The subtle red line between *combating* and *resolving* inflammation in the cardiovascular disease, a "silent sniper"

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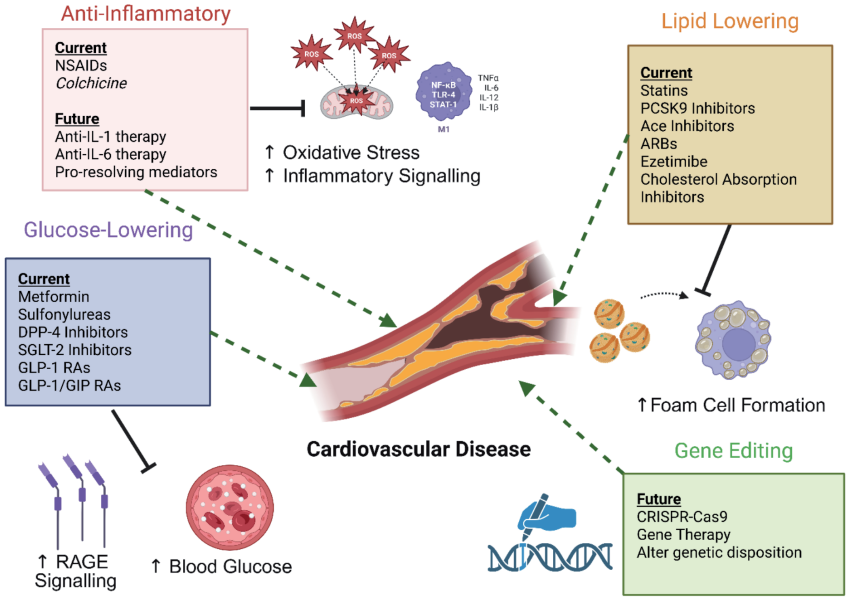
GRAPHICAL ABSTRACT



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Key words: low grade inflammation; lipid and glucose metabolism; cardiovascular therapeutics.

Contributions: all authors contributed equally, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: The authors declare no competing interests, and all authors confirm accuracy.

Received: 10 April 2025.
Accepted: 16 June 2025.

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Bleeding, Thrombosis and Vascular Biology 2025; 2:187
doi:10.4081/btvb.2025.187

ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide. Despite advancements in medical interventions, the burden of CVD continues to rise due to aging populations, lifestyle factors, and socio-economic disparities. Chronic inflammation plays a pivotal role in CVD pathogenesis, particularly in atherosclerosis, where macrophage polarization influences disease progression. Pharmacological strategies targeting lipid metabolism have evolved beyond statins to include novel therapeutics, such as PCSK9 inhibitors, ezetimibe, and bempedoic acid, offering alternative solutions for statin-intolerant individuals. Precision medicine in CVD harnesses genetic and omics data to personalize risk assessment, guide therapy, and improve outcomes, particularly through targeting genetic variants, inflammation, and clonal haematopoiesis. Additionally, gene-editing technologies, like CRISPR-Cas9, hold promise for addressing genetic contributors to CVD by modulating key regulatory targets, such as PCSK9 and ANGPTL3, potentially providing long-term solutions to hyperlipidaemia. Recent evidence suggests that glucose-lowering medications, including SGLT2 inhibitors and GLP-1 receptor agonists, confer cardiovascular benefits beyond glycaemic control by reducing inflammation, improving endothelial function, and promoting macrophage phenotype switching. Emerging therapies, such as GLP-1/GIP dual agonists, may offer superior cardioprotective effects, but further clinical trials are required to validate their efficacy in CVD. Anti-inflammatory treatments, including IL-1β inhibitors, colchicine, and statins, have demonstrated efficacy in reducing cardiovas-

cular events. However, their broad immunosuppressive effects present challenges. Resolution pharmacology, focusing on specialized pro-resolving lipid mediators (SPMs), represents a novel therapeutic approach aimed at restoring immune balance, in lieu of merely suppressing inflammation. Understanding macrophage-driven inflammation in CVD could revolutionize treatment paradigms, shifting toward targeted interventions that resolve, rather than inhibit, inflammatory processes. Overall, integrating lipid-lowering therapies, gene editing, glucose-modulating drugs, and inflammation-resolution strategies offers a multi-faceted approach to mitigating CVD risk and improving long-term patient outcomes.

