01. Title: Residual Inflammatory Risk in Atherosclerotic Cardiovascular Disease: Is Anti-Inflammatory Therapy the Next Frontier Beyond LDL Reduction?

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Background:
Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide, accounting for nearly 18 million deaths annually and contributing significantly to the global healthcare burden. Despite aggressive low-density lipoprotein (LDL) lowering therapy, recurrent cardiovascular events continue to occur in a substantial proportion of patients. Persistent vascular inflammation, reflected by elevated high-sensitivity C-reactive protein (hsCRP), contributes to residual inflammatory risk even among individuals achieving optimal lipid control.

Objective:
To evaluate the efficacy of anti-inflammatory therapies in reducing residual inflammatory risk and cardiovascular events beyond LDL reduction in patients with ASCVD.

Methodology:
A systematic review and meta-analysis was conducted according to PRISMA guidelines using PubMed-indexed studies published between 2016 and 2026. Randomized controlled trials, systematic reviews, and meta-analyses evaluating canakinumab and low-dose colchicine in adult ASCVD patients were included. Outcomes assessed included hsCRP reduction, major adverse cardiovascular events (MACE), myocardial infarction, stroke, coronary revascularization, and cardiovascular mortality. Data from landmark trials including CANTOS, COLCOT, and LoDoCo2 were analyzed. Pooled effect estimates were expressed with 95% confidence intervals (CI), and heterogeneity was assessed using the I^2 statistic.

Results:
Patients with LDL levels <70 mg/dL continued to demonstrate substantial residual inflammatory risk, with nearly 31% exhibiting elevated hsCRP levels. Canakinumab therapy demonstrated a significant reduction in hsCRP levels by up to 41% and reduced recurrent cardiovascular events by 15% (HR 0.85; 95% CI: 0.74–0.98; I^2=24%). Low-dose colchicine reduced major cardiovascular events by 23% in the COLCOT trial and by 31% in the LoDoCo2 trial. Pooled analysis demonstrated an overall reduction in MACE of approximately 25% (RR 0.75; 95% CI: 0.68–0.84; I^2=15%). Significant reductions were also observed in myocardial infarction (RR 0.85; 95% CI: 0.78–0.93; I^2=12%) and coronary revascularization (RR 0.80; 95% CI: 0.74–0.86; I^2=20%). Long-term therapy demonstrated acceptable safety profiles, although mild increases in gastrointestinal adverse events and infections were reported.

Conclusion:
Anti-inflammatory therapy represents a promising adjunctive strategy in ASCVD management by targeting residual inflammatory risk beyond conventional lipid-lowering approaches. Therapies such as canakinumab and colchicine may redefine future cardiovascular prevention through integrated lipid control and inflammation modulation, potentially improving long-term cardiovascular outcomes.

Key Words:
Atherosclerotic Cardiovascular Disease; Residual Inflammatory Risk; hsCRP; Colchicine; Canakinumab; Major Adverse Cardiovascular Events

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