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REVIEW ARTICLE

Lipid-Lowering Therapies for Atherosclerosis: Statins, Fibrates, Ezetimibe and PCSK9 Monoclonal Antibodies

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Abstract: Cardiovascular disease (CVD) remains the primary cause of global morbidity and mortality. CVD includes various life-threatening conditions such as myocardial infarction, stroke and peripheral arterial diseases. In this context, atherosclerosis continues to play the principal role in the pathogenesis of these conditions. Atherosclerosis emanates from a set of modifiable and non-modifiable risk factors that include age, male gender, family history, obesity, smoking, diabetes mellitus and hypertension. Recent evidence classifies atherosclerosis as a latent disease affecting all-sized arteries with a predilection for arterial branching points of decreased or absent blood supply. Atherosclerosis is not only a lipid metabolism disorder, but is also a chronic inflammatory one. This review providesa synoptic discussion of the underlying pathological mechanisms of atherosclerosis andthe currently applied therapeutic interventions. We then discuss the classical lipid-lowering therapies as well as the newly discovered therapies. For the classical therapies, we point out the importance of statins and ezetimibe in reducing plasma cholesterol levels by virtue of their effects on synthesis, reuptake and intestinal absorption of cholesterol. We also discuss the role of fibrates in modulating lipid metabolism and improving the ratio of high-density to low-density density lipoproteins. This study focuseson the more recent molecular and genetic interventions exemplified by proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies, evinacumab, and microRNA inhibitors. Special attention is also given to clinical trials involving these therapies.

Keywords: Atherosclerosis, statin, fibrates, ezetimibe, PCSK9 inhibitors, microRNA inhibitors, monoclonal antibodies for atherosclerosis.

1. INTRODUCTION

Atherosclerosis continues to be the chief reason behind various cardiovascular complications, including stroke, myocardial infarction and peripheral vascular disease [1, 2]. These complications are associated with significantly high rates of global disability and mortality, with an average of 17.9 million people dying each year [2]. According to the World health organization (WHO), CVD remains alarmingly prevalent in low- and middle-income developing countries, where 82% of CVD-associated mortality occurs [2]. New strategies geared towards reducing the human and economic

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burdens of atherosclerosis as well as improving the quality of patient's life have been launched [2-4]. This may explain the dramatic decrease in stroke and ischemic heart disease (IHD) mortality rates during the past forty years [5]. Indeed, while adults 35 to 69 years of age were at a 16% risk of IHD death in 1980, they were at only a 4% risk in 2010 [5].

Atherosclerosis represents a latent disease affecting more than one vascular bed. Its clinical manifestations depend greatly on the plaque site and stability, and the extent of arterial obstruction [5]. Vulnerable and unstable plaques are characterized by an abundanceof inflammatory cells, a scarcity of smooth muscle cells, as well as a presence of a thin fibrous cap or a sizeable necrotic lipid core [6]. Compared to stable plaques witha thick fibrous cap among other properties, unstable plaques are more prone to rupture and thus would more readily precipitate life-threatening vascular events such as myocardial infarction and stroke. Moreover, atherosclerosis is usually linked to an elevated concentration of LDL-cholesterol along with many other factors such as genetic hyperlipidemias, age, gender, diabetes mellitus, obesity, smoking and hypertension [7-12]. This multifactorial disease affects mainly large and medium sized arteries at the weakest sites of the arterial tree [1, 8, 13]. It usually arises adjacent to narrow branching points especially those present within coronary arteries, near the carotid bifurcation and the abdominal aorta [1, 7, 8]. However, recent studies have shown that small vessels might also be affected [4].

