Low vascular endothelial growth factor-C was a predictor for cardiovascular events in patients with atrial fibrillation and suspected or known coronary artery disease: a subanalysis of the ANOX study

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Background: Lymphatic system has been considered to play an important role in cardiovascular disease. We recently reported that vascular endothelial growth factor-C (VEGF-C), a central player in lymphangiogenesis, predicted all-cause mortality in patients with suspected or known coronary artery disease (CAD). However, relationship between VEGF-C and atrial fibrillation (AF) remains unclear.

Methods: The ANOX study is a multicenter, prospective cohort study of 2,418 patients with suspected CAD, to determine the predictive value of possible novel biomarkers related to angiogenesis or oxidative stress for major adverse cardiovascular events (MACE) among patients undergoing elective angiography. Blood samples were collected from the arterial catheter sheath at the beginning of coronary angiography. Serum levels of VEGF-C, as well as N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity troponin-I (cTnI), and high-sensitivity C-reactive protein (hsCRP), were measured. The outcome was a MACE defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

Results: Of a total of 2,418 patients, 261 patients had AF at baseline. AF group were older, and had more chronic kidney disease, history of heart failure, and history of stroke, but less diabetes, dyslipidemia, and CAD. The median level of NT-proBNP, cTnI, and hsCRP were higher in AF group [AF vs non-AF: NT-proBNP, 1048 pg/ml vs 162 pg/ml (p<0.0001); cTnI, 0.0003 ng/ml vs 0.0 ng/ml (p<0.0001); hsCRP, 1.43 ug/ml vs 0.88 ug/ml (p=0.0005)], whereas median level of VEGF-C was lower in AF group [3107 pg/ml vs 3590 pg/ml (p<0.0001)]. AF was associated with lower VEGF-C and higher hsCRP after adjustment for potential confounders. During the 3-year follow-up, 29 (11.1%) patients in AF group and 136 (6.3%) patients in non-AF group developed MACE (p=0.007). Incidence of stroke was higher in AF group (17 (6.5%) vs 52 (2.4%); p<0.0009), despite that the incidence of cardiovascular death and myocardial infarction were similar between the groups. We divided the entire cohort into two groups based on the lowest quartile of VEGF-C or highest quartile of other biomarkers, lowest quartile of VEGF-C (log rank p=0.0004), as well as highest quartile of cTnI (log rank p=0.0009), were significantly associated with MACE in AF group. After adjustment for established risk factors and these biomarkers, both lowest quartile of VEGF-C (HR, 2.73; 95% CI, 1.27-6.06) and highest quartile of cTnI (HR, 2.54; 95% CI, 1.08-6.09) were significantly associated with MACE in AF group.
Conclusions: AF was associated with lower level of VEGF-C, and low VEGF-C as well as high cTnI might serve as an independent predictor of MACE in patients with AF and suspected or known CAD.