    - Presence of muscle toxicity requires the discontinuation of the statin
- **Effect of statins on RhoGTPases**
    - Statins inhibit HMG-CoA which further down the line would have produced geranylgeranyl - PP
    - This prevents the geranyaltion of rho GTPases (RhoA, Rac1, Cdc-42)
    - One of the things that Rho GTPases do is drive inflammation
    - Geranylation - addition of lipid to protein so that it can move through guanine exchange factors in the lipid bilayer, which activate it
    - Activation = inflammation later down the line
    - Leukocytes
        - RhoGTPases do a lot for a cell, so reducing them reduces their roles
        - Reduced receptors of leukocytes, reduced motility and directionality,reduced adhesion molecules

Treatment of atherosclerosis

- Statins lower LDL (immediate) = endothelial function restored = inflammation reduced = ischemic episodes reduced = vulnerable plaques established = vascular events reduced (over years)
- Life style is changed first and drugs are only introduced after

CANTOS study – reducing inflammation without lipid lowering

- Focuses on iL1- beta antibodies - proinflammatory molecule that can lead to endothelial cell activation
- Inactive Pro iL1- beta antibodies are transformed to active iL1- beta antibodies by caspase 1
- Signal 1 ; PAMPs and DAMPs enter cell through toll like receptor
- Leads to activation of Nf- kB a proinflammatory transcription factor
- These transcribe for the production of inactive NLRP3's which can assemble into an inflammasome
- Signal 2: could be ATP, reactive oxygen or crystalline components
- The inflammasome needs signal 1 & 2 to from which then activates caspase 1 which turns pro iL1- beta antibodies into iL1- beta antibodies
- **Canakinumab Study**
- A randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β
- Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering.

Other treatments besides lipid lowering

- Increase circulating HDL levels.
    - Cholesterylester transfer protein (CETP) transfers cholesterylesters from HDL to VLDL/LDL
    - Genetic CETP deficiency in humans associated with elevated HDL
    - CETP inhibitors: torcetrapib (Pfizer), dalcetrapib (Roche), evacetrapib (Eli Lilly) and anacetrapib (Merck) elevate HDL/lower LDL
- Target lesion-associated inflammation
    - Darapladip inhibits lipoprotein-associated phospholipase A2, reduces circulating inflammatory markers and attenuates necrotic core expansion within lesion in patients with CHD
- Mobilisation of cholesterol from existing lesions