**Table 1. Approaches to organize and classify anti-inflammatory trials.**

| **Targeted Inflammatory Pathway** | **Class of Anti-inflammatory Drug**  | **Patient Population** | **Outcome Measures** | **Trial Phase** | **Trial result** |
| --- | --- | --- | --- | --- | --- |
| Studies targeting the IL-6 pathway | Studies with specific-target anti-inflammatory agents  | ACS patients | Trials assessing the impact on infarct size through anti-inflammatory interventions. | Early Phase Trials (Trials assessing safety and initial efficacy) | Positive result |
| Trials outside the IL-6 pathway | Studies with broad anti-inflammatory agents  | Stable CAD patients | Trials measuring clinical endpoints like MACE reduction. | Late Phase Trials (Larger trials evaluating effectiveness in a broader population) | Negative result |
|  |  |  | Trials evaluating the effects on specific inflammatory biomarkers. |  |  |

ACS: acute coronary syndrome; CAD: coronary artery disease; IL-6: Interleukine-6; MACE: major adverse cardiovascular event.

**Table 2. Summary of clinical studies with specific-target anti-inflammatory agents**

| **Trial Name**  | **Year** | **Intervention** | **Patient Population** | **Follow up period** | **Population (Number)** | **Key Findings** | **Notable Features and Considerations** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study)**  | 2017 | Canakinumab (IL-1β Inhibitor) | Patients with prior MI and elevated hsCRP | 48 months | 10061 | Reduction in recurrent cardiovascular events in patients receiving canakinumab. | Notable for targeting interleukin-1β and demonstrating a link between inflammation (hsCRP) and cardiovascular risk. |
| **VISTA-16 (Vascular Inflammation Suppression to Treat Acute Coronary Syndrome for 16 Weeks)** | 2014 | Varespladib (phospholipase A2 inhibitor) | ACS patients (47% STEMI, 38% NSTEMI, 15% UA) | 16 weeks | 5145 | No significant reduction in major cardiovascular events with varespladib. | Failed to prove the benefit of varespladib in patients with recent ACS who were on atorvastatin. |
| **LATITUDE-TIMI 60 trial (Losmapimod to Inhibit p38 MAP Kinase as a Therapeutic Target and Modify Outcomes After an Acute Coronary Syndrome)** | 2016 | Losmapimod (p38 MAPK inhibitor) | ACS patients (25% STEMI, 75% NSTEMI) | 24 weeks | 3503 | No reduction for recurrent MACEs events over the 12-week treatment period in patients hospitalized with ACS. | Failed to support a strategy of p38 MAPK inhibition with losmapimod in patients hospitalized with MI. |
| **SOLID-TIMI 52 trial (Stabilization of plaques using Darapladib-Thrombolysis in Myocardial Infarction)** | 2014 | Darapladib (lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor) | ACS patients (45.2% STEMI, 42.7 NSTEMI, 12.2% UA) | 2.5 years median | 13026 | Darapladib did not reduce the risk of recurrent major coronary events | Failed to support the use of targeted Lp-PLA2 inhibition with darapladib in patients stabilized after an ACS event |
| **ASSAIL-MI (ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction)** | 2021 | Tocilizumab (IL-6 receptor antagonist) | STEMI patients admitted within 6 hours | 7 days | 199 | Tocilizumab increased the myocardial salvage index compared to placebo. No significant difference in final infarct size (7.2% vs. 9.1%, p = 0.08) | Conducted at 3 high-volume PCI centres in Norway; Single infusion of 280 mg tocilizumab or placebo; Primary endpoint: Myocardial salvage index measured by MRI after 3 to 7 days. |
| **SELECT ACS (Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non-ST-Elevation Myocardial Infarction)** | 2013 | Inclacumab (anti-P-selectin) | NSTEMI patients undergoing PCI | 24 hours for efficacy and 120 days for safety evaluations | 544 | Inclacumab at 20 mg/kg demonstrated a significant reduction in troponin I levels at 24 hours (p = 0.05) and 16 hours (p = 0.07) after PCI compared to placebo. Adverse events did not significantly differ. | The P-selectin antagonist inclacumab reduces myocardial damage after PCI in patients with NSTEMI |

ACS: acute coronary syndrome; hsCRP: high sensitive C reactive protein; MI: myocardial infarction; NSTEMI: non-ST elevation MI; PCI: percutaneous coronary intervention; p38 MAPK: p38 mitogen-activated protein kinases; STEMI: ST elevation MI; UA: unstable angina.