Introduction

Cardiovascular disease (CVD) refers to a group of disorders affecting the heart and blood vessels, including coronary artery disease, stroke, heart failure, and hypertension, which affects over 500 million people globally. It is the leading cause of death worldwide and in the EU, responsible for an estimated 17.9 million deaths annually, with 1.7 million of these occurring within Europe.[1] CVD has a high incidence and prevalence, particularly in aging populations and low- and middle-income countries: in Europe alone, 62 million people are estimated to be living with CVD. The burden of disease is immense, causing significant morbidity, disability, and healthcare costs (in the EU, CVD was estimated to cost 282 billion euros in 2021, representing approximately 10% of total healthcare expenditure in the EU).[2]

Risk factors for CVD are classified as modifiable and non-modifiable. Modifiable factors include hypertension, high cholesterol, smoking, obesity, diabetes, and a sedentary lifestyle, while non-modifiable factors include age, gender, and genetic predisposition. Socio-economic factors, such as limited access to healthcare and unhealthy diets, also contribute to the rising prevalence of CVD.[3]

Prevention strategies, including lifestyle modifications, early diagnosis, and medical interventions, are essential in reducing the incidence of CVD. Public health initiatives focusing on education, smoking cessation, and improved healthcare access are critical in combating this global health crisis.[4] Combined pharmaco-therapies and non-pharmacological interventions (including lifestyle changes and more recently, also gene editing) are at the forefront of combating CVD. Current pharmacological interventions target the three main drivers of atherosclerosis, low-grade chronic inflammation, dyslipidaemia, and dysglycaemia, yet no single drug has been developed that effectively addresses all three simultaneously (Figure 1).

Current anti-inflammatory therapies in CVD

Chronic inflammation plays a crucial role in CVD development and progression, making anti-inflammatory therapies a promising avenue for treatment. Canakinumab, a monoclonal antibody targeting interleukin-1β (IL-1β), has been shown in the Canakinumab Anti-inflammatory Thrombosis Outcomes Trial (CANTOS) to reduce cardiovascular events in patients with prior heart attacks. However, its high cost and increased infection risk limit its widespread use.[5] Conversely, low-dose methotrexate, an immunosuppressive drug used in rheumatoid arthritis, failed to demonstrate cardiovascular benefits in the Cardiovascular Inflammation Reduction Trial (CIRT).[6]

Another promising therapy is colchicine; a well-known anti-inflammatory drug traditionally used for gout. Colchicine is thought to modulate inflammatory pathways by inhibiting the polymerisation of microtubules, leading to downstream effects, such as disruption of NLRP3 inflammasome activation, microtubule-based inflammatory cell chemotaxis, generation of leukotrienes and cytokines, and phagocytosis.[7] The multimodal mechanism of action of colchicine suggests potential efficacy of colchicine in other co-morbid conditions associated with gout, such as osteoarthritis and CVD. The COLCOT[8] and LoDoCo2[9] trials demonstrated that low-dose colchicine significantly reduces the risk of recurrent cardiovascular events by inhibiting neutrophil activity and inflammasome pathways. Low-dose colchicine (0.5 mg daily) is now FDA-approved for secondary prevention in patients with Coronary artery disease (CAD).[10]

Statins, primarily known for their lipid-lowering effects, also possess pleiotropic anti-inflammatory properties, by reducing C-reactive protein (CRP) levels. Other potential anti-inflammatory agents, including glucocorticoids, NSAIDs, and IL-6 inhibitors, are being investigated for their effects on cardiovascular outcomes. Future research aims to develop targeted, safer anti-inflammatory treatments to complement existing CVD therapies.

Despite their potential, current anti-inflammatory therapies have significant limitations. Canakinumab and colchicine reduce cardiovascular risk, but their use is limited by high costs, side effects, and long-term safety concerns. Canakinumab, for instance, increases susceptibility to infections, while colchicine can cause gastrointestinal discomfort. Broad immunosuppression associated with many anti-inflammatory drugs may also lead to increased risks of infections and malignancies. The CIRT trial demonstrated that methotrexate, despite its effectiveness in rheumatoid arthritis, did not reduce cardiovascular risk, underscoring the need for more precise targeting of inflammatory pathways.

Resolution pharmacology

A major limitation of current therapies is that they primarily suppress inflammation rather than promote its resolution. There is an urgent need for treatments that actively resolve inflammation, restoring vascular homeostasis without compromising immune function. Additionally, there is a lack of patient stratification, meaning that many therapies only work for specific patient subgroups. The development of better biomarkers is necessary to identify which patients would benefit most from anti-inflammatory treatments.

A promising approach is resolution pharmacology, which focuses on activating specialized pro-resolving lipid mediators (SPMs), such as lipoxins, resolvins, protectins, and maresins. These molecules help to restore vascular homeostasis, reduce inflammation, and promote tissue repair without suppressing immune function.[11] Unlike traditional anti-inflammatory drugs, resolution pharmacology aims to modulate the immune system (and particularly macrophages) in a way that facilitates healing rather than just blocking inflammatory pathways, by changing the

fate of those cells, switching from an inflammatory to a resolving phenotype.

