Pharmacological Research 213 (2025) 107635

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Pharmacological regression of atherosclerotic plaque in patients with type 2 diabetes

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ARTICLE INFO

Keywords:
Atherosclerosis
Regression plaque
Inflammation
Anti-dislipidemic therapy

ABSTRACT

Atherosclerosis of the coronary arteries continues to be one of the major global health burdens and acute coronary syndrome is responsible annually for at least 30 % of all deaths globally. Acute coronary syndrome may be the consequence of thrombus formation after erosion or rupture of obstructive or non-obstructive atherosclerotic plaque. The rupture of plaques is mostly caused by mechanical stress usually called cap fatigue. Vulnerable plaques are characterized by a softer atheromatous core and a thinner fibrous cap, with inflammation and hypercholesterolemia playing a crucial role in the atherothrombotic process. Based on animal studies that extend back to the 1920s, regression of atherosclerotic plaques in humans has just started to be considered and pursued. The idea that the human atherosclerotic plaques could regress at all met an important resistance over the decades; indeed, advanced plaques contain components, such as necrosis, calcification and fibrosis, which are hard to be removed. However, new animal models and imaging technics allowed a more complete and accurate quantitative assessment of plaque volume and are shedding new light on atherosclerosis regression. In this review, we are revisiting the existence of atherosclerosis regression in preclinical and clinical studies, with a focus on the latest mechanistic insights and on the newest pharmacological agents, particularly in patients with diabetes. Interestingly, we suggested that based on literature insights and preclinical studies, a combination of drugs to target hyperglycemia, dyslipidemia and inflammation may be desirable for a fast-track Pharmacological regression of atherosclerotic plaque in patients with type 2 diabetes.

1. Introduction

The regression of atherosclerotic plaques is one of the holy grail of cardiovascular medicine since the first studies back in the 1920s [1]. In the last decades with new available drugs, atherosclerosis regression seems to become a real possibility [2]. Mechanisms involved in the aforementioned phenomenon, include extensive lowering of plasmatic concentrations of atherogenic lipoproteins and an increase of reverse cholesterol transport from atheroma to the liver [3]. The shrinkage of the lesion is associated with a reduction of atherogenic lipids from the arterial wall, removal of cholesterol and necrotic debris by phagocytes and migration of foam cell out from the vessel wall [4]. However, the presence in advanced plaques of components such as necrotic debris, calcification and fibrosis renders the atheroma hard to reduce [5]. Literature suggested that atherosclerosis regression is strongly associated with the control of lipid profile, LDL-c and triglycerides reduction and increase in HDLc, as well as with a reduction of inflammation, probably responsible for the atherosclerotic process and the instability

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https://doi.org/10.1016/j.phrs.2025.107635
Received 21 December 2024; Received in revised form 21 January 2025; Accepted 27 January 2025
Available online 5 February 2025

of the plaques [6,7]. In this review we will provide an overview of contemporary animal and human studies, in which the regression over time of established atherosclerotic plaques has been evaluated. There is a clear need for studies on atherosclerosis regression, aiming at fully understanding the mechanism of this process, particularly in patients with diabetes.

2. Preclinical studies

Possibly the first drug which showed to reduce major cardiovascular events and slow angiographic progression of coronary atherosclerosis (Table 1) was fenofibrate [8]. The mechanism of action is via the activation of peroxisomal proliferator-activated receptor-alpha (PPAR--alpha), a nuclear transcription factor that controls a variety of cellular functions. In animal treated with fenofibrate during a hypercholesterolemic diet, a significantly regression of atherosclerotic plaque was observed [8]. The lesions were more "stable", with reduced infiltrating macrophages and increased smooth muscle cells, supporting the potential anti-atherogenic effects of PPAR-alpha agonists [8]. Another early study, in which a shrinkage of atherosclerotic lesions has been demonstrated, was conducted in animals receiving intravenous bolus injections of phosphatidylcholine; indeed, in less than two weeks the plaques were less severe in treated animals [9]. In the last decades several studies were conducted on atherosclerotic animal models during high cholesterol feeding and showed that the switch to low cholesterol feeding, induced a shrinkage of atherosclerotic plaque. Rhesus monkeys treated with high cholesterol chow for 17 months developed widespread coronary lesions with fibrosis and 60 % luminal narrowing; while the switching to a low fat or linoleate-rich diets brought the cholesterol levels down to 3.6 mmol/l (140 mg/dl) and it was associated with a reduction of necrosis, fibrosis and a shrinkage of the plaques [10]. The administration of HDL, apolipoprotein A-1 (ApoA-1) and phospholipids were found to induce atherogenic regression in rabbits, but the regression was restricted only to fatty streaks and not to established plaques (Table 1) [11]. Apo A-I transgenic overexpression promotes atherosclerosis regression in preclinical models and has a variety of effects on cholesterol flux and inflammation that may contribute to the regressive phenotype [12]. Even after an LDL reduction level to extremely low levels, HDL-targeted interventions (primarily CETP inhibition) may favor atheroma regression. A successful strategy to obtain plaque regression in mice was to increase HDL levels through the injection of an adenoviral vector carrying the gene of human ApoA-1 [13,14]. A similar study conducted in Apo E KO mice demonstrated the remodeling of the atherosclerotic lesions with reduction of infiltrating macrophages and increasing of smooth muscle cells with more stability to the plaque [15]. The other big driver of atherosclerotic plaque is inflammation (Fig. 1), which favored infiltration of the plaque, through an increased production of cytokines (i.e.: IL-6, TNF alpha, MCP-1, MMP-9) and a higher expression of adhesion molecules such as ICAM, VCAM-1. These aforementioned events are responsible for the plaque instability by inducing the thinning of the fibrous cap and by sustaining chronic inflammation at the site of lesion development [7,16–19]. The receptor for advanced glycation end products (RAGE), which is a multiligand member of the immunoglobulin superfamily of cell surface molecules, is one of the proinflammatory molecules involved in the atherosclerotic process. Engagement of RAGE by its signal transduction ligands induces inflammatory cell infiltration and activation in the vessel wall, RAGE blockade has been considered a strategy to stabilize atherosclerosis and vascular inflammation [7]. Another player is CCR7 chemokine (C–C motif) receptor 7, which is required for dendritic cell emigration [20], thus injection antibodies against the CCR7 ligands inhibited most of foam cells from emigrating from the aortic transplant lesions, establishing a functional role for CCR7 in regression. Regression of atherosclerosis occurs through several mechanisms and molecules dyslipidemia and inflammation being the major factors involved [21] (Table 1).

Table 1
The more representative animal studies to achieve plaque stabilization and regression.

