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Cardiovascular Inflammation Reduction Trial: CIRT

Discussant
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I have no COI/RWI associated with this presentation

Background – Inflammation is known to play a critical role in atherothrombosis. In CANTOS selective neutralization of interleukin-1β improved CV outcomes. Observational data - pts with arthritis and psoriasis at high CV risk LDM reduces events
Hypothesis – Inhibition of inflammation with LDM in high risk patients on statin therapy will improve CV outcomes.
Design- Randomized, Double -Blind, Placebo-Controlled NHLBI Funded
4786 pt randomized to LDM (2391) vs.placebo (2395) median FU 2.3y, max 5y,10pt -FU
417 sites/US&Canada,m age 66, 19%F, 11% Smkr, 61% MI, 39% MVD, 1/3 DM,MS,B
Results- LDM did not reduce IL-1β, IL-6, or hsCRP. No change in primary endpoint MACE (NFMI, NFStroke, CV death, plus hosp for MI with urgent revasc) nor were the secondary and primary endpoints reduced.
Adverse Events: MLD pts increase malig. Mainly non-basal cell skin cancer

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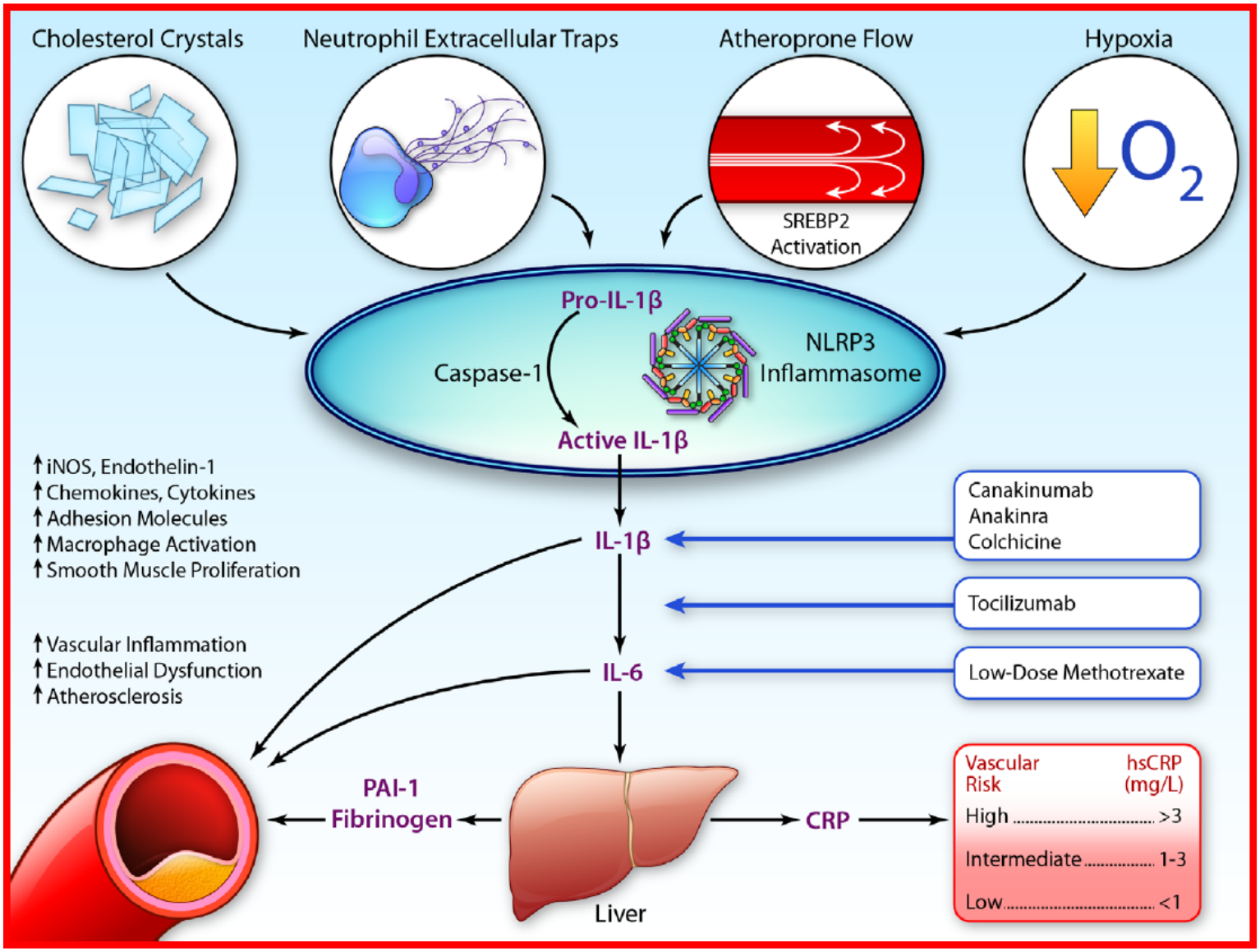
Critical Role of the IL-1β to IL-6 to CRP Pathway in Atherothrombosis



Ridker PM. Circ Res 2016;118:145-156.

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Conclusions:

1. LDM in high risk CVD patients did not improve primary CV outcomes (NFMI, NFS, CVD, UA+UReVasc), similarly no change in secondary outcomes.
2. Side effects with LDM include higher incidence of cancer (mainly non-basal-cell skin cancer) and mouth sores, oral pain, elevated ALT and AST levels.
3. Of interest no change in IL-1β, IL-6, hsCRP occurred with LDM whereas in CANTOS, which required increased inflammatory risk (hsCRP mean 4.2 mg) canakinumab targeting and reducing IL-1β with associated reduction in IL-6 and hsCRP had 17% reduction in MACE.(hsCRP in CIRT = 1.50)
4. Mean LDL-C was reduced to 2018 GL levels for intensive statin therapy (68 mg/dL) in CIRT but was higher in CANTOS (mean 82 mg/dL, 75%tile =107 mgdL). More information is needed on relationship between efficacy of anti-inflammatory agents at varying LDL-C levels and statin dose.
5. Taken together CIRT and CANTOS provide potentially helpful mechanistic observations about selective drug effects in targeting Inflammation. Two trials (LoDoCo) and (COLCOT) involving colchicine which also acts on IL-1B should provide valuable information in this regard.
6. CIRT is yet another testimony to the value of RCTs and the limitations of observational and animal data in determining the efficacy of drug interventions on patient outcomes.
7. Congratulations to 1)Ridker et al for conducting this study; 2) NHLBI for funding and 3)AHA CSS for presenting a RCT with “negative” results.