Inflammation and Atherosclerotic Cardiovascular Disease (ASCVD)

There exists a bewildering number of inflammatory mediators that form our response to injury, danger signals, foreign organisms or substances that trigger local and systemic reactions. Multiple pathways have been identified as potential targets for the prevention and treatment of cardiovascular diseases. Corticosteroids increase cardiovascular risk and non-steroidal anti-inflammatory agents, including celecoxib are, at best, neutral. Most clinical trials targeting specific downstream targets, such as oxidation of LDL, secretory and lipoprotein-associated phospholipase A2 (sPLA2 and LpPLA2), and p-selectin has failed to meet their primary end-points with respect to a decrease in cardiovascular disease or selected surrogate end-point.

New Targets: Interleukin 6 (IL-6), Tumor Necrosis Factor-α (TNFα); Neutrophil mobility (Colchicine), Interleukin-1β (Canakinumab); low-dose methotrexate.

TNFα and IL-6. In a review of treatments given to patients with rheumatic arthritis, agents that block TNFα and IL-6, as well as methotrexate were associated with a marked reduction in cardiovascular events (myocardial infarction, heart failure and strokes, while non-steroidal anti-inflammatory drugs are associated with a small increase in cardiovascular events (HR 1.18; 95% CI 1.01 -138, p=0,04). Both TNFα and IL-6 monoclonal antibodies are used extensively for the treatment of rheumatoid arthritis, psoriatic arthritis and several inflammatory conditions.

Interleukin IL-1β (IL-1β). The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) trial. The monoclonal antibody canakinumab was administered to patients with ASCVD and a high-sensitivity C-reactive protein > 2 mg/L at doses of 50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months compared to placebo in 10,061 patients. The primary efficacy end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death was met for the doses of 150 mg (HR 0.85; 95% CI, 0.74 to 0.98; P=0.021) and the combined 150 and 300 mg doses. The event rate for the combined major cardiovascular end-points of cardiovascular death, non-fatal myocardial infarction and strokes plus hospitalization for unstable angina leading to urgent revascularization was nearly 5% per year. These were reduced significantly on the 150 dose (HR 0.83; 95% CI, 0.73 to 0.95; p= 0.005). Canakinumab was associated with a higher incidence of fatal infection than placebo; there was no difference in all-cause mortality for all canakinumab doses. When compared with subjects who decreased hsCRP. In a pre-specified exploratory analysis, cancer mortality was significantly reduced in the canakinumab group (p=0.0007) and lung cancer was less frequent in the 150 and 300 mg doses (p=0.001).