Macrophages are highly plastic immune cells capable of altering their phenotype in response to environmental cues, influencing both inflammatory and reparative processes in blood vessels.[12] Macrophage polarization is a critical factor in the pathogenesis of CVD, particularly atherosclerosis. Persistent exposure to oxidized low-density lipoprotein (oxLDL) favours M1 polarization, exacerbating atherosclerosis, whereas specialized pro-resolving mediators, including lipoxins and resolvins, promote de-differentiation and trans-differentiation toward an M2 phenotype, restoring immune balance.[13]

Growing consensus around the pivotal role of macrophages in atheroprogression and regression is making these cells an attractive drug target. Once broadly classified into M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages, we now know they exist along a phenotypic spectrum with distinct functional roles. Macrophages exhibit significant plasticity, allowing them to adapt to microenvironmental *stimuli* and contribute to both inflammation and tissue repair.[14]

Understanding macrophage polarisation in atherosclerosis could enable novel interventions to mitigate chronic inflammation and improve patient outcomes in CVD. Given their plasticity, targeting macrophage phenotypic switching is an emerging therapeutic pro-resolving strategy (Figure 1).[12]

Emerging lipid-lowering therapies

The management of circulating ratios of high- and low-density lipoproteins (HDL and LDL) is a central component of primary CVD risk prevention, by tackling residual cholesterol risk (RCR) (Figure 2).[15] Statins have long been the primary treatment for dyslipidaemia, inhibiting the synthesis of cholesterol by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)-reductase, and subsequently increasing surface LDL receptor (LDLR) expression.[16] While statins remain the first-line treatment for dyslipidaemia, some individuals are statin-resistant or statin-intolerant, necessitating alternative therapeutics.[17]

