Inflammation and ASCVD

CANTOS and JUPITER Studies

Inflammation in ASCVD: Major Risk Factors

Major risk factors	Additional risk factors	Nontraditional risk factors
Advancing age	Obesity, abdominal obesity	⇧ Lipoprotein (a)
⇧ Total serum cholesterol level	Family history of hyperlipidemia	⇧ Clotting factors
⇧ Non–HDL-C	⇧ Small, dense LDL-C	**⇧ Inflammation markers (hsCRP; Lp-PLA$_2$)**
⇧ LDL-C	⇧ Apo B	⇧ Homocysteine levels
Low HDL-C	⇧ LDL particle concentration	Apo E4 isoform
Diabetes mellitus	Fasting/postprandial hypertriglyceridemia	⇧ Uric acid
Hypertension	PCOS	⇧ TG-rich remnants
Stage 3 or 4 chronic kidney disease	Dyslipidemic triad	
Cigarette smoking		
Family history of ASCVD		

Apo=apolipoprotein; ASCVD=atherosclerotic cardiovascular disease; HDL-C=high-density lipoprotein cholesterol; hsCRP=high-sensitivity C-reactive protein; LDL=low-density lipoprotein;
LDL-C=low-density lipoprotein cholesterol; Lp-PLA2=lipoprotein-associated phospholipase; PCOS=polycystic ovary syndrome.

Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.

Inflammation in ASCVD: Pathogenesis

- Leukocyte accumulation, predominantly macrophages, is a prominent feature of atherosclerosis from initiation to advanced stages.
- Lipid accumulation in macrophages induces inflammation, which promotes and augments atherosclerotic development in a positive feedback loop.[1]
- Lipid-laden macrophage accumulation in the subendothelial area of the arterial wall is a hallmark of atherosclerosis. These cells promote inflammatory responses and lead to pathologic consequences such as hemorrhage, rupture, and calcification.[1]
- The successful application of biomarkers of inflammation, such as hsCRP, to sharpen CV risk assessment, and their independence from traditional risk factors, suggests that these biomarkers could identify additional at-risk individuals.[2]

hsCRP=high-sensitivity C-reactive protein; CV=cardiovascular.

[1]Lu H, Daugherty A. *Arterioscler Thromb Vasc Biol.* (2015) 35(3):485–491.
[2]Libby P. *Arterioscler Thromb Vasc Biol.* (2012) 32(9): 2045–2051.

Clinical Trials Targeting Inflammation

JUPITER

Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin

Targeting Inflammation: The JUPITER Trial

- JUPITER was a formal hypothesis-testing trial based on prior observations that:
  - Inflammation plays a crucial role in atherogenesis.
  - The inflammatory biomarker hsCRP independently predicts vascular events and improves global classification of risk regardless of LDL-C level.
  - Statin therapy reduces hsCRP in a manner largely independent of LDL-C reductions.
  - In acute coronary syndrome, as well as stable patients, the magnitude of benefit associated with statins relates in part to achieved levels of hsCRP.
  - In a previous hypothesis-generating analysis of the AFCAPS/TexCAPS trial, no clinical benefit of statin therapy was observed among those with LDL-C <150 mg/dL who had hsCRP <2 mg/L, yet a substantial clinical benefit was observed among those with LDL-C <150 mg/dL who had hsCRP >2 mg/L.

AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; hsCRP=high-sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol.

Ridker PM. *Circ Cardiovasc Qual Outcomes*. (2009) 2:279–285.

Targeting Inflammation: The JUPITER Trial

STUDY COMPONENT	DETAIL
Objective	To determine whether statin therapy might effectively prevent first-ever CV events among men and women at risk for vascular disease due to elevated hsCRP, and who are not candidates for statin therapy under accepted guidelines due to LDL-C levels <130 mg/dL.
Methods	The JUPITER trial was a collaborative effort involving 1,315 physicians in 26 countries; 11,001 men and 6,801 women with hsCRP >2 mg/L (median, 4.2 mg/L) and LDL-C <130 mg/dL (median, 108 mg/dL) were randomly assigned to either rosuvastatin 20 mg or placebo. The primary endpoint was first-ever MI, stroke, hospitalization for unstable angina, arterial revascularization, or CV death.
Results/Conclusion	The trial stopped early after a median follow-up of 1.9 years because of a 44% reduction in the primary endpoint of all vascular events (P<0.00001), a 54% reduction in MI (P<0.0002), a 48% reduction in stroke (P<0.002), a 46% reduction in need for arterial revascularization (P<0.001), and a 20% reduction in all-cause mortality (P<0.02).