Besides being a lipid metabolism disorder, atherosclerosis is equally, and perhaps more appreciably, recognized as a chronic inflammatory arterial disease [8, 14]. This inflammatory process involves both innate and acquired immunity executed by macrophages and T lymphocytes, respectively. Dysregulated activity of these cells along with impaired inflammatory resolution trigger the development and progression of the atherosclerotic plaque. This becomes seriously deleterious if followed by plaque rupture, thrombus formation and arterial occlusion [8]. Therefore, an early diagnosis would greatly reduce the incidence of atherosclerosis-associated cardiovascular events. To this end, numerous diagnostic tools are employed to detect this multidimensional process, including blood tests (for triglyceride, cholesterol and glucose levels), EKG, angiogram, imaging modalities (X-Ray, ultrasound, CT scan, PET scan and MRI) as well as cardiac stress test [15].

2. MOLECULAR AND CELLULAR BASIS OF ATHEROSCLEROSIS

Atherosclerosis is an enduring inflammatory process that occurs mostly at the weakest points of the arterial tree. Sites with impaired blood supply near branching points are classically the most prone for atherosclerotic plaqueformation [16, 17].These regions are characterized by a physiological thickening of the arterial intima arising immediately after birth [1]. This physiologic adaptation makes these particular sites a favorable ground for the development of atherosclerosis [1]. A series of consecutive events leadto the formation of the atherosclerotic plaque. The earliest step is the uptake of LDL by endothelial cells, via two receptors, endothelial LDL receptor (LDL-R), and scavenger receptor B1 (SR-B1) [18, 19]. While the interaction of LDL-R and LDL apoprotein B-100 (Apo B-100) has been well-studied, much remains to be understood about the mechanism mediated by SR-B1 [18]. Recently, the interaction between LDL and SR-B1, and subsequently the transcytosis of LDL in endothelial cells, appears to be mediated by the membrane-associated cellular protein Dedicator of Cytokinesis 4 (DOCK4). Indeed, theinteraction of DOCK4 with SR-B1 is believed to mediate LDL internalization, and to couple this internalization with the activation of intracellular pathways [19]. Transcytosis of LDL is then followed by accumulation and retention in the subendothelial space of the tiny LDL particles that managed to pass through the endothelial barrier [1, 20]. Retention is mediated by the binding of LDL Apo B-100 to the endothelial proteoglycans [20, 21]. These lipid molecules may encounter a series of modifications such as acylation, aggregation, fusion, lipolysis, oxidation and proteolysis [1, 7, 20]. Most importantly, they are oxidized by reactive oxygen species (ROS) generated by various vascular cells [7, 20]. Oxidized LDL then stimulates immune cells by inducing expression of adhesion molecules such as vascular cells adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) on the surface of both endothelial and smooth muscle cells [1, 20]. These cells also secret chemoattractants and growth factors that facilitate immune cell migration, adhesion (to the endothelium) and differentiation [1, 20].

Monocytes and macrophages play an important role in promoting an inflammatory milieu suitable for the development and progression of atherosclerosis. Indeed, monocyte-derived macrophages may trigger an anti-inflammatory or a pro-inflammatory response depending on their phenotype [1, 16]. Macrophages having an M1 phenotype elicit a pro-inflammatory activity inducing secretion of numerous cytokines, enzymes

and ROS, thus promoting additional retention and oxidation of lipoproteins [1, 16, 21]. This occurs after binding of oxidized LDL molecules to macrophage Toll-like receptors (TLRs) or scavenger receptors, including primarily CD36 and CD68 [1, 16, 22]. On the other hand, macrophages with an M2 phenotype secret anti-inflammatory cytokines such as TGF-β causing the inflammatory process to resolve [1, 16]. Similarly, cell-mediated immunity plays a major role in the formation and progression of atherosclerotic plaque. For instance, T cells secrete a variety of pro-inflammatory cytokines post recognition of oxidized LDL molecules and other atherosclerotic autoantigens [1, 23]. The uptake of oxidized LDL by M1 Macrophages leads to lipid accumulation and foam cell formation. Apoptosis followed by necrosis of these lipid rich macrophages and surrounding smooth muscle cells promotes the formation of a lipid rich core that is also known as a necrotic core [1, 20]. This occurs primarily due to several stressful conditions such as elevated levels of ROS, lack of cellular energy in the form of ATP, defective efferocytosis (dead cell clearance) and elevated cellular calcium [24, 25]. Necrotic cells may spill their intracellular content resulting in further inflammation and thus immune cell recruitment, differentiation and accumulation at the level of the endothelium.

