P=0.048 for integrated discrimination improvement [IDI]), but not that of CV death (P=0.016 for NRI, P=0.245 for IDI) or MACE (P=0.166 for NRI, P=0.311 for IDI) in CKD, whereas the addition of VEGF-C levels did not improve the prediction of all-cause death (P=0.053 for NRI, P=0.012 for IDI), CV death (P=0.864 for NRI, P=0.602 for IDI) or MACE (P=0.999 for NRI, P=0.154 for IDI) in non-CKD.

Conclusions: The VEGF-C level inversely and independently predicted all-cause mortality in CKD, but not in non-CKD patients with suspected CAD. The inverse relationship between VEGF-C and all-cause mortality in patients with suspected CAD seems to be remarkable in the presence of CKD.