Publication	Treatment/Strategy	Model	Result
Friedman M. Proc Soc Exp biol Med 1957	Phosphatide infusion and low-fat chow	Rabbit	Regression
Armstrong ML Circ Res 1970	Low fat or linoleate-rich diet	Monkey	Regression
Miyazaki A ATVB 1995	Intravenous injectionof HDL, ApoA−1 and phospholipidis	Rabbit	Regression restricted to fatty streaks plaques
Forster R Cell 1999	CCR7 antibodies	Mice	Regression
Shah PK Circ 2001	High dose recombinant Apolipoprotein A−1	Mice	Regression
Bucciarelli LG Circ 2002	sRAGE Treatment in diabetic apoE-/-	Mice	Stabilization
Corti R Atherosclerosis 2007	Fenofibrate in atherosclerotic rabbit obtained by double ballon injury and hypercolesterolemic diet	Rabbit	Regression
Van gils JM Nat Immunol 2012	Nitrin−1 inhibition	Mice	Regression
Rader DJ JAMA Cardiol 2018	ApoA-I overexpression in Apo E-/- mice	Mice	Regression

3. Human studies

Aggressive lowering LDL was probably the first treatment that correlated significantly with the reduction in calcium-volume score indicating that calcified plaques can shrink too. The first two main trials (Table 2), which were able to demonstrate atherosclerosis regression were the REVERSAL trial (Reversal of Atherosclerosis with Aggressive Lipid Lowering) [22] and the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) [23]. Patients with acute coronary syndrome were treated for over a year with high-dose statins and evaluated by coronary intravascular ultrasonography. In the REVERSAL trial, patients treated with conventional therapy were subjected to the progression of atherosclerosis, while in the high dose statin group a reduction in atheroma volume was observed particularly in patients with a reduction of LDL peripheral levels of more than 50 % [22]. In the ASTEROID trial (Table 2) all patients who received high-dose therapy for 24 months experienced an important shrinking of the plaque volume of nearly 7 % as compared to pretreatment. The greater reduction in atheroma volume in the ASTEROID trial could be explained by the longer treatment (i.e. + 6 months) and by the greater reduction in LDL levels (i.e.–20 mg/dl) [27,28]. Both studies employed statins which are known for their lipid-lowering effect. However, different types and doses of statins were used in these studies, which could influence the outcomes; furthermore, patients with established coronary artery disease in secondary prevention, but not primary intervention, were included. In the ARBITER trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol), atorvastatin induced a regression of carotid intima-media thickness, whereas this was not observed in the pravastatin group [24]. Marked LDL reduction to absolute value below 100 mg/dL with a high-potency statin provided atherosclerosis regression at 1 year, as evaluated with quantification of carotid intima-media thickness [24]. The METEOR trial demonstrated that rosuvastatin can induce a reduction of carotid intimamedia thickness in low-risk individuals with subclinical atherosclerosis [25,26]. In the SATURN trial (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) the effect of 2 high-intensity regimens of rosuvastatin and atorvastatin on plaque were studied over 24 months treatment, and a significant atheroma regression was observed with both treatments [27]. Radiofrequency analysis revealed a reduction in

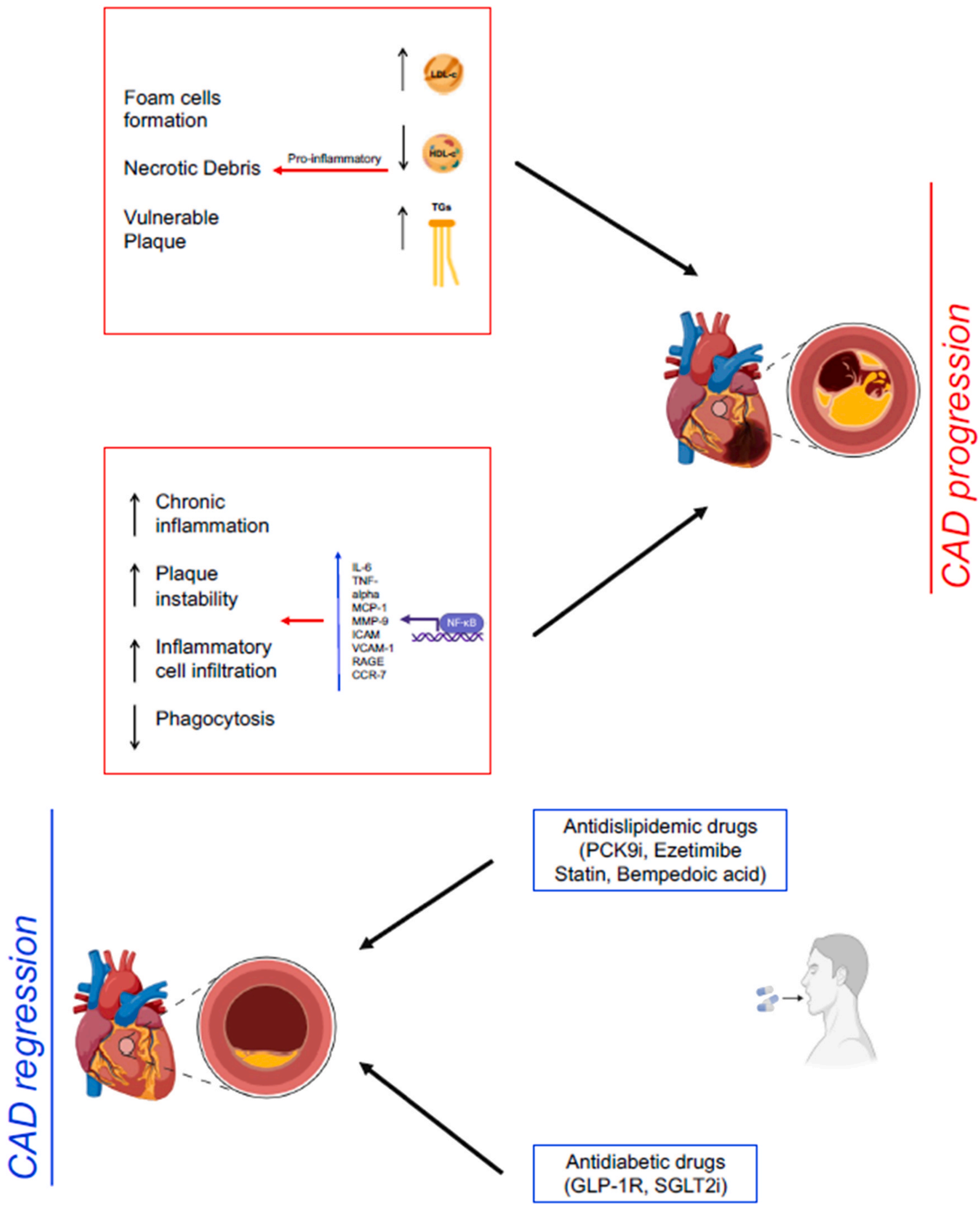

Fig. 1. Mechanisms of plaque's formation and drug therapy to obtain atherosclerosis regression.

fibrofatty plaque component and an increase in plaque calcium with both high-intensity statins. This process called plaque delipidation is associated with fibrous healing and increased in calcium component which reflect plaque stabilization [27] (Table 2). Another important player of clinical trials is ezetimibe, which targets the Niemann– Pick C1–like 1 protein, thereby reducing absorption of cholesterol from the intestine. Intensive statin treatment was evaluated versus low-dose statin plus ezetimibe and the effect on fibrous cap thickness of coronary vulnerable plaques was assessed. At 12 months of follow up total cholesterol and LDLc were further decreased in the combination therapy group [28], with reduction of the fibrous cap thickness (-32.5 %) and better stability to the plaque [28]. Interestingly, treated-patients who did not experienced a fall in C-reactive protein demonstrated less coronary atheroma regression, suggesting that systemic inflammation may contribute to residual cardiovascular risk in optimally treated patients [29]. Larger trials, including the HEAVEN trial (Virtual Histology Evaluation of Atherosclerosis

Regression During Atorvastatin and Ezetimibe Administration) [30], the PRECISE-IVUS trial

(Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by

Intravascular Ultrasound) [31], the OCTIVUS trial (Ezetimibe In Addition To Atorvastatin Therapy On The Plaque Composition in Patients with Acute Myocardial Infarction) [32] and the ZIPANGU trial (ezetimibe clinical investigation for regression of intracoronary plaque evaluated by angioscopy and ultrasound) [33], showed numerically

Table 2
Human clinical trials testing statins and ezetimibe.