Similarly, foam cells, derived either from macrophages or vascular smooth muscle cells (VSMCs), secrete several growth factors such as platelet-derived growth factor (PDGF) and fibroblast growth factor(FGF), triggering the formation of a fibrous cap [16, 26]. Foam cells can also induce deposition of extracellular matrix and collagen fibers by vascular smooth muscle cells [16, 26]. In fact, VSMCs represent another key modulator of atheroma formation [27-30]. They comprise up to 50% of the foam cells population, and are critical predictors of plaque stability as mentioned previously [28]. Interestingly, their fate is predicted by various epigenetic, genetic and inflammatory factors. For instance, athero-protective VSMCs are contractile, highly differentiated cells that exert a key role in improving plaque stability [27, 31]. However, they may undergo a phenotypic switch to a proliferative, synthetic phenotype characterized by increased migratory and invasive capacity [31-34]. Moreover, they can de-differentiate to a macrophage-like phenotype that facilitates their transformation into foam cells. The extent of their de-differentiation into inflammatory-like cells is a major determinant of plaque progression and instability [27]. Indeed, this progression may be fatal if followed by plaque rupture which can provoke thrombosis and subsequently arterial occlusion [8, 26].

3. ATHEROSCLEROSIS: THERAPY

Owing to its fatal cardiovascular complications striking all-sized arteries, atherosclerosis has received increased attention over the past several decades [35, 36]. Several approaches have been suggested to manage or treat this disease and the associated factors [37-44]. Achieving a low cholesterol level is considered the cornerstone of atherosclerosis management and thus has received the lion's share of current available treatment for this disease [35, 36]. To this end, a multitude of drugs acting on cholesterol synthesis, intestinal absorption, degradation or reuptake of cholesterol from the atherosclerotic plaque by HDL molecules havebeen developed [35, 36, 45]. These drugs are considered cholesterol-dependent therapies which include statin, fibric acid derivatives (fibrates), nicotinic acid (Niacin) and ezetimibe, respectively [35, 36, 45, 46].

New drugs employing mechanisms other than the above are being developed and used for atherosclerosis management and prevention. For instance, drugs targeting VLDL assembly are currently employed to cure atherosclerosis. They reduce VLDL levels and subsequently LDL levels. This then reduces the availability of LDL molecules and thus their ability to reach atherosclerotic plaques. These drugs include primarily two medicines, lomitapide (a microsomal transfer protein (MTP) inhibitor) and mipomersen (an antisense oligonucleotide (ASO) targeting ApoB-100) which directly target distinct steps in the synthesis of VLDL and indirectly the formation of VLDL-derived LDL molecules [35, 47-49]. Additionally, cellular and molecular-based therapies seem to be powerful modifiers of atherosclerosis. MicroRNAs are gaining a lot of attention owing to their apparently significant role in regulating thedevelopment and progression of atherosclerosis, largely due to their ability to modulate theactivity of inflammatory cells as well as maintain cholesterol homeostasis, respectively [50-52]. Similarly, anti-inflammatory and immunosuppressive drugs could also be used to modulate atherosclerosis due to their importance in the inhibition and prevention of the chronic atherosclerotic inflammatory process [35, 36, 53-55]. Anti-hypertensive, anti-thrombotic and fibrinolytic drugs also seem to be involved in the treatment of atherosclerosis by the virtue of their ability to resolve fatal thrombotic and vasoconstrictive events implicated in atherosclerotic complications [35, 36, 53-55].

