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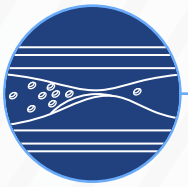
Targeting Inflammation as a Therapeutic Strategy for Dyslipidaemia and Atherosclerotic Cardiovascular Disease

Atherosclerotic cardiovascular disease (ASCVD) is one of the most common causes of morbidity and mortality worldwide[1]



Dyslipidaemia is a well-established risk factor for ASCVD[1,2]

Lowering the levels of cholesterol-bound low-density lipoprotein using lipid-lowering therapies (LLT) like statins has remained the cornerstone in the management of ASCVD[1,2]

However, many patients continue to experience cardiovascular (CV) events despite receiving optimized LLT[1,2]

Prevention and management of ASCVD is primarily based on:

Lifestyle changes | Controlling risk factors | LLT

Chronic and low-degree inflammation is a hallmark feature of ASCVD and has emerged as a crucial determinant of residual CV disease (CVD) risk and associated mortality[1]

Triggers of inflammatory responses leading to ASCVD[3]

Traditional CV risk factors
- Elevated levels of low-density lipoprotein cholesterol (LDL-C) and triglyceride-rich lipoproteins
- Hypertension • Smoking • Physical inactivity • Diabetes • Obesity

Chronic autoimmune diseases

Mental stress

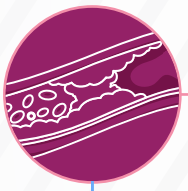
Ageing

Chronic or acute infections

Proinflammatory diet and lifestyle

Understanding the inflammatory and immune mechanisms involved in ASCVD can help uncover novel biomarkers and therapeutic targets

Visit https://ascvd-lipidology.knowledgehub.wiley.com for additional resources



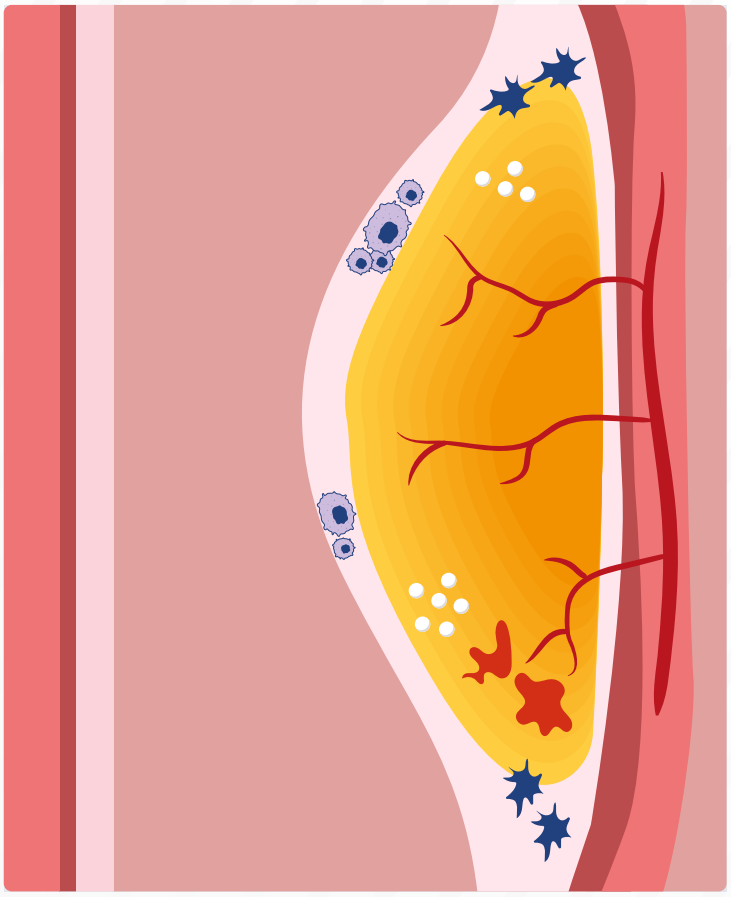
Inflammation plays a key role in the development and progression of ASCVD[3]

Elevated serum level of high sensitivity C-reactive protein (hsCRP) — a biomarker of inflammation — has been consistently associated with an increased risk of CVD[3]

Elevated levels of monocyte chemoattractant protein-1 in the plasma have been associated with[4]:
— Traditional risk factors for ASCVD
— An increased risk of clinical adverse events in patients with acute coronary syndrome[4]

An imbalance between pro- and anti-inflammatory cytokines triggers atherogenic plaque formation[3]

Inflammatory mechanisms in ASCVD[2,3]



Endothelial dysfunction
- Decreased bioavailability of vasodilators like nitric oxide
- Loss of vascular tone and protective anti-inflammatory properties
- Damaged endothelial junctions
- Release of pro-inflammatory cytokines and pro-thrombotic tissue factor
- Increased permeability to macromolecules

