ANTI-INFLAMMATORY DRUGS IN CARDIOLOGY: CURRENT STATUS (2026)

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I THE INFLAMMATORY HYPOTHESIS

- **Residual Inflammatory Risk:** Cardiovascular management has moved beyond lowering cholesterol alone to targeting residual inflammatory risk in patients who have reached their LDL cholesterol goals but still have elevated inflammation measured by high-sensitivity C-reactive protein (hsCRP).
- **Primary Signaling Pathway:** The primary therapeutic target is the canonical inflammatory cascade involving the **NLRP3 inflammasome**, **Interleukin-1 (IL-1beta)**, **Interleukin-6 (IL-6)**, and **hsCRP**.
- **Mechanism of Plaque Instability:** Intra-plaque inflammation causes thinning of the fibrous cap and increased proteolytic enzyme activity, leading to plaque rupture and thrombosis.

II KEY CLINICAL TRIALS AND EVIDENCE

- **CANTOS Trial (Canakinumab):**
  - **Mechanism:** Monoclonal antibody that directly neutralizes **Interleukin-1 beta**.
  - **Key Finding:** The first trial to prove that blocking inflammation reduces heart attacks and strokes (by 15 percent in post-MI patients with hsCRP greater than 2 mg/L) independently of cholesterol lowering.
  - **Clinical Status:** Not used in routine clinical practice due to high cost and an increased risk of fatal infections.
  - **COLCOT and LoDoCo2 Trials (Colchicine):**
  - **Mechanism:** Low-dose **Colchicine (0.5 mg daily)** inhibits tubulin polymerization and disrupts the NLRP3 inflammasome, reducing IL-1beta and IL-6 levels.
  - **Key Finding:** Demonstrated significant reductions in cardiovascular events in both recent myocardial infarction patients (23 percent reduction in COLCOT) and patients with stable chronic coronary disease (31 percent reduction in LoDoCo2).
  - **Clinical Status:** FDA-approved (0.5 mg, 2023) and recommended in secondary prevention (ESC 2024 CCS Class IIa; ACC/AHA 2023 Class IIb).
  - **CLEAR SYNERGY / OASIS 9 Trial:**
  - **Study Focus:** Evaluated low-dose Colchicine versus placebo in acute myocardial infarction patients.
  - **Key Finding:** Showed **no significant benefit** in reducing major cardiovascular events and noted a higher incidence of side effects such as diarrhea.
  - **Clinical Impact:** Shifted clinical practice toward selective use of Colchicine in stable chronic coronary disease rather than routine initiation during acute myocardial infarction.
  - **RESCUE, ZEUS, and HERMES Trials (Ziltivekimab):**
  - **Mechanism:** Fully human monoclonal antibody targeting the **Interleukin-6 (IL-6)** ligand.
  - **Key Finding:** The Phase 2 **RESCUE Trial** demonstrated profound, dose-dependent reductions in hsCRP, fibrinogen, and other inflammatory biomarkers with minimal side effects, leading to the **ZEUS** trial (CKD and ASCVD) and the **HERMES** trial (HFpEF). **ZEUS missed its MACE endpoint (July 2026)** and **HERMES was stopped for futility (September 2026)**.
  - **CIRT Trial (Methotrexate):**
  - **Key Finding:** Low-dose **Methotrexate** (a broad systemic anti-inflammatory) failed to reduce cardiovascular events, suggesting that atheroprotection requires specific targeting of the NLRP3/IL-1beta/IL-6 pathway rather than general immunosuppression.

Clinical Trial	Anti-Inflammatory Agent	Molecular Target	Key Clinical Outcome & Status
CANTOS	**Canakinumab**	Interleukin-1 beta	Reduced MACE by 15% independent of lipid lowering; not in routine use due to cost and fatal infection risk
COLCOT & LoDoCo2	**Colchicine (0.5 mg daily)**	Tubulin / NLRP3 inflammasome	Reduced MACE by 23% (post-MI) and 31% (stable CAD); FDA-approved; ESC 2024 Class IIa
CLEAR SYNERGY (OASIS 9)	**Colchicine (0.5 mg daily)**	Tubulin / NLRP3 inflammasome	No significant MACE reduction in acute MI; increased diarrhea; favors selective chronic use
CIRT	**Methotrexate**	Broad purine / DMARD pathway	Failed to reduce cardiovascular events
RESCUE / ZEUS / HERMES	**Ziltivekimab**	Interleukin-6 (IL-6) ligand	Dose-dependent CRP reduction in RESCUE; ZEUS missed MACE endpoint and HERMES stopped for futility (2026)

III CURRENT CLINICAL STATUS AND DRUGS

- **Low-Dose Colchicine (0.5 mg Once Daily):**
  - **Clinical Role:** The primary widely available and affordable oral anti-inflammatory agent for atherosclerotic cardiovascular disease.
  - **Indication:** Patients with stable chronic coronary disease on optimal statin therapy, particularly with residual inflammatory risk (hsCRP greater than 2.0 mg/L); note the trials did not require an elevated hsCRP.
  - **Contraindications:** Must be avoided in severe renal or hepatic disease and with strong CYP3A4 / P-glycoprotein inhibitors.
  - **Statins (First-Line Dual Therapy):**
  - **Clinical Role:** Beyond lowering LDL cholesterol, statins exert potent pleiotropic anti-inflammatory effects (as shown in the **JUPITER Trial** with Rosuvastatin) and remain the first-line therapy for lowering both lipids and hsCRP.
  - **Targeted Interleukin-6 Inhibitors:**
  - **Clinical Role: Ziltivekimab** lowered inflammatory markers but failed to improve outcomes in ZEUS and HERMES (2026), so IL-6 inhibition currently has no established role in ASCVD.

IV SUMMARY FOR EXAM SHEET

- **Target Pathway:** NLRP3 Inflammasome to Interleukin-1beta to Interleukin-6 to hsCRP.
- **Primary Biomarker:** High-sensitivity C-reactive protein (**hsCRP greater than 2.0 mg/L** identifies high residual inflammatory risk).
- **Main Trial Evidence: CANTOS** (IL-1beta), **COLCOT / LoDoCo2 / CLEAR SYNERGY** (Colchicine), **CIRT** (Methotrexate failure), and **RESCUE / ZEUS / HERMES** (IL-6).
- **Clinical Algorithm:** Optimize high-intensity statins (+ Ezetimibe/PCSK9i) first; add **Colchicine 0.5 mg once daily** for stable ASCVD patients with persistent inflammatory risk.

KEY REFERENCES

- **Ridker PM, et al. (CANTOS Trial):** Antiinflammatory therapy with Canakinumab for atherosclerotic disease, *New England Journal of Medicine*.
- **Tardif JC, et al. (COLCOT Trial) & Nidorf SM, et al. (LoDoCo2 Trial):** Low-dose Colchicine in post-myocardial infarction and chronic coronary disease.
- **CLEAR SYNERGY (OASIS 9) Investigators:** Colchicine in acute myocardial infarction.