Other therapeutic strategies include monoclonal antibodies targeting pro-protein convertase subtilisin/kexin type 9 (PCSK9), a serine protease that inhibits the uptake of LDL by hepatocytes [52, 56-60]. This

protease might be mutated in many patients, causing increased or decreased hepatic uptake of LDL [52, 56-60]. These drugs constitute novel and promising medicines on which most of this review will be focused. Indeed, genetic and molecular inhibition of these proteases arecurrently applied to treat patients with severe hypercholesterolemia refractory to classical therapies [52, 56-60]. Furthermore, evinacumab, a newer monoclonal antibody targeted against Angiopoietin--like 3 (ANGPTL3), is recognized as a potential lipid-lowering medication that is particularly effective in treating inherited refractory hypercholesterolemia [61].

Many therapies are being tested and employed in atherosclerosis regression. They are subclassified into two categories: classical and novel cholesterol-lowering therapies. In this review, we will focus on statin, fibrates and ezetimibe being part of the classical drugs, as well as on PCSK9 monoclonal antibodies, evinacumab, and microRNAs inhibitors being the novel cholesterol-lowering medications.

3.1. Statins

Statins are considered the first line therapy for atherosclerotic cardiovascular complications [62]. They elicit their effect through the competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme of cholesterol biosynthesis [35, 63-65]. Statins exert several anti-atherosclerotic mechanisms because of their involvement in plasma cholesterol reduction. They also impart a similar effect on plasma LDL by virtue of their involvement in LDL surface receptor (LDL-R) upregulation, which mediates increased uptake of LDL cholesterol by hepatocytes [36, 66]. Additionally, statins stimulate the expression of the scavenger receptor SR-B1, an HDL receptor that facilitates the selective uptake of cholesteryl ester from HDL molecules [36, 67]. This results in high HDL levels and thus in atherosclerosis regression due to HDL anti-atherosclerotic and anti-inflammatory properties [46, 68-70].

Besides being a lipid-lowering therapy, statins contribute to atherosclerosis regression and even reversion through a series of cholesterol-independent therapeutic effects Fig. (**1**). They disturb various atherosclerotic mechanisms both on the genetic and molecular levels [36]. For instance, statins exert a vasculo-protective effect by upregulating a multitude of genes implicated in the regulation of the endothelial barrier [36, 71, 72]. This leads eventually to the development of an efficient endothelial barrier function and thus to the prevention of inflammatory cell leakage and deposition at the level of the subendothelium [36, 71, 72]. Similarly, statins stimulate vasodilation by upregulating endothelial nitric oxide synthase (eNOS) and increasing levels of nitric oxide (NO) [36, 71-73]. Importantly, statins may also downregulate vasoconstrictive factors such as endothelin-1, thereby favoring vasodilation as well [36, 73].

The anti-inflammatory capacities of statins underlie part of their anti-atherosclerotic effects. Indeed, statins attenuate the chronic inflammatory process by reducing the expression of various pro-inflammatory mediators such as the chemoattractant molecules interleukin 8 (IL-8) and monocyte chemoattractant protein-1 (M-CP-1) [36, 73, 74]. As such, they avert the recruitment and migration of inflammatory cells to the atherosclerotic space. Similarly, statins lead to impaired antigen processing and presentation due to their ability to downregulate MHC II [71]. This leads to a defective inflammatory process and substantially prevents plaque progression and consequent complications [71].

HMG-CoA inhibitors elicit their effects by favoring plaque stabilization as well as inducing expression of coagulation inhibitors and fibrinolytic factors. This helps reduce the occurrence of ischemic and thrombotic events that follow atherosclerotic plaque rupture [36, 72, 74, 75]. Statins downregulate the expression of several coagulative markers involved in the recruitment, activation and aggregation of platelets [72]. Additionally, they favor anti-thrombotic events by inducing increased expression of thrombomodulin and reduced expression of platelet tissue factor [72, 74, 75]. Lastly, they promote fibrinolysis due to the increased expression of the pro-fibrinolytic tissue-type plasminogen activator [71-73]. This is further enhanced because of the inhibition of the plasminogen activator inhibitor type 1 [71-73].