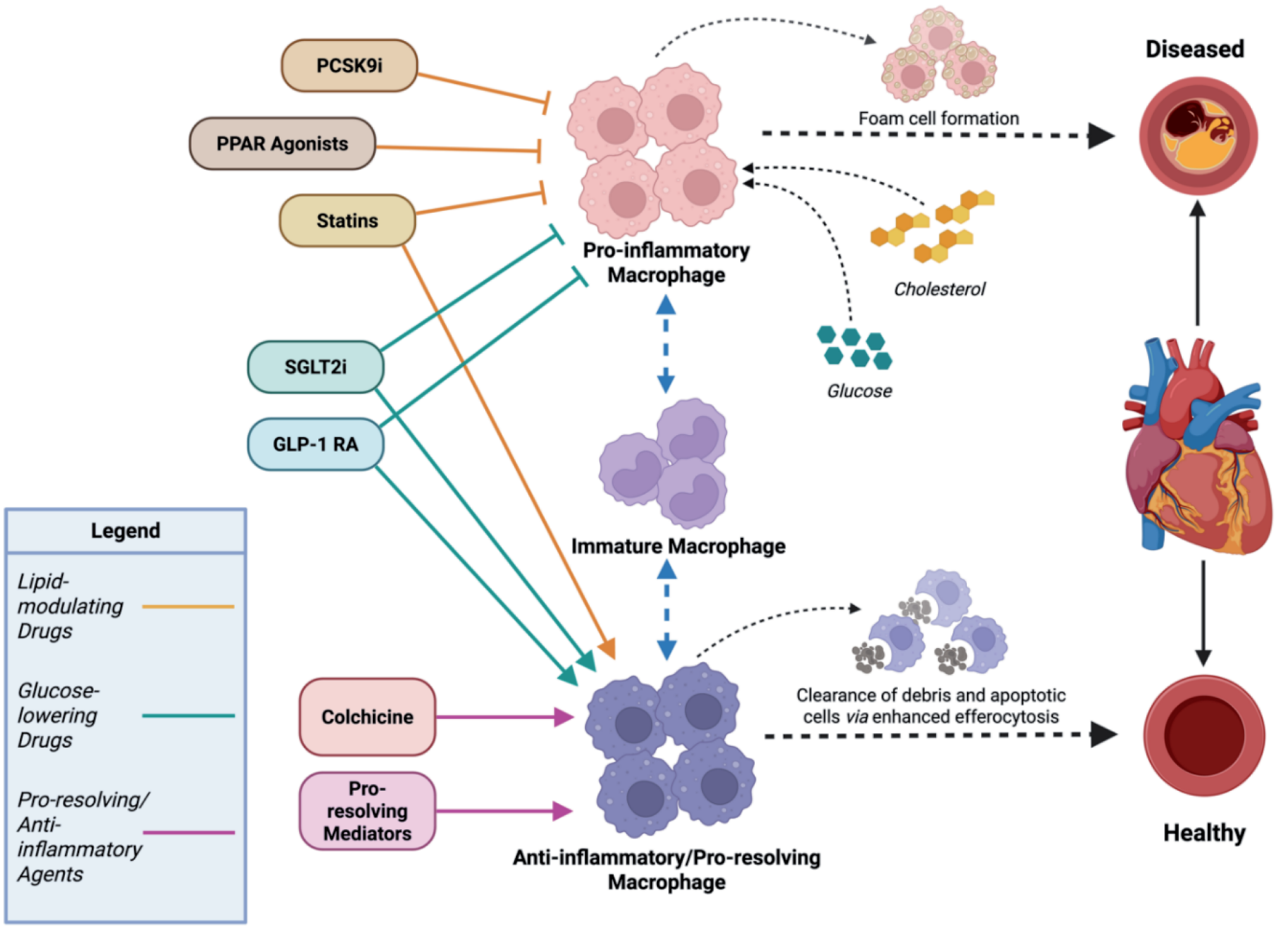

Figure 1. Role of inflammation in atherogenesis, a key driver of cardiovascular disease (CVD), and pharmacological strategies targeting its progression and resolution. While traditional therapies suppress inflammation, emerging treatments aim to resolve it. Resolution pharmacology promotes immune balance through macrophage reprogramming and specialized pro-resolving mediators, offering a novel strategy to halt disease progression and improve cardiovascular outcomes.
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One such therapeutic is ezetimibe, a Niemann-Pick C1-Like 1 (NPC111) inhibitor that blocks intestinal cholesterol absorption.[18] FDA-approved in 2002, ezetimibe has been shown to reduce LDL Cholesterol (LDL-C) levels by 13-20%.[19] It has also been successfully combined with statins, with studies demonstrating that ezetimibe added to statin therapy produces a greater reduction in LDL-C than increasing the statin dosage alone.[20] Furthermore, ezetimibe has been shown to significantly reduce residual inflammatory risk (RIR) by lowering circulating hsCRP levels.[21]

Alternatively, bempedoic acid (trialled as ETC-1002) is a relatively new therapeutic to offer an alternative to statin therapy. Like statins, bempedoic acid acts by inhibiting cholesterol biosynthesis, however, this is done upstream of HMG-CoA-reductase by blocking ATP citrate lyase (ACL) and subsequently preventing the synthesis of precursors necessary for fatty acid and cholesterol synthesis.[22] Therapeutic approval for bempedoic acid was granted in 2020 by the FDA and the EMA and demonstrated promising results when given in combination with ezetimibe, and in patients with a history of statin-intolerance.[23-25]

Another breakthrough in cholesterol management came with the development of alirocumab and evolocumab, first-in-class therapies targeting proprotein convertase subtilisin kexin type 9 (PCSK9). Approved just days apart by the European commission and the US Food and drug administration in 2015, these therapies increase LDL-C clearance from the bloodstream by preventing the degradation of LDL receptors (LDLR).[26] Both therapies have been shown to improve cardiovascular outcomes and reduce LDL-C in patients when administered alongside statin therapy, while alirocumab has been shown to be a suitable alternative therapy for statin-intolerant patients.[27-30]

Liver X receptors (LXR) are a family of nuclear hormone receptors heavily involved in cholesterol homeostasis and metabolism and as such represent attractive targets for the management of dyslipidaemia. Although previous studies targeting LXRa in mice resulted in increased hepatic lipogenesis, activation of *LXRb* has been shown to reverse atherosclerosis and cholesterol overload in mice lacking *LXRa* and *apoE*.[31] Trials of WAY-252623 (LXR-623), a *LXRα* partial / *LXRβ* full agonist, in non-human primates showed strong reduction in total cholesterol and LDL-C (50-55% and 70-77% respectively), while reducing atherosclerosis in mice.[32]

While agonists for Peroxisome Proliferator Activated Receptor (PPAR) a and g isoforms are respectively used to tackle dyslipidaemia and diabetes, treatments targeting the d isoform are not currently used in clinical practice outside of Primary Biliary Cholangitis (a rare inflammatory fibrotic liver disease).[33-36] Trials of MBX-8025, a PPAR-δ agonist, showed favourable effects on multiple metabolic parameters in dyslipidaemic patients, treatments targeting this isoform have yet to enter clinical use for treatment for dyslipidaemia.[37]

