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

M. Iguchi[1], M. Suzuki[2], M. Matsuda[3], Y. Ajiro[4], T. Shinozaki[5], S. Sakagami[6], K. Yonezawa[7], M. Shimizu[8], J. Funada[9], T. Takenaka[10], M. Wada[1], M. Abe[1], M. Akao[1], K. Hasegawa[1], H. Wada[1]

[1]National Hospital Organization Kyoto Medical Center, Kyoto, Japan; [2]National Hospital Organization Saitama Hospital, Wako, Japan; [3]National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Kure, Japan; [4]National Hospital Organization Yokohama Medical Center, Yokohama, Japan; [5]National Hospital Organization Sendai Medical Center, Sendai, Japan; [6]National Hospital Organization Kanazawa Medical Center, Kanazawa, Japan; [7]National Hospital Organization Hakodate National Hospital, Hakodate, Japan; [8]National Hospital Organization Kobe Medical Center, Kobe, Japan; [9]National Hospital Organization Ehime Medical Center, Toon, Japan; [10]National Hospital Organization Hokkaido Medical Center, Sapporo, Japan

On behalf of The ANOX study investigators

Funding Acknowledgement: Type of funding source: Public Institution(s). Main funding source(s): The ANOX study is supported by a Grant-in-Aid for Clinical Research from the National Hospital Organization.

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 anemia on the relationship between VEGF-C and mortality in those patients is unclear.

Methods: Serum VEGF-C 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. Anemia was defined as a hemoglobin level of less than 13 g/dL in men and <12 g/dL in women. Patients were divided into 2 groups according to the presence (anemic, n=882) or absence (non-anemic, n=1,536) of anemia. 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, 164 anemic and 90 non-anemic patients died from any cause, 64 anemic and 24 non-anemic patients died from CV disease, and 96 anemic and 69 non-anemic patients 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, 0.71; 95% confidence interval [CI], 0.59–0.84), CV death (HR, 0.60; 95% CI, 0.44–0.79), and MACE (HR, 0.76; 95% CI, 0.60–0.95) in anemic, while VEGF-C levels were not significantly associated with all-cause death (HR, 0.87; 95% CI, 0.69–1.11), CV death (HR, 1.32; 95% CI, 0.85–1.93), or MACE (HR, 1.12; 95% CI, 0.87–1.42) in non-anemic patients. 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<0.001 for continuous net reclassification improvement [NRI], P=0.006 for integrated discrimination improvement [IDI]) and CV death (P<0.001 for NRI, P=0.005 for IDI), but not that of MACE (P=0.021 for NRI, P=0.059 for IDI) in anemic, whereas the addition of VEGF-C levels did not improved the prediction of all-cause death (P=0.234 for NRI, P=0.415 for IDI), CV death (P=0.190 for NRI, P=0.392 for IDI) or MACE (P=0.897 for NRI, P=0.128 for IDI) in non-anemic patients.

Conclusions: The VEGF-C level was inversely and independently associated with all-cause and CV mortality in anemic, but not in non-anemic patients with suspected or known CAD. The inverse relationship between VEGF-C and mortality may depend on the presence of anemia.