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**Markers of vascular damage in cardiovascular events prediction: results from cluster analysis**

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Background As a low grade systemic inflammation plays an important role in the pathogenesis of atherosclerosis-associated diseases and diabetes mellitus (DM) there is an interest in the relevance of circulating markers of immune inflammation to clinical manifestation of cardiovascular disease (CVD), especially in the setting of DM.

Purpose of our investigation was to assess the predictive value of numerous immune markers (pro-inflammatory cytokines, anti-connective tissue antibodies) in relation with circulating markers of endothelial dysfunction (ED) in persons with documented ischemic heart disease (IHD), DM, and asymptomatic atherosclerosis (AA).

Methods 393 persons (147 pts with IHD, 126 pts with T2DM, 120 pts with AA) were observed during 3-year period. The baseline levels of pro-inflammatory cytokines (IL1ß, IL6, TNF-a), antibodies against connective tissue components (collagen –anti- ab, hyaluronic acid – antiHA-ab, chondroitin sulfate antiCS-ab), soluble markers of ED: von Willebrand factor (vWF), endothelin 1 (ET-1), endogenous NO synthase (eNOs) were evaluated by ELISA. The incidence and severity of cardiovascular events (CVE) in the relation with baseline levels of measured markers were evaluated by cluster analysis in 4 cohorts formed according to presence of AA, current IHD and T2DM (AA, IHD, T2DM, IHD+T2DM). From 2 to 4 clusters were separated depending on the incidence and severity of CVE.

Results We have defined that in AA the numerous of circulating markers: ET-1, IL-1ß, TNFa, antiC-ab, antiCS-ab was associated with clinically significant CVE. In IHD the most severe clinical manifestations were documented in cluster, characterized by increased ET1, vWF, IL6, antiC-ab levels and decreased eNOs, In T2DM without evidenced IHD CVE were associated with next profile: ET1, eNOs, IL-6, antiC-ab, and antiHA-ab. In combination of IHD with T2DM the worst cluster was presented with raised levels of vWF, TNF-a, IL-6, antiC-ab, anti-HA and CRP as well as decreased eNOs.

Conclusions Circulating markers of ED and immune-mediated inflammation reflect the clinical manifestation of IHD in high-risk persons with AA and T2DM. Cluster analysis has demonstrated the relationship between specific baseline profile of investigated biomarkers and clinical significant CVE. Obtained data broads our understanding regarding the inflammatory mechanism of atherosclerosis and also suggest a set of circulating markers as predictors of adverse cardiovascular events.