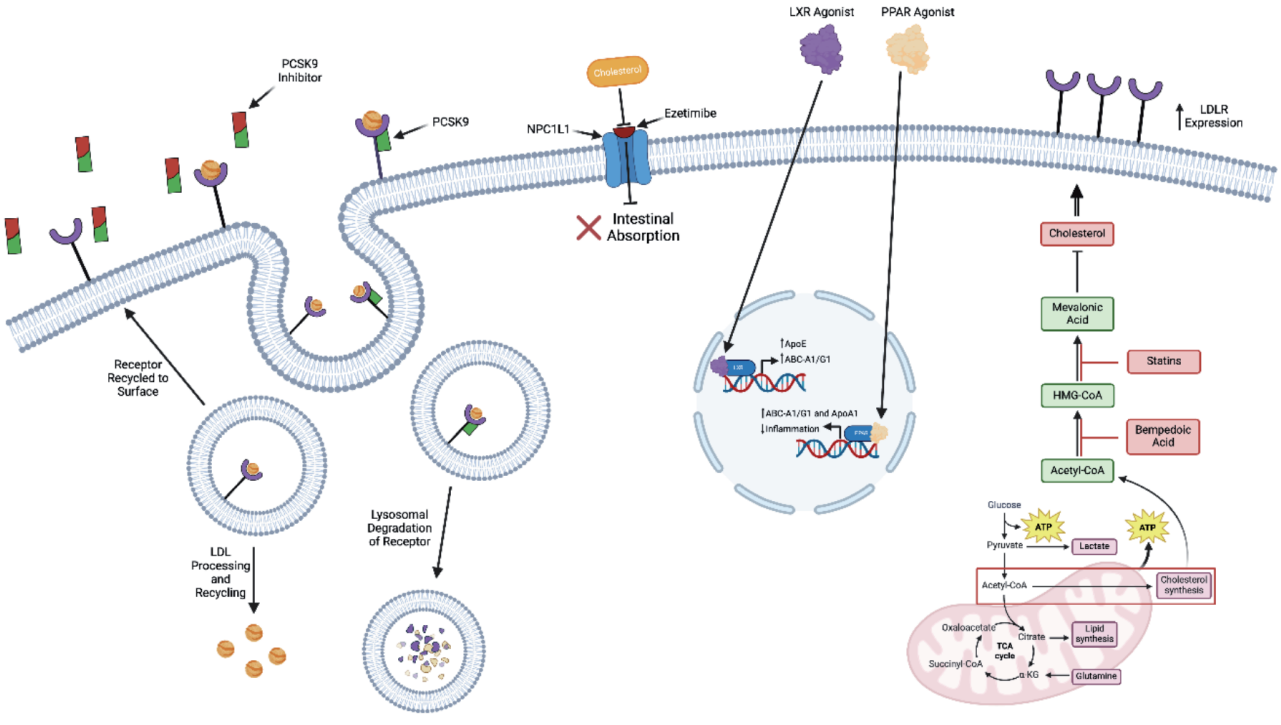

Figure 2. Mechanisms and pharmacological interventions for cholesterol regulation - overview of cholesterol metabolism and drug interventions. The figure highlights LDL receptor recycling, PCSK9 inhibition, cholesterol absorption blockade by ezetimibe, and the effects of LXR and PPAR agonists on gene expression. It also illustrates cholesterol biosynthesis and the inhibitory actions of statins and bempedoic acid.
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Glucose-lowering medications repurposing in CVD

CVD is often primarily considered a dyslipidaemic disease, which is also closely associated with metabolic dysfunction, particularly insulin resistance and diabetes. Diabetics have a two-fold greater risk of developing CVD compared to non-diabetics.[38] Sustained hyperglycaemia is one critical factor which drives inflammation, creating a toxic feedback loop, where excessive glucose promotes further inflammation, and this inflammation worsens both metabolic and cardiac function (Figure 3). Hyperglycaemia also contributes to CVD through mechanisms such as the formation of advanced glycation end-products (AGEs) which enhance