Trial	Treatment/strategy	Time/N. Pts/Technique	Result	Range of lipid profile
ARBITRER Circ 2002	AT 80 mg vs PV 40 mg treatment	12 months/ 161 pts with CAD/ Ultrasound	CMIT regression in AT group Stabilization in the PV group	AT LDL-c−48.5 % (76 +/−23 mg/d) PV LDL-c was −27.2 % (110 +/−30 mg/dL)**
REVERSAL JAMA 2004	AT 80 mg vs PV 40 mg treatment	18 months/654 Pts/IVUS	AT group reduced progression of atherosclerosis	AT LDL-c - 50 % 2.0 mmol/L (79 mg/dL) PV LDL-c 2.8 mmol/L (110 mg/dL)***
ASTEROID Jama 2006	RO 40 mg	24 month/ 507 Pts/ IVUS	Regression of total atheroma (−6.8 %)	RO LDL-c −53.2 % (60.8 mg/dl)** RO HDL-c + 14.7 % (49 mg/dl)
METEOR Jama 2007	RO 40 mg vs placebo	24 months/ Pts with subclinical atherosclerosis/ Ultrasound	Reduction of progression of CMIT in low risk pts	RO LDL-c −49 % (78 mg/dL)**
SATURN NEJM 2011	RO 40 mg vs AT 80 mg	24 months/1385 pts with CAD/ IVUS	Regression greater in RO (PAV: −1.6%)**	RO LDL-c < 52 mg/dl vs AT LDLc< −70 mg/dL**) RO CRP −0.2 mg/l and RO HDLc; + 2.8 mg/dL**)
HEAVEN Circ 2012	AT 80 mg +EZT 10 mg vs standard therapy	12 months/89 pts pts with stable angina/Virtual Istology IVUS	Regression plaque PAV −0.4 %,vs + 1.4 %* Lumen + 40, 5 % vs + 14–9 %*	AT 80 mg +EZT LDL-c < 2 mmol/l (79 mg/dl)*
PRECISEIVUS J Am Coll Card 2015	AT max tollerated +EZT 10 mg vs AT max tollerated	12 months/ PCI/IVUS	Regression plaque Absolute change in PAV –1.4 % vs −0.3 % PAV reduction 78 % vs. 58 %;	AT+EZT vs AT LDL-c 63.2 mg/dl vs. 73.3 mg/dl**
ZIPANGU Circ 2017	AT 10–20 mg and EZT 10 mg/day vs AT 10–20 mg	9 months PCI/IVUS	Plaque stabilization PAV 50.0 % vs.49.8 %	AT+EZ LDL-c decreased from 103–63 mg/dL** AT LDL -c decreased from 100 to 75 mg/dl in AT**

Abbreviations: Pravastatin (PV); Atorvastatin (AT); Rosuvastatin (RO); Carotid intima-media thickness (CMIT); Atherosclerosis regression (AR), Cardiovascular disease (CAD); Ezetimibe (EZT); PAV (percentage atheroma volume);

* $p < 0.05$;
** $P < 0.001$;
*** $P < 0.0001$.

Table 3
Human clinical trials testing PCSK9 inhibitors.

Trial	Treatment/strategy	Time/N. Pts/Technique	Result	Range of lipid profile
GLAGOV Phase 3 JAMA 2016	EV 420 mg/month+maximally tollerated statin vs statin alone	76 wks/968 pts with CAD/IVUS	Regression plaque PAV vs 47.3 %;64.3 % TAV 48.9 % vs 61.5 %**	LDL-c reduction of 75 % 93.0 vs 36.6 mg/dl**
HUYGENS Phase 3 Cardiovasc Diagn Ther 2021	EV 420 mg/month+ maximally tollerated statin	50 weeks/150 pts with non-ST-elevation ACSV/OCT/IVUS	Amilioreted the high-risk features of coronary plaques	LDL-c reduction of 75 %
PACMAN-AMI Phase 3 JAMA 2022	AL 150 mg biweekly sc+high intensity statin	52 weeks/300 Pts/IVUS OCT NIFS	Regression in non-infarct-related arteries «Triple regression» : in 31.7 % (1/3 pts)**	LDL-c 23.6 mg/dl vs. 74.4 mg/dl**
ARCHITECT Phase 4 Circ 2023	AL 150 mg + high intensity statin	78 weeks/104 pts with familial hypercholesterolemia without clinical atherosclerotic CVD if LDL< 100 mg/dl was not achieved/ CCTA	Reduction of PAV, ameliorate architecture and composition (rise in calcified and fibrous cap; decrease in fibro-fatty and necrotic plaques)	-LDL-c from 138 to 45 mg/dl, - 67.6 % reduction** -Total chol from 209–118 mg/dl** -HDL from 51 to 53 mg/dl P = 0.267

Abbreviations: Atorvastatin (AT); Ezetimibe (EZT); PAV (percentage atheroma volume), Evolocumab (EV), Alirocumab (AL), Cardiovascular disease (CAD), Total atheroma volume (TAV);
*$p < 0.05$;
***$P < 0.0001$.
** $P < 0.001$;

greater plaque regression in patients treated with ezetimibe in combination with statin as compared to those treated with statin alone (Table 2). The discovery of the role of proprotein convertase subtilisin/kexin type 9 (PCSK9) in LDL-c metabolism has led to develop of potent LDL-c lowering drugs, the PCSK9 inhibitor. The GLAGOV trial (Global

Assessment of Plaque Regression with a PCSK9 Antibody as measured by Intravascular Ultrasound) (Table 3), a phase III multicenter, double blind, randomized, placebo controlled study, evaluated the effect of evolocumab, a human IgG2 monoclonal antibody with high binding affinity for PCSK9, on the change in burden of coronary atherosclerosis as measured by the intravascular ultrasound-derived percentage atheroma volume in subjects undergoing a clinically indicated coronary angiogram with evidence of cardiovascular disease, who are receiving maximally tolerated statin therapy. Addition of evolocumab reduced LDL-C from 93.0 to 36.6 mg/dL and was associated with a reduction in percentage atheroma volume by 0.95 % after 76 weeks of treatment [34–36]. The HUYGENS study determined whether intensified lipid lowering therapy with evolocumab in addition to maximally tolerated statin therapy will have incremental benefits on high-risk features of coronary artery plaques [37]. Patients were randomized 1:1 to treatment with evolocumab or placebo with primary endpoint being the absolute change in minimum fibrous cap thickness in a matched arterial segment from baseline to week 50. The inverse association between achieved LDL-c levels and plaque calcification, suggests that this effect is a result of lipid lowering, rather than a pleiotropic effect of statins [37].