Despite being a safe first-line therapy for atherosclerotic complications, statins are not without side effects [62, 76]. While these effects are well-tolerated [36, 66], in up to 20-30% of CVD patients, statins are not well-tolerated as a lipid-lowering therapy due to a multitude of side effects: allergy, muscle aches, myopathy, rhabdomyolysis, hepatotoxicity, and new-onset diabetes [77, 78]. Similarly, in many patients with severe dyslipidemia, statins are inefficient as a monotherapy. Indeed, in these patients, statins are often combined with a non-statin lipid lowering medicine such as fibrates, niacin or ezetimibe [65, 72]. Contextually, in statin-intolerant patients, an alternative lipid-lowering agent is used as well, but only after a distinct statin is tried first. For instance, simvastatin-intolerant patients can be switched to an equivalent dose of lovastatin, provastatin or fluvastatin [77]. Moreover, an ineffec-

tive statin regimen can be optimized by switching to an alternative statin or increasing the dose. The efficacy of statin in reducing total cholesterol and LDL-cholesterol increases by 5% and 7%, respectively, with each dose doubling. This refers to "*The rule of 5 and the rule of 7 in lipid-lowering by statin drugs*" suggested by Dr. William Roberts in 1997 [79]. Ultimately, this rule can still be applied in optimizing the lipid profile of CVD patients treated with statins as the first-line therapy.