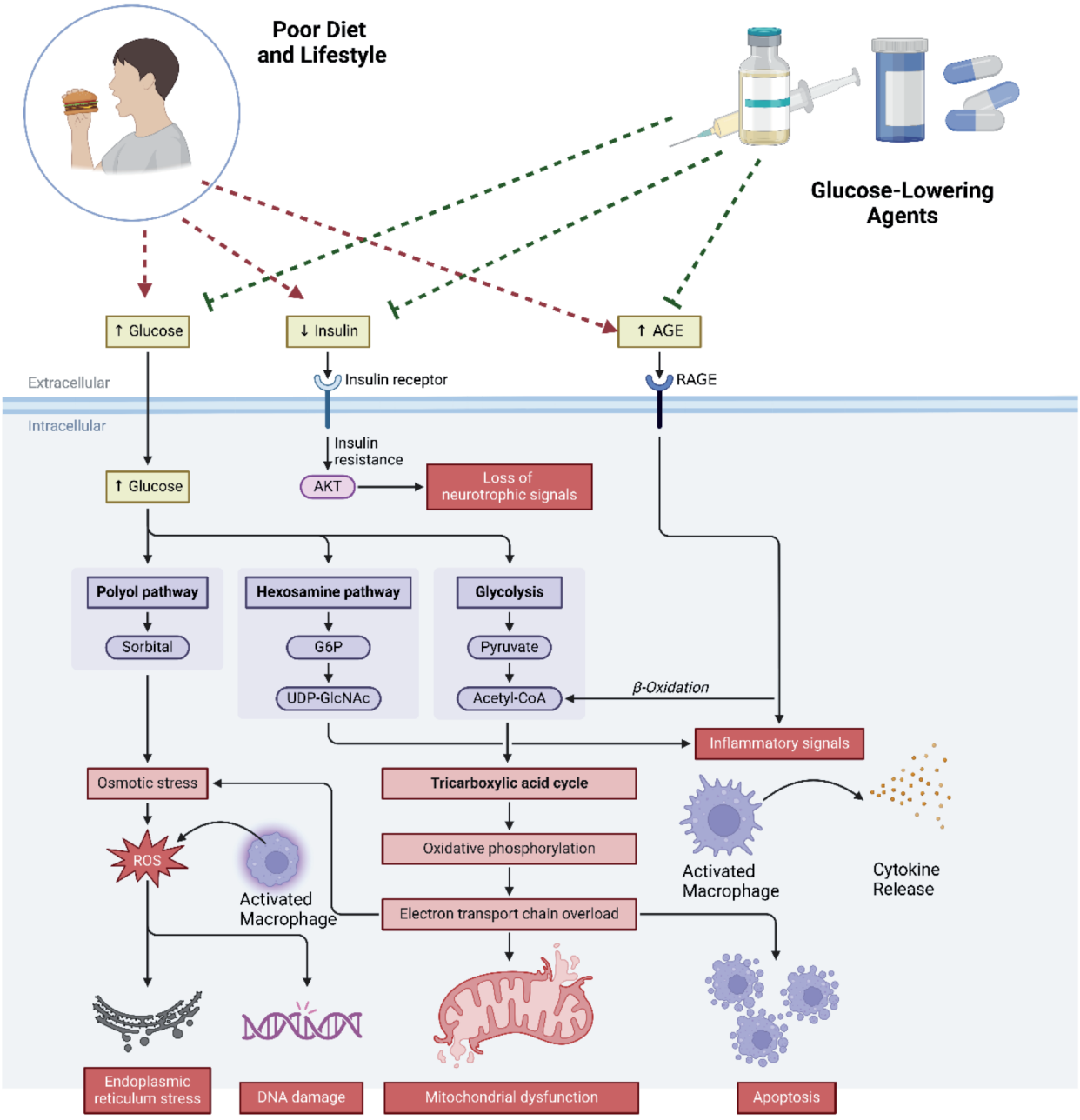

Figure 3. Link between poor diet, hyperglycaemia, and cardiovascular disease. Illustration of how poor diet and lifestyle contribute to hyperglycaemia, insulin resistance, and AGE formation, triggering oxidative stress, inflammation, and cardiovascular damage. The effect of excessive glucose signalling is shown on key metabolic pathways, highlighting the negative ramifications of hyperglycaemia on a cellular levels.
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inflammation, endothelial dysfunction, and monocyte recruitment into blood vessels.[39] AGEs also activate *NF-κB*, a key master regulator of inflammation, which further exacerbates disease progression.[4].

Modern glucose-lowering therapies, not only help to manage blood sugar levels, but also provide impressive cardiovascular benefits. Several classes of anti-diabetic agents now exist, many of which have also been shown to reduce cardiovascular risk. Some of the older drug classes, such as sulfonylureas, have fallen out of favour, as many of these agents were found to increase CVD risk and hence, are now rarely used.[41] In contrast, newer medications, particularly sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become standard of care for diabetics considered to have elevated risk of developing CVD or history of acute heart disease.

SGLT2 inhibitors, such as *dapagliflozin* and *empagliflozin*, have been shown to decrease pro-inflammatory macrophage activity, inducing a shift towards pro-resolving macrophages, and hence, improving cardiovascular outcomes.[42]

GLP-1 RAs, have been shown to reduce the incidence of a wide-range of diseases: neurodegenerative disorders (e.g. Alzheimer's disease), psychiatric disorder (e.g. schizophrenia), CVD (myocardial infarction, stroke and heart failure) as well as chronic kidney disease.[43] One mechanism which likely plays a key role is through their potent anti-inflammatory effects. In addition to their main role in reducing energy intake and blood sugar, GLP-1 RAs exert anti-inflammatory effects by lowering reactive oxygen species (ROS) production, reducing macrophage infiltration, and modulating inflammatory cytokines, such as IL-1β, IL-6, and IL-10.[44] The pleiotropic anti-inflammatory mechanisms of these medications emphasize the importance of targeting inflammation in CVD treatment.[45]

The risk-benefit evaluation of GLP-1 agonists is still ongoing. Despite their undeniable effectiveness in treating diabetes and obesity, their use has been associated with an increased risk of gastrointestinal disorders, hypotension, syncope, arthritic disorders, nephrolithiasis, interstitial nephritis, and drug-induced pancreatitis compared to standard care.[43]

A recent meta-analysis by Yu-Min Lin *et al.* which compared SGLT2 inhibitors and GLP-1 RAs demonstrated that SGLT-2 inhibitors have unique effects for treating atherosclerosis and chronic kidney disease, whereas GLP-1 RAs are superior for the treatment of peripheral artery disease. Additionally, both drug classes reduced risk of adverse cardiovascular events patients with atherosclerosis.[46]

Newer multi-agonist therapies may prove superior for the treatment of CVD, with early evidence suggesting that the dual GLP-1/ glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, tirzepatide, may confer additional cardiovascular benefits compared to basic GLP-1 RAs.[47] Retatrutide is a triple agonist targeting GLP-1/GIP/glucagon receptors which is currently undergoing phase 3 clinical trials and has displayed powerful weight loss effects.[48] Though current evidence for the cardiovascular efficacy of tirzepatide and retatrutide is limited, it is likely that these compounds may have even greater cardioprotective effects than existing GLP-1 agonist therapies. Active clinical trials, such as the SURPASS-CVOT and TRIUMPH-3, should help answer the questions to whether these dual/triple-agonists confer additional cardiovascular benefits compared to GLP-1 agonism alone.