CV=cardiovascular; hsCRP=high-sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction.
Ridker PM. *Circ Cardiovasc Qual Outcomes*. (2009) 2:279–285.

JUPITER Trial: Incidence of Cardiovascular Events

JUPITER is the first statin prevention trial to demonstrate clear benefits in the primary trial endpoint* for:

- Women: (HR, 0.54; 95% CI, 0.37 to 0.80)
- Black and Hispanic patients (HR, 0.63; 95% CI, 0.41 to 0.98)
- Elderly patients (≥70 years, HR, 0.61; 95% CI, 0.46 to 0.82).

*First-ever MI, stroke, hospitalization for unstable angina, arterial revascularization, or CV death

CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MI=myocardial infarction.

Ridker PM. *Circ Cardiovasc Qual Outcomes*. (2009) 2:279–285.

JUPITER Trial Follow-up

- Recent overviews indicate that all statin agents are associated with a modest increase in incident T2D risk; intensive statin therapy may be associated with somewhat higher risk than moderate-dose therapy.
- On March 1, 2012, the FDA added a warning regarding diabetes risk to the labeling of all statin agents; similar concern has been raised by European drug authorities.
- JUPITER trial authors conducted a 5-year follow up analysis to determine whether the CV benefit of statin treatment exceeded diabetes risk, particularly in primary prevention.
- Overall, incident diabetes occurred more frequently in the rosuvastatin than placebo group (270/486 [56%] vs 216/486 [44%], respectively).
- Virtually all excess diabetes risk associated with rosuvastatin occurred among patients with baseline evidence of impaired fasting glucose.
- JUPITER authors concluded that the CV and mortality benefits of statin therapy exceeded the diabetes hazard; this includes patients at higher risk for developing diabetes.

CV=cardiovascular; T2D=type 2 diabetes.

Ridker PM, et al. *Lancet. (*2012) 380(9841):565–571.

Clinical Trials Targeting Inflammation

CANTOS

Canakinumab Anti-inflammatory Thrombosis Outcome Study

Targeting Inflammation: CANTOS Trial

STUDY COMPONENT	DETAIL
Objective	To evaluate whether canakinumab prevents recurrent vascular events in men and women with a persistent proinflammatory response, defined as hsCRP ≥2 mg/l.[1]
Methods	Eligible patients (N=10,061) had a history of MI and hsCRP ≥2 mg/l despite aggressive secondary prevention. Patients were randomly assigned to placebo or canakinumab 50 mg, 150 mg, or 300 mg (SC injection every 3 months). The primary endpoint was the first occurrence of nonfatal MI, any nonfatal stroke, or CVD. Key secondary endpoints included: 1) primary endpoint components plus hospitalization for unstable angina resulting in urgent revascularization; and, 2) the incidence of new-onset T2D among patients with prediabetes at randomization.
Results/Conclusion	Patients in the canakinumab 150-mg group had a 15% lower risk of the primary endpoint vs the placebo group, and a 17% reduced risk of the first key secondary CV endpoint vs placebo.[1] Canakinumab treatment did not affect T2D incidence.

CV=cardiovascular; CVD=cardiovascular disease; hsCRP=high-sensitivity C-reactive protein; MI=myocardial infarction; SC=subcutaneous; T2D=type 2 diabetes.

Ridker PM, et al. N Engl J Med. (2017) 377(12):1119-1131.
Everett BM, et al. JACC. (2018) DOI: 10.1016/j.jacc.2018.03.002. Epub ahead of print.

Summary and Conclusions

- Inflammation is a critical contributor to atherosclerosis development and an independent target for treatment.
- The JUPITER trial evaluated the impact of statin therapy in patients with elevated hsCRP but normal LDL-C levels; patients receiving statin treatment experienced significant reductions in all vascular endpoints.
- In a 5-year JUPITER follow-up analysis, the CV and mortality benefits of statin therapy exceeded the diabetes hazard.
- The CANTOS trial evaluated whether canakinumab could prevent recurrent vascular events in patients with a persistent pro-inflammatory response. Patients who received canakinumab had a significantly lower rate of recurrent CV events vs placebo, independent of lipid-lowering, as well as a significant reduction in the inflammatory biomarker hsCRP.

CANTOS=Canakinumab Anti-inflammatory Thrombosis Outcome Study; CV=cardiovascular; hsCRP=high-sensitivity C-reactive protein; JUPITER=Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL-C=low-density lipoprotein cholesterol.