The more recent PACMAN-AMI trial (Effect of Alirocumab added to High-Intensity statin therapy on Coronary Atherosclerosis in Patients with Acute Myocardial Infarction) a double-blind, placebocontrolled, randomized clinical trial enrolled 300 patients undergoing percutaneous coronary intervention for acute myocardial infarction. The primary efficacy end point was the change in intravascular ultrasound derived percentage atheroma volume from baseline to week 52. The addition of subcutaneous alirocumab, compared with placebo, to high-intensity statin therapy resulted in significantly greater coronary plaque regression in non–infarct-related arteries [38]. The PACMAN- AMI trial was designed to investigate rates, determinants, and prognostic implications of “Triple Regression” (concomitant atheroma volume reduction, lipid content reduction, and increase in fibrous cap thickness). Indeed, “Triple Regression” occurred in one-third of patients with acute myocardial infarction, who were receiving high-intensity lipid-lowering therapy and was associated with alirocumab treatment [39]. Very recently, data from the ARCHITECT trial (Effect of Alirocumab on Atherosclerotic Plaque Volume, Architecture and Composition) showed that alirocumab favored the regression of coronary plaque burden and plaque stabilization as assessed by coronary computed tomographic angiography over 78 weeks in patients with familial hypercholesterolemia without clinical atherosclerotic cardiovascular disease [40] (Table 3). Among the non-statin treatment, niacin was tested in a high risk patients treated on either statin or statin plus niacin [41]. In the HATS study (HDL-atherosclerosis treatment STUDY), a reduction in coronary artery stenosis and in cardiovascular events was observed in niacin-treated patients who experienced an increase of HDL [42]. The EVAPORATE trial (Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy)) enrolled 80 patients affected by coronary atherosclerosis documented by MDCT (multidetector computed tomography), on statin therapy and with persistently elevated triglycerides levels. According to the protocol it was added to the statin therapy 4 g/day of icosapent ethyl ester (IPE), a highly purified eicosapentaenoic acid ethyl ester and after 18 months the treated patients compared to placebo group achieved a low-attenuation plaque (LAP) volume by 17 %, while in the placebo group the LAP volume was more than double + 109 %, also the fibrous and fibrofatty plaque volumes were significantly reduce in the treated group providing important mechanistic data on plaque characteristics [43]. Recently cholesteryl ester transfer protein inhibitors were investigated as pharmacological agents for their ability to raise HDL levels and Apo A-I levels and to reduce LDL-C and apo levels. The first cholesteryl ester transfer protein inhibitor tested in a clinical trial, torcetrapib, increased the all-cause mortality and cardiovascular events, which led to the premature ending of the ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) trial, even if regression of coronary atherosclerosis assessed by intravascular ultrasound was observed in patients who achieved the highest HDL-c levels [44,45]. Dalcetrapib and Anacetrapib, two more recent molecules, showed to increase HDL-c levels by 138 %, accompanied by a more robust reductions in LDL-c [46].

In spite of the positive results of the REVEAL trial (The Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification), Merck decided not to proceed in asking regulatory approval for anacetrapib. Dalcetrapib (Dal-GenE study) remains a molecule within this area still in clinical development [47]. The latest arrival is bempedoic acid, an oral pro-drug that is activated in the liver and inhibits cholesterol synthesis in hepatocytes, and that recently received clinical approval. Bempedoic acid may provide an oral therapeutic option complementary to ezetimibe in statin intolerant patients who require additional LDL-c lowering. Bempedoic acid added to background lipid-modifying therapy that included ezetimibe reduced LDL-c by 28.5 % more than placebo [48]. There are no trials which investigated if bempedoic acid can induce regression or at least alt the progression of atherosclerosis [49].

4. Clinical studies in patients with diabetes

Patients with diabetes mellitus have a substantially higher rate of major cardiovascular event and worst outcome after myocardial infarction and percutaneous coronary intervention [50]. Data from a sub-analysis of the COSMOS trial (Coronary Atherosclerosis Study Measuring Effects of

Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects) [51] suggest that atherosclerosis regression in patients with diabetes mellitus was less pronounced in patients with high HbA1c levels compared with those with low HbA1c levels ≤ 6.5 % [51]. The JAPAN-ACS trial (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome), suggested that diabetes mellitus is a major negative determinant of coronary artery plaque regression during statin therapy in patients with acute coronary syndrome by intravascular ultrasound [52]. Results showed that early statin treatment after acute coronary syndrome induced regression of coronary plaque volume, but in the diabetic patients more intensive therapy is needed to obtain the same benefit [52]. These data were confirmed by the TRUTH trial (treatment with Statin on Atheroma Regression Evaluated by Intravascular Ultrasound with Virtual Histology) [53]. All the studies demonstrated that very high-risk patients for cardiovascular disease, such as patients with diabetes must be treated with high intensity statin treatment to obtain regression of coronary plaque [54]. A post-hoc pooled analysis of data from seven prospective, randomized trials included more than 3000 patients in the analysis, suggested that higher are the levels of HbA1 the higher is the rate of coronary atheroma progression rates and worst are the clinical outcomes [55]. This reinforced the idea that glycometabolic control is an important player in the progression of atherosclerotic plaque. Optimal glycometabolic control is as important as antihypertensive treatment and the lipidic lowering agents’ strategy when it comes to plaque regression [55]. In a post-hoc analysis of the SATURN trial (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) the long-term high--intensity statin arm promoted coronary atheroma regression in 1039 patients with diabetes [56]. High-intensity statin therapy induced atherosclerosis regression in patients with diabetes to a similar degree with nondiabetic patients only when LDL-c were reduced below 70 mg/dl (1.8 mmol/l). Moreover, atheroma volume regression was significantly less evident in patients with diabetes, but similar to patients without diabetes when LDL-c levels were below or equal to 70 mg/dl (1.8 mmol/l) [56]. In the PACMAN AMI trial PCSK9i used alone or in combination with statins facilitate the reduction of LDL-c below the 50 % reduction or less than 70 mg/dl (1.8 mmol/l) resulted in significantly greater coronary plaque regression with 8 % of them achieving triple regression [38,39]. The PERISCOPE trial (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary

Obstruction Prospective Evaluation), showed that pioglitazone led to a significantly greater decline in HbA1c levels compared to glimepiride and was associated with more atheroma volume regression [57]. Multiple therapies should be used in patients with diabetes to obtain atheroma regression [58,61] (Table 4).

5. Discussion

New imaging techniques [62] have unequivocally established that pharmacological interventions have the capacity to promote plaque regression, depending on the degree of lipid lowering achieved, while new drugs have the ability to reduce inflammation and to improve glycometabolic control in patients with diabetes [17,63–65]. Clinical guidelines suggested the importance of optimizing statin intensity or achieving low LDL-C targets in the setting of established atherosclerotic disease.