Precision medicine and cardiovascular disease

With the ever-increasing popularity and decreasing costs of "omics" techniques, we have seen rapid evolution of precision medicine approaches in the treatment of CVD. It has long been known that an individual's risk of developing CVD is made up of a complex interaction between many elements, both modifiable (such as BMI and diet) as well as non-modifiable (such as genetic and epigenetic factors). One of the aims of the precision medicine movement is the use of "omics" data for the application of targeted treatment approaches to better treat the individual, rather than merely focusing on treating the disease.

Inherited variants within a person's genome can contribute significantly to an individual's risk of developing CVD during their lifetime, with variants in genes like Lipoprotein Lipase (*LPL*),[49] lipoprotein (a) (*LPA*),[50] ATP-binding cassette subfamily G member 5 (*ABCG5*),[51] and Low-density Lipoprotein Receptor (*LDLR*),[52] known to confer increased risk of developing CVD during a patient's lifespan. While much focus is placed on genetic alterations conferring increased risk of CVD, there are also many variations which can drive reduced susceptibility to CVD, such as genetic variants in angiopoietin-like 3 (*ANGPTL3*)[53] or apolipoprotein C3 (*APOC3*).[54] Knowing a patient's genetic risk factors may in the future help guide treatment decisions: for example, someone with significant genetic risks and moderate clinical risk factors may be started on prophylactic treatment ahead of a patient with lower burden of genetic risk factors. These variations may also assist in tailoring treatments and dosages to individual patients depending on their predicted response to treatments.

One classic example of this is using a patients genotype to predict clinically appropriate dosing for warfarin therapies. Warfarin is one of the most widely prescribed oral anticoagulants but has an especially narrow therapeutic window, making appropriate dosing a challenge. To add to this, it has also been noted that there is a significant degree of variability in the response of individual patients to specific dosages.[55] This variability in response has been shown to not only be caused by clinical and lifestyle factors (such as age, BMI or gender) but are also largely driven by genetic factors (for example, variants in the *CYP2C9* and *VKORC1* genes).[55,56] These associations have made warfarin a popular example for the potential of precision medicine to greatly improve patient care and outcomes, with many studies highlighting the potential for pharmacogenomic testing to prevent adverse patient outcomes.[57,58] Another emerging example of this is the targeting of the IL-6 signalling pathway in CVD. IL-6 is an inflammatory cytokine which over the recent years has emerged as a key mediator of inflammation with increased levels associated with increased CVD risk and adverse cardiovascular outcomes.[59-62] Multiple genetic variants have been identified in genes related to this signalling pathway (*IL6*, *IL6R*, *IL6ST*) which either increase or decrease an individual's circulating IL-6 levels, increasing or reducing their CVD risk accordingly.[60,63-66] While therapies targeting this pathway, such as tocilizumab, a monoclonal antibody targeting the IL-6 receptor, are still actively being looked at for different types of CVD, there is already evidence that genetic variants within these pathways can affect treatment outcomes in multiple contexts.[67-69]

Clonal haematopoiesis (CH) is another factor which has recently been shown to increase the risk of CVD. CH is defined as the ability of cells to acquire somatic mutations during the lifespan of an organism. This occurs primarily in hematopoietic stem cells or other blood progenitor cells. The role of CH in various disease contexts from cancer to CVD is now beginning to be better understood. More specifically, in atherosclerosis monocytes can attain these deleterious mutations which can then impair their cellular function and can also promote their transformation into atherogenic lipid-laden macrophages.[70] Recently evidence has shown that these mutated macrophages can accumulate within human plaque tissue.[71] Several detrimental CH mutations in genes like *JAK2* (Janus kinase-2), *TET2* (Tet methylcytosine dioxygenase 2) and *DNMT3* (DNA methyltransferase 3 alpha) have also been shown to be increase the future risk of cardiovascular events.[72,73] Screening for CH mutants may offer utility to identify a personalised medicine approach for CVD treatment. Identifying the presence of specific gene mutants can indicate the relative inflammatory burden in a patient which could indicate whether a patient would be a suitable candidate for a specific targeted therapy, such as canakinumab (anti-IL-1βR antibody) or tocilizumab (anti-IL-6R antibody). This highlights the heterogeneity and multifactorial nature of CVD, indicating how a personalised medicine approach may offer the best solution to stratify patients based on their differing genotypes, disease severity, age, gender, ethnicity and inflammatory status.[74] The limited success of inflammation-modulating therapies for CVD and atherosclerosis thus far could indicate how these treatments may be more suitable for individuals who have demonstrated enhanced inflammatory risk due to the presence of specific CH mutations.