**Table 3. Summary of clinical studies with broad spectrum anti-inflammatory agents**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial Name** | **Year** | **Intervention** | **Patient population** | **Follow up period** | **Population (Number)** | **Key findings** | **Notable Features and Considerations** |
| **COLCOT (Colchicine Cardiovascular Outcomes Trial)** | 2019 | Colchicine | Patients post-MI | Median 22.6 months | 4745 | Reduction in cardiovascular events in patients receiving colchicine. | Diarrhoea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group (P=0.35). |
| **LoDoCo2 (Low-Dose Colchicine after Myocardial Infarction)** | 2020 | Colchicine | Patients post-MI | Median 28.6 months | 5522 | Reduction in major cardiovascular events with low-dose colchicine. | Focused on evaluating the efficacy of a lower colchicine dose in cardiovascular event prevention. |
| **COPS (Colchicine in Patients with Acute Coronary Syndromes)** | 2020 | Colchicine | ACS | 12 months | 795 | The addition of colchicine to standard medical therapy did not significantly affect cardiovascular outcomes at 12 months in patients with ACS | Colchicine was associated with a higher rate of mortality. |
| **CIRT (Cardiovascular Inflammation Reduction Trial)** | 2019 | Methotrexate | History of MI or multi-vessel CAD and type 2 DM and/or metabolic syndrome | Median 2.3 years | 4786 | Methotrexate did not affect cardiovascular outcomes or plasma markers. | Methotrexate was associated with modest elevations in liver enzyme levels and reductions in leukocyte counts and hematocrit levels, as well as a higher incidence of non–basal-cell skin cancers than placebo. |
| **AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes)** | 2011 | Extended-Release Niacin | Patients with a history of cardiovascular disease | 3 years | 3414 | The trial did not demonstrate additional cardiovascular benefit from niacin therapy. | Raised questions about the efficacy of niacin in improving cardiovascular outcomes in this patient population. |
| **ALL-HEART study ((Allopurinol versus usual care in UK patients with ischemic heart disease)** |  | Allopurinol | Patients with a history of cardiovascular disease and without gout |  |  |  |  |

ACS: acute coronary syndrome; CAD: coronary artery disease; DM: diabetes mellitus; MI: myocardial infarction.

 **Table 4. Summary of ongoing clinical studies of treatments targeting inflammation in the context of atherosclerosis and acute myocardial infarction.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial Name** | **Study design** | **Intervention** | **Target** | **Patient population** | **Population (Number)** | **Primary Outcome** | **Clinical Trials Identifier** |
| **ZEUS** | Phase III, multicenter, double-blind, randomized, placebo-controlled | Ziltivekimab | IL-6 blocking monoclonal antibody | Patients with CKD stage 3 to 4, known CAD, and hs-CRP >2 mg/L | 6200 | Time to first occurrence of MACE | [NCT05021835](https://clinicaltrials.gov/ct2/show/NCT05021835) |
| **Lp(a)****HORIZON** | Phase III, multicenter, double-blind, randomized, placebo-controlled | Pelacarsen | Antisense oligonucleotide targeting Apo(a)  | Patients with established CVD and Lp(a) ≥70 mg/dL | 7680 | Time to first occurrence of expanded MACE in patients with Lp(a) ≥ 70 mg/dL or Lp(a) ≥ 90 mg/dL | [NCT04023552](https://clinicaltrials.gov/ct2/show/NCT04023552) |
| **GOLDILOX** | Phase IIB, multicenter, double-blind, randomized, placebo-controlled | MEDI6570 | LOX-1 receptor blocking monoclonal antibody | Patients aged ≥21 years with a history of MI and hs-CRP >1 mg/L | 400 | Change in non-calcified plaque volume measured by CTA | [NCT04610892](https://clinicaltrials.gov/ct2/show/NCT04610892) |
| **anaRITA MI2** | Phase II multicenter, double-blind, randomized, placebo-controlled | Rituximab | B-cell depletion with CD20 | Patients with STEMI | 558 | LVEF at 6 months with cardiac magnetic resonance | [NCT05211401](https://clinicaltrials.gov/ct2/show/NCT05211401) |
| **PULSE-MI** | Randomized, multicenter, double-blind, placebo-controlled clinical trial | Methylprednisolone 250 mg IV in prehospital setting | Ischemia-reperfusion injury prevention and wide anti-inflammatory effect | Patients with STEMI | 400 | Infarct size measured by late-gadolinium enhancement on CMR at 90-day | [NCT05462730](https://clinicaltrials.gov/ct2/show/NCT05462730) |
| **IVORY** | Phase II, randomized, double-blind, placebo-controlled, parallel group | Low dose IL-2 | Induces expansion of regulatory T cells | Patients with ACS or UA who have hsCRP >2 mg/L | 60 | Change in vascular inflammation measured by mean TBRmax in the index 18F-FDG PET/CT | NCT04241601 |

ACS: acute coronary syndrome; CAD: coronary artery disease; CKD: chronic kidney disease; CMR: cardiac magnetic resonance; CTA: computed tomography angiography; FDG PET/CT: fluorodeoxyglucose -positron emission tomography; hsCRP: high sensitive C reactive protein; IL-2: interleukin-2; IL-6: Interleukin 6; IV: intravenous; Lp(a): lipoprotein (a); LVEF: left ventricular ejection fraction; MACE: major adverse cardiovascular event; MI: myocardial infarction; STEMI: ST elevation MI; TBR: target-to-blood pool ratio; UA: unstable angina.