Considerable residual cardiovascular risk is apparent in patients already prescribed statin therapies if LDL target is not achieved, especially in those at high cardiovascular risk as diabetic patients, or in those achieving lower LDL-C levels according to the guidelines [6,66]. The presence of low-level systemic inflammation may be a key-component particularly in patients with diabetes [17,67]. PCSK9i added to statin and non-statin drugs can help to achieve atheroma regression in the diabetic and non-diabetic patients [38–40,68]. A multitude of therapeutic options are available to reduce the risk of cardiovascular events by inducing plaque regression, thus an intensive management of a global coronary risk, rather than a single risk factor, may lead to the prevention of atheroma progression and cardiovascular events [69]. A major issue to be considered is patients' adherence, which can be somehow reduced by complex therapy; indeed, compliance and statin side effects are 2 major downsides of most of the study. Recently, the introduction of ezetimibe, bempedoic acid and PCSK9i helped to reduce statin dose and to reach desired lipid levels avoiding statin side effects. Since the inflammation is a key point in the development of atherosclerosis, any potential anti-inflammatory drug may be tested for the ability to revert atherosclerosis. For instance, Anakinra, an IL-1 receptor antagonist, may be able to reduce the residual cardiovascular risk. Interestingly some preclinical studies have demonstrated a plaque regression and remodeling when anti-IL-1 receptor was used, but no studies are available in humans [70,71]. Interleukin-1β (IL-1β) plays a central role in stimulation of innate immune system and inflammation and in several chronic inflammatory diseases. One of the molecules mainly involved in IL-1β maturation is the Purinergic 2 × 7 receptor (P2X7R), which is involved in the progression of atherosclerosis [72,73]. P2X7R blockade with suppression of NLRP3 activation may be associated with plaque regression [72,73]. These studies provide preliminary evidence for the powerful anti-inflammatory action of P2X7R targeting and its potential role in the attenuation and stabilization of atherosclerotic plaque. The TNF-alpha Converting Enzyme, also called ADAM17 is a type I transmembrane metalloproteinase. ADAM17 promotes vascular inflammation in endothelial cells, smooth muscle cells, and macrophages, and regulates the occurrence and development of atherosclerosis. ADAM17 is an attractive candidate to study its role in inflammatory disorders and it could be considered as a therapeutical target to obtain plaque regression [74]. Given the new therapeutical treatments for diabetes [59,60,68,75,76] and the more potent treatments available for dyslipidemia [38,39], we suggested that multi-treatment with GLP1Ras [60], SGLT2is [59] and intensive therapy with statins, ezetimibe, bempedoic acid and PCSK9 inhibitors, may be employed to achieve LDL target and induce the regression of atherosclerotic coronary plaques [51,52] (Fig. 1).

Funding

P.F. is supported by the Italian Ministry of University Research grant 20229ZA2YF.

CRediT authorship contribution statement

Bucciarelli Loredana: Writing – original draft. **Andreini Daniele:** Writing – review & editing. **Fiorina Paolo:** Writing – review & editing. **Marchetti Davide:** Writing – review & editing. **Catapano Federica:**

Table 4
Principal human Clinical Trials in patients with type 2 diabetes.

Trials in DM population	Treatment/strategy	Time/N. Pts/Technique	Result	Range of lipid profile
PERISCOPE JAMA 2008	Pioglitazone vs glimepiride	34.5 months 5238 pts of which 543 pts coronary intravascular ultrasonography (18 months)	Regression of PAV with a greater decline of HbA1c PAV + 0.73 % with glimepiride, - 0.16 % with pioglitazone*	
JAPAN-ACS in Acute coronary Syndrome Circ 2010	PI 4 mg and AT 20 mg	within 72 h after PCI/73 DM over 251 pts	Regression plaque achieved only for lower LDL-C level compared to non DM patients	
SATURN NEJM 2011	RO 40 mg vs atorvastatin 80 mg	24 months/159 DM over 1039 Pts/IVUS	Regression of plaques by PAV	Regression only for LDL< 70 mg/dl
COSMOS subanalysis Cardiovac diabetol 2012	RO 2.5 mg up –titrated to 20 mg/die	76 week/40 pts with HbA1c >o = 6.5 % (HG) 86 pts with HbA1c< 6.5 % (LG)	Plaque **regression** less in ptz with HbA1c>or = 6.5 % compared to ptz HbA1c< 6.5 % group PAV significantly correlated with baseline HbA1c.	LDL< 80 mg/dl LDL reduced 37 % HG, 39 % LG HDL increased 16 % HG, 22 % LG
TRUTH Circ 2012	PI 4 mg or PV 40 mg	8 months/50 DM over 119 Pts	Regression of fibro-fatty part less pronunced in DM ptz	
GLAGOV JAMA 2016	EV+maximun dose of tollerated statin	18 months/20 % DM pts/IVUS	Sub analysis for DM were not made	LDL reduction of 75 %
PACMAN-AMI JAMA 2022	AL +high intensity statin	52weeks/26 % DM pts/IVUS OCT NIFS	Regression in non-infarct-related arteries «Triple regression» : in 8 % of DM (1/3 diabetic Pts)	LDL< 70 mg/dl or 50 % reduction from baseline

Abbreviations: Diabetes Mellitus (DM), Atorvastatin (AT); Ezetimibe (EZT); PAV (percentage atheroma volume), Evolocumab (EV), Alirocumab (AL), Cardiovascular disease (CAD), 642 Rosuvastatin (RO) Pitavastatin (PI), Pravastatin (PV).

Writing – review & editing. **Conte Edoardo:** Writing – review & editing. **Francone Marco:** Writing – review & editing. **Stefanini Giulio:** Writing – review & editing. **Lunati Maria Elena:** Writing – review & editing. **Fiorina Roberta Maria:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank “Fondazione Romeo and Enrica Invernizzi” for their extraordinary support.

Data Availability

No data was used for the research described in the article.

