ANTI-INFLAMMATORY THERAPIES IN SECONDARY PREVENTION OF ASCVD

Prepared by **Dr. Sidhartha Mullapudi**, DrNB (Cardiology), MD (General Medicine)
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I RATIONALE (THE INFLAMMATORY HYPOTHESIS OF ATHEROTHROMBOSIS)

- **Residual Inflammatory Risk:** A substantial proportion of patients with established Atherosclerotic Cardiovascular Disease (ASCVD) experience recurrent Major Adverse Cardiovascular Events (MACE) despite achieving guideline-mandated LDL-C targets; this residual risk is driven by the canonical **NLRP3 Inflammasome – Interleukin-1beta (IL-1b) – Interleukin-6 (IL-6) – C-Reactive Protein (hs-CRP)** innate immunity signaling axis.
- **Pathophysiological Mechanism:** Cholesterol crystals, oxidized LDL, and disturbed shear stress activate the intraplaque macrophage NLRP3 inflammasome, stimulating matrix metalloproteinase secretion, collagen degradation, thinning of the protective fibrous cap, and acute plaque rupture or erosion.

II COLCHICINE (THE TARGETED TUBULIN / NLRP3 INHIBITOR)

- **Mechanism of Action:** Binds tubulin heterodimers to inhibit microtubule polymerization, thereby blocking **NLRP3 inflammasome assembly**, neutrophil chemotaxis/degranulation, and platelet-leukocyte aggregation, reducing downstream **IL-1beta, IL-18, IL-6, and hs-CRP**.
- **Landmark Clinical Trials:**
  - **COLCOT Trial (*NEJM* 2019 — Early Post-MI):** In patients randomized within 30 days of an acute myocardial infarction, **low-dose Colchicine (0.5 mg once daily)** reduced the primary composite endpoint of CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring revascularization by **23 percent**.
  - **LoDoCo2 Trial (*NEJM* 2020 — Chronic Coronary Syndrome):** In patients with stable chronic coronary disease on optimal lipid-lowering therapy, **Colchicine 0.5 mg daily** reduced the primary composite of CV death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization by **31 percent**.
  - **CLEAR SYNERGY (OASIS-9) Trial (*NEJM* 2024 — Acute MI Undergoing PCI):** In 7,062 patients initiated immediately after acute MI treated with PCI, Colchicine 0.5 mg daily showed **no reduction in MACE** at 3 years despite lowering CRP, tempering routine acute post-MI initiation while supporting selective use in chronic stable ASCVD with persistent inflammatory risk.
  - **Guideline Status (2024 ESC Chronic Coronary Syndromes Guidelines):** Upgraded to a **Class IIa (Level A) recommendation**: low-dose **Colchicine (0.5 mg once daily)** should be considered in patients with atherosclerotic CAD to reduce MI, stroke, and need for revascularization, particularly when residual inflammatory risk (**hs-CRP greater than 2.0 mg/L**) or recurrent events persist despite optimal statin/lipid therapy (avoiding use in severe CKD or concurrent strong CYP3A4/P-gp inhibitors).

III CANAKINUMAB (PROOF OF CONCEPT FOR THE IL-1BETA PATHWAY)

- **Mechanism of Action:** Fully human monoclonal antibody that selectively binds and neutralizes circulating **Interleukin-1beta (IL-1b)**.
- **Landmark Trial — CANTOS (*NEJM* 2017):** Randomized 10,061 patients with prior myocardial infarction and persistent **hs-CRP of 2.0 mg/L or greater** to subcutaneous Canakinumab versus placebo. The 150 mg dose reduced recurrent MACE by **15 percent** with **zero change in LDL-C**, providing the first definitive proof of the inflammatory hypothesis of human atherosclerosis.
- **Clinical Status:** Not approved or used in routine cardiovascular practice due to high cost and a small but statistically significant increase in **fatal infection/sepsis**, though it established the IL-1b/IL-6 pathway as a validated therapeutic target.