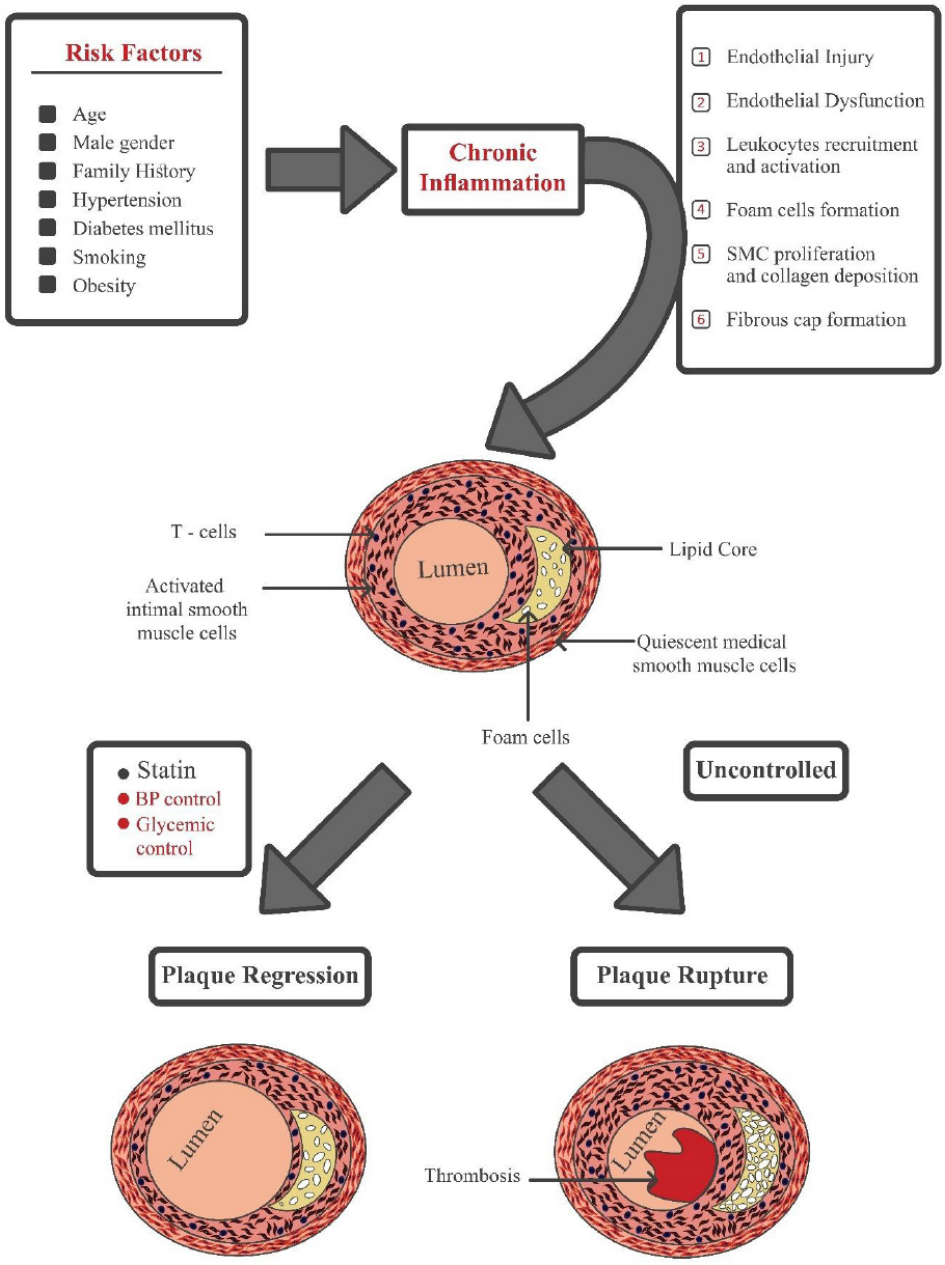

Fig. (1). Interplay of various factors and risk factors in the onset and pathogenesis of atherosclerosis. Chronic inflammation is a major culprit as it gradually leads to the formation of a lipid-rich plaque. If left untreated, this plaque may increase in size leading to arterial luminal narrowing and decreased tissue perfusion. Additionally, plaque rupture induces thrombosis and worsens arterial obstruction that may result in tissue ischemia. Lipid-lowering therapy significantly averts the progression of the atherosclerotic lesion and induces its regression. Similarly, the control of modifiable risk factors, such as HTN and DM, may likely prevent the progression of the plaque and ease its regression. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.2. Fibrates

Fibrates, or fibric acid derivatives, represent a lipid-lowering therapy prescribed for the management and prevention of hyperlipidemic disorders especially for statin-intolerant patients [36, 46]. The underlying mechanisms of fibrates appear to involve stimulation of the nuclear receptor peroxisome proliferator-activated receptor alpha (PPARα) [46, 66, 80, 81]. PPARα is a key regulator of inflammation, lipid metabolism as well as thrombogenesis [46, 66, 80, 81]. Fibrate-induced activation of PPARα provokes a multitude of anti-atherogenic effects. For instance, fibrates stimulate the synthesis of two apolipoproteins, apoA-I and apoA-II, leading to increased production of HDL particles which are therapeutically beneficial in atherosclerosis [36, 46, 80-84]. Similarly, fibrates upregulate the expression of both SR-B1 and ATP-binding cassette A1 transporter (ABCA1), leading to increased HDL-dependent uptake of cholesterol from foam cells [36, 46, 80, 83].

Equally important, fibrates reduce the production of the lipoprotein lipase (LPL) inhibitor apoC-III [36, 46, 80-84]. This causes increased activity of LPL and consequently leads to lower levels of serum triglycerides [36, 46, 80-84]. Additionally, they modulate lipid and lipoproteins metabolism due to the upregulation of various genes implicated in both activation of fatty acids beta oxidation and inhibition of hepatic lipogenesis [36, 46, 82-84].

Fibrates favor uptake of fatty acids and promote their intracellular conversion into fatty acyl-CoA by the acyl-CoA synthetase enzyme of hepatocytes [85]. This is then followed by fatty acid oxidation coupled with a reduction in fatty acid synthesis and consequently in triglyceride formation. Importantly, this inhibition of triglyceride synthesis is potentiated by fibrates' ability to suppress hormone-sensitive fat tissue lipase [85]. Owing to these PPARα-mediated effects, a net reduction in serum triglycerides coupled with a reduction in LDL cholesterol and an increase in serum HDL is achieved by fibrates.

