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IL6 trans-signalling affects risk of cardiovascular events pre-eminently in menL. Ziegler¹, P. Frumento², H. Wallen³, U. De Faire², B. Gigante²¹Karolinska Institute, Stockholm, Sweden; ²Karolinska Institute, Institute of Environmental Medicine, Stockholm, Sweden; ³Danderyd University Hospital, Department of Clinical Sciences, Stockholm, Sweden**Funding Acknowledgement:** The Stockholm County Council ALF project, Strategic research in Epidemiology

Background: Interleukin 6 (IL6) is a known cardiovascular risk marker. The pro-atherogenic effects of IL6 are mediated by the IL6 trans-signalling pathway via a binary complex of IL6 and the soluble IL6 receptor (IL6:sIL6R). The binary complex is however neutralised by the natural inhibitor, sgp130 when forming the ternary complex (IL6:sIL6R:sgp130). To assess the risk of cardiovascular events (CVE) with IL6 trans-signalling, a ratio between the active binary complex and the neutralised ternary complex was calculated. We recently demonstrated that high levels of the binary/ternary complex ratio (b/t ratio > the median) representing an excess of the active binary complex, was independently associated with a 44% increased risk of future CVE in subjects free of prevalent cardiovascular disease.

Purpose: In this study we aimed to analyse the risk of CVE and time to event associated with the b/t ratio in men and women separately.

Methods: In a cohort of 60 year old men and women from Stockholm, the molar concentrations of the binary and ternary IL6 complex were estimated at baseline. Subjects free of prevalent cardiovascular disease were followed through national registers to assess future CVE (myocardial infarction, hospitalised angina pectoris and ischemic stroke). During a 16 year follow-up, 525 first time CVEs were registered. The risk for CVE and time

to CVE was calculated for men and women, separately. To evaluate the risk associated with IL6 trans-signalling, the b/t ratio dichotomised at the median was modelled in a Cox regression model and risk was expressed as hazard ratios (HR) with 95% confidence intervals (CI). In addition, analysis was performed using censored quantile regression that allows measuring the effect of covariates on different quantiles of the time to CVE.

Results: Approximately half of the population were men and 64% of the CVE occurred in men. The risk of CVE during follow-up was significantly higher in men with b/t ratio > median (HR 1.70; 95% CI 1.35–2.15), while no significant difference was found in women (HR 1.12; 95% CI 0.84–1.50). Consistently, quantile regression showed that, men with a b/t ratio > median suffered their CVEs at an earlier time point. The time at which 15% of the male population was observed to have experienced CVE was 5.6 years shorter (95% CI: 4.0–7.2) in the high b/t ratio group. In women there was no significant difference in time to CVE.

Conclusion: The risk of CVE and early events associated with IL6 trans-signalling estimated by a b/t ratio > median is significantly increased in men.