References

[1] L. Nedkoff, T. Briffa, D. Zemedikun, S. Herrington, F.L. Wright, Global trends in atherosclerotic cardiovascular disease, Clin. Ther. 45 (11) (2023) 1087–1091.
[2] A. Mormone, G. Tortorella, F. Esposito, A. Caturano, A. Marrone, D. Cozzolino, R. Galiero, R. Marfella, F.C. Sasso, L. Rinaldi, Advances in pharmacological approaches for managing hypercholesterolemia: a comprehensive overview of novel treatments, Biomedicines 12 (2) (2024).
[3] C.J. Fielding, P.E. Fielding, Molecular physiology of reverse cholesterol transport, J. Lipid Res 36 (2) (1995) 211–228.
[4] K.J. Williams, J.E. Feig, E.A. Fisher, Rapid regression of atherosclerosis: insights from the clinical and experimental literature, Nat. Clin. Pr. Cardiovasc Med 5 (2) (2008) 91–102.
[5] R. Ross, The pathogenesis of atherosclerosis: a perspective for the 1990s, Nature 362 (6423) (1993) 801–809.
[6] S.S. Virani, L.K. Newby, S.V. Arnold, V. Bittner, L.C. Brewer, S.H. Demeter, D. L. Dixon, W.F. Fearon, B. Hess, H.M. Johnson, et al., 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines, Circulation 148 (9) (2023) e9–e119.
[7] L.G. Bucciarelli, T. Wendt, W. Qu, Y. Lu, E. Lalla, L.L. Rong, M.T. Goova, B. Moser, T. Kislinger, D.C. Lee, et al., RAGE blockade stabilizes established atherosclerosis in diabetic apolipoprotein E-null mice, Circulation 106 (22) (2002) 2827–2835.
[8] R. Corti, J. Osende, R. Hutter, J.F. Viles-Gonzalez, U. Zafar, C. Valdivieso, G. Mizsei, J.T. Fallon, V. Fuster, J.J. Badimon, Fenofibrate induces plaque regression in hypercholesterolemic atherosclerotic rabbits: in vivo demonstration by high-resolution MRI, Atherosclerosis 190 (1) (2007) 106–113.
[9] M. Friedman, S.O. Byers, R.H. Rosenman, Resolution of aortic atherosclerotic infiltration in the rabbit by phosphatide infusion, Proc. Soc. Exp. Biol. Med. 95 (3) (1957) 586–588.
[10] M.L. Armstrong, E.D. Warner, W.E. Connor, Regression of coronary atheromatosis in rhesus monkeys, Circ. Res 27 (1) (1970) 59–67.
[11] A. Miyazaki, S. Sakuma, W. Morikawa, T. Takiue, F. Miake, T. Terano, M. Sakai, H. Hakamata, Y. Sakamoto, M. Natio, et al., Intravenous injection of rabbit apolipoprotein A-I inhibits the progression of atherosclerosis in cholesterol-fed rabbits, Arterioscler. Thromb. Vasc. Biol. 15 (11) (1995) 1882–1888.
[12] D.J. Rader, Apolipoprotein A-I infusion therapies for coronary disease: two outs in the ninth inning and swinging for the fences, JAMA Cardiol. 3 (9) (2018) 799–801.
[13] P.K. Shah, J. Yano, O. Reyes, K.Y. Chyu, S. Kaul, C.L. Bisgaier, S. Drake, B. Cercek, High-dose recombinant apolipoprotein A-I(milano) mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein e-deficient mice, Potential Implic. Acute Plaque Stab. Circ. 103 (25) (2001) 30473050.
[14] R.K. Tangirala, K. Tsukamoto, S.H. Chun, D. Usher, E. Pure, D.J. Rader, Regression of atherosclerosis induced by liver-directed gene transfer of apolipoprotein A-I in mice, Circulation 100 (17) (1999) 1816–1822.
[15] J.X. Rong, J. Li, E.D. Reis, R.P. Choudhury, H.M. Dansky, V.I. Elmalem, J.T. Fallon, J.L. Breslow, E.A. Fisher, Elevating high-density lipoprotein cholesterol in apolipoprotein E-deficient mice remodels advanced atherosclerotic lesions by decreasing macrophage and increasing smooth muscle cell content, Circulation 104 (20) (2001) 2447–2452.
[16] L.G. Bucciarelli, T. Wendt, L. Rong, E. Lalla, M.A. Hofmann, M.T. Goova, A. Taguchi, S.F. Yan, S.D. Yan, D.M. Stern, et al., RAGE is a multiligand receptor of the immunoglobulin superfamily: implications for homeostasis and chronic disease, Cell Mol. Life Sci. 59 (7) (2002) 1117–1128.
[17] T. Wendt, E. Harja, L. Bucciarelli, W. Qu, Y. Lu, L.L. Rong, D.G. Jenkins, G. Stein, A. M. Schmidt, S.F. Yan, RAGE modulates vascular inflammation and atherosclerosis in a murine model of type 2 diabetes, Atherosclerosis 185 (1) (2006) 70–77.
[18] Y. Naka, L.G. Bucciarelli, T. Wendt, L.K. Lee, L.L. Rong, R. Ramasamy, S.F. Yan, A. M. Schmidt, RAGE axis: animal models and novel insights into the vascular complications of diabetes, Arterioscler. Thromb. Vasc. Biol. 24 (8) (2004) 1342–1349.
[19] T. Wendt, L. Bucciarelli, W. Qu, Y. Lu, S.F. Yan, D.M. Stern, A.M. Schmidt, Receptor for advanced glycation endproducts (RAGE) and vascular inflammation: insights into the pathogenesis of macrovascular complications in diabetes, Curr. Atheroscler. Rep. 4 (3) (2002) 228–237.
[20] R. Forster, A. Schubel, D. Breitfeld, E. Kremmer, I. Renner-Muller, E. Wolf, M. Lipp, CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs, Cell 99 (1) (1999) 23–33.
[21] J.M. van Gils, M.C. Derby, L.R. Fernandes, B. Ramkhelawon, T.D. Ray, K.J. Rayner, S. Parathath, E. Distel, J.L. Feig, J.I. Alvarez-Leite, et al., The neuroimmune guidance cue netrin-1 promotes atherosclerosis by inhibiting the emigration of macrophages from plaques, Nat. Immunol. 13 (2) (2012) 136–143.
[22] S.E. Nissen, E.M. Tuzcu, P. Schoenhagen, B.G. Brown, P. Ganz, R.A. Vogel, T. Crowe, G. Howard, C.J. Cooper, B. Brodie, et al., Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial, JAMA 291 (9) (2004) 1071–1080.
[23] S.E. Nissen, S.J. Nicholls, I. Sipahi, P. Libby, J.S. Raichlen, C.M. Ballantyne, J. Davignon, R. Erbel, J.C. Fruchart, J.C. Tardif, et al., Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial, JAMA 295 (13) (2006) 1556–1565.
[24] A.J. Taylor, S.M. Kent, P.J. Flaherty, L.C. Coyle, T.T. Markwood, M.N. Vernalis, ARBITER: arterial biology for the investigation of the treatment effects of reducing cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness, Circulation 106 (16) (2002) 2055–2060.
[25] J.R. Crouse 3rd, J.S. Raichlen, W.A. Riley, G.W. Evans, M.K. Palmer, D.H. O'Leary, D.E. Grobbee, M.L. Bots, M.S. Group, Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial, JAMA 297 (12) (2007) 1344–1353.
[26] R.M. Haddad, C.M. Ballantyne, METEOR trial reports on the effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis, Phys. Sport. 38 (2) (2010) 180–182.
[27] R. Puri, P. Libby, S.E. Nissen, K. Wolski, C.M. Ballantyne, P.J. Barter, M. J. Chapman, R. Erbel, J.S. Raichlen, K. Uno, et al., Long-term effects of maximally intensive statin therapy on changes in coronary atheroma composition: insights from SATURN, Eur. Heart J. Cardiovasc Imaging 15 (4) (2014) 380–388.
[28] P.N. Meng, D.L. Yin, W.Q. Lu, T. Xu, W. You, Z.M. Wu, X.Q. Wu, F. Ye, Intensive statin versus low-dose statin + ezetimibe treatment for fibrous cap thickness of coronary vulnerable plaques, Chin. Med J. 133 (20) (2020) 2415–2421.
[29] R. Puri, S.E. Nissen, P. Libby, M. Shao, C.M. Ballantyne, P.J. Barter, M.J. Chapman, R. Erbel, J.S. Raichlen, K. Uno, et al., C-reactive protein, but not low-density lipoprotein cholesterol levels, associate with coronary atheroma regression and cardiovascular events after maximally intensive statin therapy, Circulation 128 (22) (2013) 2395–2403.
[30] T. Kovarnik, G.S. Mintz, H. Skalicka, A. Kral, J. Horak, R. Skulec, J. Uhrova, P. Martasek, R.W. Downe, A. Wahle, et al., Virtual histology evaluation of atherosclerosis regression during atorvastatin and ezetimibe administration: HEAVEN study, Circ. J. 76 (1) (2012) 176–183.
[31] K. Tsujita, S. Sugiyama, H. Sumida, H. Shimomura, T. Yamashita, K. Yamanaga, N. Komura, K. Sakamoto, H. Oka, K. Nakao, et al., Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial, J. Am. Coll. Cardiol. 66 (5) (2015) 495–507.
[32] M. Hougaard, H.S. Hansen, P. Thayssen, L. Antonsen, A. Junker, K. Veien, L. O. Jensen, Influence of ezetimibe in addition to high-dose atorvastatin therapy on plaque composition in patients with ST-segment elevation myocardial infarction assessed by serial: Intravascular ultrasound with iMap: the OCTIVUS trial, Cardiovasc Revasc Med. 18 (2) (2017) 110–117.
[33] Y. Ueda, T. Hiro, A. Hirayama, S. Komatsu, H. Matsuoka, T. Takayama, M. Ishihara, T. Hayashi, S. Saito, K. Kodama, et al., Effect of ezetimibe on stabilization and regression of intracoronary plaque - the ZIPANGU study, Circ. J. 81 (11) (2017) 1611–1619.
[34] S.J. Nicholls, R. Puri, T. Anderson, C.M. Ballantyne, L. Cho, J.J. Kastelein, W. Koenig, R. Somaratne, H. Kassahun, J. Yang, et al., Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial, JAMA 316 (22) (2016) 2373–2384.
[35] R.P. Giugliano, N.R. Desai, P. Kohli, W.J. Rogers, R. Somaratne, F. Huang, T. Liu, S. Mohanavelu, E.B. Hoffman, S.T. McDonald, et al., Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebocontrolled, dose-ranging, phase 2 study, Lancet 380 (9858) (2012) 2007–2017.
[36] D. Sullivan, A.G. Olsson, R. Scott, J.B. Kim, A. Xue, V. Gebski, S.M. Wasserman, E. A. Stein, Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial, JAMA 308 (23) (2012) 2497–2506.
[37] S.J. Nicholls, S.E. Nissen, F. Prati, S. Windecker, Y. Kataoka, R. Puri, T. Hucko, H. Kassahun, J. Liao, R. Somaratne, et al., Assessing the impact of PCSK9 inhibition on coronary plaque phenotype with optical coherence tomography: rationale and design of the randomized, placebo-controlled HUYGENS study, Cardiovasc Diagn. Ther. 11 (1) (2021) 120–129.
[38] L. Raber, Y. Ueki, T. Otsuka, S. Losdat, J.D. Haner, J. Lonborg, G. Fahrni, J. F. Iglesias, R.J. van Geuns, A.S. Ondracek, et al., Effect of alirocumab added to