Sub-endothelial accumulation of cholesterol-containing lipoproteins
- Increased oxidation and aggregation of LDL-C
- Metabolic shift towards small and dense LDL-C particles with greater atherogenicity

Activation of endothelial cells
- Recruitment of monocytes and their differentiation into macrophages
- Endothelial-mesenchymal transition and migration of endothelial cells across intima of arteries

Secretion of cytokines and cell adhesion molecules
- Vascular cell adhesion molecule
- Intercellular adhesion molecule
- E-selectin

Increased wall shear stress in side branches
- Intimal thickening and inflammation
- Formation of foam cells and necrotic lesions

Activation of innate (macrophages) and adaptive (dendritic cells and B and T lymphocytes) immune responses
- Secretion of pro-inflammatory cytokines - interleukins IL-1α, IL-1β, IL-6, IL-12, IL-15, IL-18, and the tumour necrosis factor-α

Coronary plaque development and calcification
- Secretion of metalloproteinases by macrophages
- Microcalcifications
- Reduced activity of lysyl oxidase (LOX) secreted by endothelial cells

Plaque destabilization and rupture of vulnerable and high-risk plaques
- Myocardial infarction (MI)

Antiinflammatory interventions and CV risk

A paradigm shift to consider ASCVD as an inflammatory disease has opened avenues to the application of various systemic anti-inflammatory treatments[2,3,5-8]

Anti-inflammatory intervention	Target and mechanism	Trial	Outcomes
Statins	Reduction in LDL-C and hsCRP levels	Established treatment for ASCVD	Reduction in coronary plaque formation, MI, and strokes
Canakinumab	Monoclonal interleukin-1β antibody	CANTOS	Reduction in recurrent CV events
Methotrexate	Suppression of immune cells through the inhibition of nucleotide synthesis	CIRT	No difference in inflammatory markers, CV risk, and mortality
Colchicine - plant-derived alkaloid	Tubulin disruption, and reduction in neutrophil function and migration	COLCOT LoDoCo2	Reduction in CV death, MI, and stroke
Bempedoic acid	Reduction in LDL-C and hsCRP	CLEAR-outcomes trial	Reduction in CV events
Eicosapentaenoic acid (EPA)	Reduction in triglycerides and anti-inflammatory effects	JELIS	Reduction in major coronary events
Icosapent ethyl	Highly purified EPA ethyl ester lowering triglycerides and potential anti-inflammatory properties	REDUCE-IT	Lowered CV events in patients with high triglycerides and residual risk despite statin therapy

Anti-inflammatory treatments and CV risk in patients with rheumatoid arthritis

Hydroxychloroquine	Inhibits the stimulation of toll-like receptor and decreases the activation of innate immunity	Reduction in ASCVD risk, stroke, peripheral arterial disease, and sudden cardiac death
Tocilizumab	IL-6 receptor	Reduced risk of MI
Sarilumab	IL-6 receptor	Currently being investigated

Patients experiencing MI may also benefit from anti-inflammatory therapies[5]

Inflammation can disrupt cardiac remodelling following MI, leading to worsening of prognosis[5]

Therefore, it is important to identify therapeutic interventions which are effective and economically feasible in the long term for controlling the inflammatory storm post-MI[5]

Ongoing clinical studies targeting inflammation in ASCVD[5]

Therapeutic agent	Target and mechanism	Trial
Hydroxychloroquine	Immunosuppressant	CHANGAN
Montelukast	Leukotriene receptor antagonist	Phase IV, multicentre, blind, placebo-controlled
Sarilumab	IL-6 receptor blocking antibody	SARIPET
Paclitaxel	Inhibits cell proliferation by blocking microtubule activity	PAC-MAN
Ziltivekimab	IL-6 blocking antibody	ZEUS
MEDI6570	LOX-1 receptor-blocking antibody	GOLDILOX

Investigational anti-inflammatory interventions[2,5]

- Matrix metalloproteinase 2 blockade
- Anti-phosphorylcholine antibody
- Modulation of apoptosis and necroptosis
- Selective mTOR inhibition
- Low-dose IL-2 supplementation
- MicroRNA therapy
- B-cell depletion
- Stem cell therapies
- Gut microbiome modulation
- CRP apheresis
- Autophagy regulation

Future directions

Targeting inflammatory pathways in addition to LLT to reduce the residual risk of ASCVD in selected patients

Identifying selective inflammatory pathways related to ASCVD that can be targeted without compromising immune function against pathogens

Devising preventive anti-inflammatory interventions to control early atherosclerotic development

Combining circulating, cellular, and imaging-based biomarkers for a more robust stratification of high-risk patients with CVD

Challenges

Despite promising results in preclinical studies, strategies for IL-10 supplementation or adoptive transfer of T-reg cells have not yet been successfully translated into the clinical therapies for ASCVD

Key message

Targeting inflammatory pathways involved in ASCVD can help delay the development of atherosclerotic plaques and reduce recurrent CV events and associated mortality

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