Gene editing in CVD

It is well-established that genetics plays an important role in the pathogenesis of CVD, encompassing both monogenic disorders arising from pathogenic variants in individual genes, as well as polygenic disorders, where variations in multiple genes substantially affect an individual's predisposition to CVD.[75,76]

With recent developments in CRISPR (clustered, regularly interspaced short palindromic repeats) based gene editing technology, we are seeing the emergence of powerful tools in the treatment of CVD. Correcting disease-causing mutations directly has the potential to address the root cause of many CVD cases, allowing a move away from a purely symptom-management approach.

Interim results of an ongoing clinical trial of lipid-based nanoparticles targeting PCSK9 have shown promising results in treating heterozygous familial hyperlipidaemia by precisely editing a single base pair using a *Cas9*-based base editor, to switch off hepatic production of PCSK9 (clinical trial NCT05398029). In this trial, a single infusion of VERV-101 resulted in a reduction of LDL-C levels of 39-55% and a reduction of circulating PCSK9 levels of 47-84% in patients given potentially therapeutic doses of the new therapeutic.[77] This result persisted out to the 180-day study window following just a single infusion of nanoparticles and may provide a "one-and-done" solution to cure familial hypercholesterolemia. Similar studies aiming to switch off *Angptl3* production in the liver have shown significant reductions in serum ANGPTL3 protein, LDL-C and triglyceride levels in mice and non-human primates.[78,79]

While these therapies are delivered using lipid nanoparticles to target the liver, recent advances have been made in engineering CRISPR systems to better enhance specificity and deliverability.[80] One example of this is the development of NanoCas, a compact engineered nuclease which is small enough to potentially allow for single-AAV editing of multiple target tissues.

These advancements in gene editing technology mark a significant shift toward curative treatments for cardiovascular disease, offering the potential to move beyond lifelong pharmacological management and toward precise, one-time interventions which address the underlying genetic causes of disease.

Conclusions

Addressing chronic inflammation is essential for combating CVD. While current therapies provide promising insight into the future of atherosclerosis therapy, the 'two-pronged approach' of this disease (chronic inflammation and dyslipidaemia) is often overlooked. The associated RIR and RCR of atherosclerosis is yet to be simultaneously tackled by new therapeutics. Further research into targeted treatments and resolution pharmacology is crucial to developing safer, more effective strategies for managing inflammation in CVD, in order to address both RIR and RCR. Great strides have been made in efforts to combat RCR in atherosclerosis with the generation of new and future therapeutics, specifically targeting circulating LDL-C levels. Additionally, the more recent surge in appreciation towards glucose-lowering drugs such as SGLT2i's GLP-1RAs have developed the field of research more, providing new paths to discovery of effective combined therapies.

However, at the centre of this research lies the crucial macrophages. Understanding the molecular mechanisms underlying macrophage polarisation, in atherosclerosis and other CVD, could lay the foundations for innovative therapeutic approaches that target immune dysfunction, offering new strategies to improve patient outcomes and reduce the burden of CVD. Recent research suggests that SPMs, such as lipoxins and resolvins, can modulate macrophage polarization by promoting de-differentiation of M1 macrophages back to an M0 state, followed by reprogramming into an M2 phenotype. This process of trans-differentiation holds great promise for developing novel treatments to combat chronic vascular inflammation and restore immune balance in CVD patients.

Adjuvant resolving therapies combined with cutting edge lipid-lowering drugs (i.e., PCSK9 inhibitors) or repurposed glucose-lowering standard of care (i.e., GLP-1RAs) could pave the way to ground-breaking therapeutic avenues in the treatment and prevention of CVD by simultaneously targeting RIR and RCR, and additionally, promoting tissue regeneration.

Precision medicine leverages genetic, epigenetic, and molecular profiling to enable more targeted and effective prevention and treatment strategies for CVD, reflecting its complex and multifactorial nature. An example is targeting the role of CH on the macrophage plasticity in atherogenesis. In parallel, CRISPR-based gene editing is opening the door to curative, one-time treatments that address the genetic roots of CVD, particularly in monogenic lipid disorders. The editing of pivotal genes in lipid or glucose metabolism could represent the forefront of CVD management for more vulnerable cohorts of patients, providing them with similar recovery options as those tolerant to current and upcoming therapeutics.

Altogether, these advances signal a shift from symptom-focused care to precision, multi-targeted interventions that integrate immune modulation, metabolic regulation, and genetic therapy paving the way for a more effective and durable approach to combating CVD.

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