Interleukin-6 Levels and Cardiovascular Events in the Cardiovascular Inflammation Reduction Trial: Consistent Associations for Incident Coronary, Cerebrovascular, and Peripheral Artery Disease

Lucas Marinho,1 Aaron W. Aday,1 Nancy R. Cook,1 Alan R. Morrison,2 Navaneet Narula,1 Jagat Narula,1 Francesca Bartoli-Leonard,3 Elena Alvaro,4 Jocelyn M. Beach,6 Paul M. Ridker,1 Aruna D. Pradhan1, Brigham and Women’s Hospital, Boston, MA; 2Vanderbilt Medical Center, Nashville, TN; 3Alpert Medical School at Brown University, Providence, RI; 4New York, NY; 5Boston, MA; 6Dartmouth-Hitchcock Medical Center, Lebanon, NH

Background: Inflammation is causally related to atherosclerosis. Interleukin-6 (IL-6) and IL-1β require NLRP3 inflammasome activation and have downstream effects on IL-6—markers previously associated with high risk of coronary artery and cerebrovascular disease (CCVD). However, data pertaining to peripheral artery disease (PAD) are sparse and could offer druggable targets in this disease.

Methods: We conducted a prospective cohort study of 4248 patients with type 2 diabetes or metabolic syndrome and prior coronary artery disease who participated in the National Institutes of Health-funded Cardiovascular Inflammation Reduction Trial. Participants were followed for up to 5 years for incident CCVD and symptomatic PAD events. Randomized treatment with low-dose methotrexate (vs placebo) had no effect on event rates or plasma levels of inflammatory biomarkers. Baseline levels of IL-6, IL-1β, and IL-6 were tested for association with incident vascular events. Kaplan-Meier curves and Cox proportional hazards models (adjusted for traditional risk factors) were estimated.

Results: In multivariable-adjusted analyses, hazard ratios for the lowest (referent) to highest baseline quartiles of IL-6 were 3.0, 1.5, 1.8, and 2.0 (P-trend < .001) and 1.0, 1.2, 2.5, and 2.0 (P-trend = .04) for incident CCVD (n = 349) and PAD (n = 87), respectively. Baseline IL-6 levels above versus below the median (2.50 pg/ml) were associated with a 56% increased risk of CCVD (hazard ratio, 1.56; 95% confidence interval, 1.26-1.93) and a 113% increased risk of PAD (hazard ratio, 2.13; 95% confidence interval, 1.36-3.32) (Figure). Baseline levels of IL-6 and IL-1β did not associate with incident CCVD or PAD.

Conclusions: In this contemporary cohort of secondary prevention patients, elevated IL-6 was associated with both incident CCVD and PAD. These data support exploration of direct IL-6 inhibition for PAD prevention, a strategy currently being pursued to reduce risk of coronary artery and cerebrovascular disease.