high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction: the PACMAN-AMI randomized clinical trial, JAMA 327 (18) (2022) 1771–1781.
[39] F.G. Biccire, J. Haner, S. Losdat, Y. Ueki, H. Shibutani, T. Otsuka, R. Kakizaki, T. M. Hofbauer, R.J. van Geuns, S. Stortecky, et al., Concomitant coronary atheroma regression and stabilization in response to lipid-lowering therapy, J. Am. Coll. Cardiol. 82 (18) (2023) 1737–1747.
[40] L. Perez de Isla, J.L. Diaz-Diaz, M.J. Romero, O. Muniz-Grijalvo, J.D. Mediavilla, R. Argueso, J.F. Sanchez Munoz-Torrero, P. Rubio, P. Alvarez-Banos, P. Ponte, et al., Alirocumab and coronary atherosclerosis in asymptomatic patients with familial hypercholesterolemia: the ARCHITECT study, Circulation 147 (19) (2023) 1436–1443.
[41] B.L. Yu, S.P. Zhao, Anti-inflammatory effect is an important property of niacin on atherosclerosis beyond its lipid-altering effects, Med. Hypotheses 69 (1) (2007) 90–94.
[42] B.G. Brown, X.Q. Zhao, A. Chait, L.D. Fisher, M.C. Cheung, J.S. Morse, A.A. Dowdy, E.K. Marino, E.L. Bolson, P. Alaupovic, et al., Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease, N. Engl. J. Med. 345 (22) (2001) 15831592.
[43] M.J. Budoff, D.L. Bhatt, A. Kinninger, S. Lakshmanan, J.B. Muhlestein, V.T. Le, H. T. May, K. Shaikh, C. Shekar, S.K. Roy, et al., Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial, Eur. Heart J. 41 (40) (2020) 3925–3932.
[44] S.J. Nicholls, E.M. Tuzcu, D.M. Brennan, J.C. Tardif, S.E. Nissen, Cholesteryl ester transfer protein inhibition, high-density lipoprotein raising, and progression of coronary atherosclerosis: insights from ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation), Circulation 118 (24) (2008) 2506–2514.
[45] P.J. Barter, M. Caulfield, M. Eriksson, S.M. Grundy, J.J. Kastelein, M. Komajda, J. Lopez-Sendon, L. Mosca, J.C. Tardif, D.D. Waters, et al., Effects of torcetrapib in patients at high risk for coronary events, N. Engl. J. Med. 357 (21) (2007) 2109–2122.
[46] C.P. Cannon, H.M. Dansky, M. Davidson, A.M. Gotto Jr., E.A. Brinton, A.L. Gould, M. Stepanavage, S.X. Liu, S. Shah, J. Rubino, et al., Design of the DEFINE trial: determining the EFficacy and tolerability of CETP INhibition with AnacEtrapib, Am. Heart J. 158 (4) (2009) 513–519, e513.
[47] N. Ferri, A. Corsini, C.R. Sirtori, M. Ruscica, Present therapeutic role of cholesteryl ester transfer protein inhibitors, Pharm. Res 128 (2018) 29–41.
[48] S. Nicholls, A.M. Lincoff, H.E. Bays, L. Cho, D.E. Grobbee, J.J. Kastelein, P. Libby, P.M. Moriarty, J. Plutzky, K.K. Ray, et al., Rationale and design of the CLEAR-outcomes trial: Evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance, Am. Heart J. 235 (2021) 104–112.
[49] Y. Li, H. Gao, J. Zhao, L. Ma, D. Hu, Safety and efficacy of bempedoic acid among patients with statin intolerance and those without: a meta-analysis and a systematic randomized controlled trial review, PLoS One 19 (1) (2024) e0297854.
[50] S.J. Nicholls, E.M. Tuzcu, S. Kalidindi, K. Wolski, K.W. Moon, I. Sipahi, P. Schoenhagen, S.E. Nissen, Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials, J. Am. Coll. Cardiol. 52 (4) (2008) 255–262.
[51] H. Daida, T. Takayama, T. Hiro, M. Yamagishi, A. Hirayama, S. Saito, T. Yamaguchi, M. Matsuzaki, C. Investigators, High HbA1c levels correlate with reduced plaque regression during statin treatment in patients with stable coronary artery disease: results of the coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS), Cardiovasc Diabetol. 11 (2012) 87.
[52] T. Hiro, T. Kimura, T. Morimoto, K. Miyauchi, Y. Nakagawa, M. Yamagishi, Y. Ozaki, K. Kimura, S. Saito, T. Yamaguchi, et al., Diabetes mellitus is a major negative determinant of coronary plaque regression during statin therapy in patients with acute coronary syndrome–serial intravascular ultrasound observations from the Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome Trial (the JAPAN-ACS Trial), Circ. J. 74 (6) (2010) 1165–1174.
[53] T. Nozue, S. Yamamoto, S. Tohyama, K. Fukui, S. Umezawa, Y. Onishi, T. Kunishima, A. Sato, T. Nozato, S. Miyake, et al., Impact of diabetes mellitus on coronary atherosclerosis and plaque composition under statin therapy - subanalysis of the TRUTH study, Circ. J. 76 (9) (2012) 2188–2196.
[54] R. Puri, S.E. Nissen, M. Shao, C.M. Ballantyne, P.J. Barter, M.J. Chapman, R. Erbel, P. Libby, J.S. Raichlen, K. Uno, et al., Coronary atheroma volume and cardiovascular events during maximally intensive statin therapy, Eur. Heart J. 34 (41) (2013) 3182–3190.
[55] I. Dykun, O. Bayturan, J. Carlo, S.E. Nissen, S.R. Kapadia, E.M. Tuzcu, S.J. Nicholls, R. Puri, HbA1c, Coronary atheroma progression and cardiovascular outcomes, Am. J. Prev. Cardiol. 9 (2022) 100317.
[56] B. Stegman, R. Puri, L. Cho, M. Shao, C.M. Ballantyne, P.J. Barter, M.J. Chapman, R. Erbel, P. Libby, J.S. Raichlen, et al., High-intensity statin therapy alters the natural history of diabetic coronary atherosclerosis: insights from SATURN, Diabetes Care 37 (11) (2014) 3114–3120.