Anti-Inflammatory Agent	Molecular Target	Landmark Trial(s)	Primary MACE Outcome & Clinical Status
Colchicine (0.5 mg OD)	Tubulin / **NLRP3 inflammasome** & neutrophil function	**COLCOT** (2019), **LoDoCo2** (2020), **CLEAR SYNERGY** (2024)	**23% RRR** in COLCOT; **31% RRR** in LoDoCo2 (neutral in acute MI in CLEAR SYNERGY); **ESC 2024 Class IIa** in CCS
Canakinumab	Monoclonal antibody against **IL-1beta**	**CANTOS** (*NEJM* 2017)	**15% RRR in MACE** independent of LDL-C; proof-of-concept, not used clinically due to cost & fatal infection risk
Low-Dose Methotrexate	Dihydrofolate reductase / adenosine purine pathway	**CIRT** (2019)	**Neutral (0% reduction in MACE)** and did not lower IL-1b, IL-6, or hs-CRP; **not recommended**
Ziltivekimab	Monoclonal antibody against **IL-6 ligand**	**RESCUE** (Phase II); **ZEUS / HERMES** (Phase III)	Lowered hs-CRP by ~80–90% in RESCUE; **Phase III ZEUS missed primary MACE endpoint and HERMES halted for futility in Sept 2026**

IV METHOTREXATE (THE FAILED BROAD IMMUNOSUPPRESSANT)

- **Mechanism and Landmark Trial (CIRT):** Low-dose **Methotrexate (15 to 20 mg weekly)** was evaluated in the **Cardiovascular Inflammation Reduction Trial (CIRT)** in patients with prior MI/multivessel CAD and diabetes or metabolic syndrome.
- **Key Lesson:** Methotrexate **failed to reduce IL-1beta, IL-6, or hs-CRP levels and had zero effect on MACE**, proving that atheroprotection requires specific inhibition of the **canonical NLRP3–IL-1b–IL-6 pathway** rather than non-specific immunosuppression.

V ZILTIVEKIMAB AND DIRECT INTERLEUKIN-6 TARGETING

- **Mechanism and Phase II Evidence: Ziltivekimab** is a fully human monoclonal antibody directed against the **Interleukin-6 (IL-6) ligand**. In the Phase II **RESCUE Trial**, Ziltivekimab produced dose-dependent **77 to 92 percent reductions in hs-CRP**, fibrinogen, serum amyloid A, and lipoprotein(a) in patients with moderate-to-severe CKD.
- **Phase III Outcomes Update (ZEUS and HERMES Trials, 2026):** Although Phase III trials (**ZEUS** in atherosclerotic CKD with hs-CRP >=2 mg/L and **HERMES** in HFmrEF/HFpEF) were launched to test whether direct IL-6 inhibition reduces MACE, topline results in 2026 showed that **ZEUS missed its primary MACE endpoint and HERMES was subsequently halted early for futility**, leaving **low-dose Colchicine** and **high-intensity Statins (JUPITER Trial)** as the only clinically established oral anti-inflammatory therapies in ASCVD.

VI CLINICAL SUMMARY ALGORITHM FOR SECONDARY PREVENTION

- **Dual-Target Assessment (“Residual Cholesterol Risk” vs. “Residual Inflammatory Risk”):** In patients with established ASCVD on maximally tolerated high-intensity statin + ezetimibe (+/- PCSK9 inhibitor or bempedoic acid):
- **If LDL-C remains >=55 mg/dL (or ApoB >=65 mg/dL):** Intensify lipid-lowering therapy (**Ezetimibe, PCSK9 mAb/Inclisiran, or Bempedoic Acid**).
- **If LDL-C is at goal (<55 mg/dL) but hs-CRP remains persistently >=2.0 mg/L (or recurrent ischemic events occur):** Consider adding **Low-Dose Colchicine 0.5 mg once daily (ESC 2024 Class IIa)**.

KEY REFERENCES

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