[57] S.E. Nissen, S.J. Nicholls, K. Wolski, R. Nesto, S. Kupfer, A. Perez, H. Jure, R. De Larochelliere, C.S. Staniloae, K. Mavromatis, et al., Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial, JAMA 299 (13) (2008) 1561–1573.
[58] Y. Kataoka, M. Shao, K. Wolski, K. Uno, R. Puri, E.M. Tuzcu, S.E. Nissen, S. J. Nicholls, Multiple risk factor intervention and progression of coronary atherosclerosis in patients with type 2 diabetes mellitus, Eur. J. Prev. Cardiol. 20 (2) (2013) 209–217.
[59] G. Bendotti, L. Montefusco, I. Pastore, E. Lazzaroni, M.E. Lunati, P. Fiorina, The antiinflammatory and immunological properties of SGLT-2 inhibitors, J. Endocrinol. Invest 46 (12) (2023) 2445–2452.
[60] G. Bendotti, L. Montefusco, M.E. Lunati, V. Usuelli, I. Pastore, E. Lazzaroni, E. Assi, A.J. Seelam, B. El Essawy, J. Jang, et al., The anti-inflammatory and immunological properties of GLP1 receptor agonists, Pharm. Res 182 (2022) 106320.
[61] P. Fiorina, E. La Rocca, M. Venturini, F. Minicucci, I. Fermo, R. Paroni, A. D'Angelo, M. Sblendido, V. Di Carlo, M. Cristallo, et al., Effects of kidney-pancreas transplantation on atherosclerotic risk factors and endothelial function in patients with uremia and type 1 diabetes, Diabetes 50 (3) (2001) 496–501.
[62] P. Ibrahimi, F. Jashari, R. Nicoll, G. Bajraktari, P. Wester, M.Y. Henein, Coronary and carotid atherosclerosis: how useful is the imaging? Atherosclerosis 231 (2) (2013) 323–333.
[63] A. Sforza, V. Vigorelli, E. Rurali, G.L. Perrucci, E. Gambini, M. Arici, A. Metallo, R. Rinaldi, P. Fiorina, A. Barbuti, et al., Liraglutide preserves CD34(+) stem cells from dysfunction Induced by high glucose exposure, Cardiovasc Diabetol. 21 (1) (2022) 51.
[64] A. Petrelli, R. Di Fenza, M. Carvello, F. Gatti, A. Secchi, P. Fiorina, Strategies to reverse endothelial progenitor cell dysfunction in diabetes, Exp. Diabetes Res. 2012 (2012) 471823.
[65] F. Santilli, L. Bucciarelli, D. Noto, A.B. Cefalu, V. Davi, E. Ferrante, C. Pettinella, M. R. Averna, G. Ciabattoni, G. Davi, Decreased plasma soluble RAGE in patients with hypercholesterolemia: effects of statins, Free Radic. Biol. Med. 43 (9) (2007) 1255–1262.
[66] F. Cosentino, P.J. Grant, V. Aboyans, C.J. Bailey, A. Ceriello, V. Delgado, M. Federici, G. Filippatos, D.E. Grobbee, T.B. Hansen, et al., 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD, Eur. Heart J. 41 (2) (2020) 255–323.
[67] P. Fiorina, M. Lanfredini, A. Montanari, M.G. Peca, A. Veronelli, A. Mello, E. Astorri, A. Craveri, Plasma homocysteine and folate are related to arterial blood pressure in type 2 diabetes mellitus, Am. J. Hypertens. 11 (9) (1998) 1100–1107.
[68] L.S.F. de Carvalho, A.C.C. Nogueira, I. Bonilha, B. Luchiari, A. Benchimol, C.E. B. Couri, J.L. Borges, J. Barreto, A.C. Sposito, Glucose-lowering and the risk of cardiovascular events with antidiabetic therapies: a systematic review and additive-effects network metaanalysis, Front. Cardiovasc Med. 9 (2022) 876795.
[69] O. Bayturan, S. Kapadia, S.J. Nicholls, E.M. Tuzcu, M. Shao, K. Uno, A. Shreevatsa, A.J. Lavoie, K. Wolski, P. Schoenhagen, et al., Clinical predictors of plaque progression despite very low levels of low-density lipoprotein cholesterol, J. Am. Coll. Cardiol. 55 (24) (2010) 2736–2742.
[70] E.J. Ku, B.R. Kim, J.I. Lee, Y.K. Lee, T.J. Oh, H.C. Jang, S.H. Choi, The anti-atherosclerosis effect of Anakinra, a recombinant human interleukin-1 receptor antagonist, in apolipoprotein E knockout mice, Int J. Mol. Sci. 23 (9) (2022).
[71] D. Dragoljevic, M.K.S. Lee, C. Louis, W. Shihata, M.J. Kraakman, J. Hansen, S. L. Masters, B.Y. Hanaoka, P.R. Nagareddy, G.I. Lancaster, et al., Inhibition of interleukin-1beta signalling promotes atherosclerotic lesion remodelling in mice with inflammatory arthritis, Clin. Transl. Immunol. 9 (11) (2020) e1206.
[72] F. D'Addio, A. Vergani, L. Potena, A. Maestroni, V. Usuelli, M. Ben Nasr, R. Bassi, S. Tezza, S. Dellepiane, B. El Essawy, et al., P2X7R mutation disrupts the NLRP3-mediated Th program and predicts poor cardiac allograft outcomes, J. Clin. Invest 128 (8) (2018) 34903503.
[73] K. Peng, L. Liu, D. Wei, Y. Lv, G. Wang, W. Xiong, X. Wang, A. Altaf, L. Wang, D. He, et al., P2X7R is involved in the progression of atherosclerosis by promoting NLRP3 inflammasome activation, Int. J. Mol. Med. 35 (5) (2015) 1179–1188.
[74] R. Menghini, L. Fiorentino, V. Casagrande, R. Lauro, M. Federici, The role of ADAM17 in metabolic inflammation, Atherosclerosis 228 (1) (2013) 12–17.
[75] N. Marx, M. Husain, M. Lehrke, S. Verma, N. Sattar, GLP-1 receptor agonists for the reduction of atherosclerotic cardiovascular risk in patients with type 2 diabetes, Circulation 146 (24) (2022) 1882–1894.
[76] M. Ben Nasr, V. Usuelli, S. Dellepiane, A.J. Seelam, T.V. Fiorentino, F. D'Addio, E. Fiorina, C. Xu, Y. Xie, H.B. Balasubramanian, et al., Glucagon-like peptide 1 receptor is a T cell-negative costimulatory molecule, Cell Metab. 36 (6) (2024) 1302–1319, e1312.