Besides their direct lipid-lowering effects, fibrates exert anti-oxidant, anti-inflammatory and anti-thrombotic effects [36, 46, 80, 86]. They attenuate the inflammatory process owing to their potent inhibitory effect on nuclear factor kappa B (NF-κB) signaling pathway [8, 46, 80, 84, 86]. This inhibition leads to reduced levels of numerous proinflammatory mediators such as chemokines (MCP-1), cytokines (IL-1, IL-6 and TNF-α), enzymes and growth factors [8, 46, 80, 84, 86]. Fibrates also inhibit the expression of adhesion molecules (VCAM-1 and ICAM-1) thereby preventing leukocyte and monocyte recruitment to the sub-endothelium [80, 84, 86].

Recent studies also highlight the anti-thrombotic effects of fibrates. For instance, fibrates have been shown to inhibit plasminogen activator inhibitor-1 (PAI-1), thus favoring anti-thrombotic and fibrinolytic events [46, 80, 82]. This also occurs due to the reduction of fibrinogen production which is the ultimate player in the coagulation cascade [46, 80, 84]. Additionally, they dampen the activity of macrophages and thus limit their ability to produce metalloproteinases involved in the digestion of the fibrous cap. This stabilizes the plaque, making it less prone to rupture and thus limits the occurrence of atherothrombotic events [46, 80, 84].

The efficacy of combination therapy of statins and fibrates in reducing CVD mortality has been examined by a multitude of clinical trials. In a large former randomized clinical trial called the ACCORD-Lipid study that was published in 2010, 5518 diabetes patients were randomly allocated to two groups, one receiving a combination therapy of simvastatin and fenofibrate, and the other receiving simvastatin and placebo [87]. Patients were followed up for an average period of 4.7 years. Overall, no significant improvement in CVD mortality was observed in the first group treated with statins and fibrates. Similarly, no significant improvement in nonfatal cardiovascular events was achieved by the addition of fibrates to statins [87]. Following this study, the addition of fibrates to the standard of care has constituted a significant controversy, and has triggered the initiation of further studies. Recently, in the ACCORDION study, survivors of the ACCORD-Lipid study were evaluated again [88]. Most of them were still taking statins for dyslipidemia. Nonetheless, only a minority of them were maintained on a combination of statins and fibrates. Significantly lower rates of CVD mortality and complications were noted in thegroup receiving fibrates [88]. Hence, we are of the opinion that further higher-quality, multi-center, longer-term studies are needed to more conclusively elucidate the therapeutic benefit of add-on fibrate therapy.

Overall, fibrates represent a promising therapy targeting multiple points of the atherosclerotic process. They are considered relatively well-tolerated drugs where gastrointestinal side effects and skin rashes are the most frequently reported adverse effects [46]. Additionally, they could be given as mono or combined therapies to treat both hypertriglyceridemic and hypercholesteremic patients, unlike statins which are confined for the treatment of cholesterol disorders [36, 46].

3.3. Ezetimibe

Ezetimibe is one of the lipid-lowering agents classified under "cholesterol absorption inhibitors" [89]. Ezetimibe induces its cholesterol lowering effect through inhibition of the intestinal Niemann-Pick C1 like1 (NPC1L1) transporter Fig. (**2**) [90]. NPC1L1, which is highly expressed on the apical side of enterocytes and canalicular membrane of human and rat (but not mouse) hepatocytes, is a major sterol transporter that mediates cholesterol absorption [91]. In addition, NPC1L1 might also be involved in the regulation of lipid metabolism and insulin sensitivity. This may explain why its blockade exerts beneficial effects on features of metabolic syndrome. Hence, by targeting this transporter, ezetimibe decreases plasma cholesterol levels, increases insulin sensitivity, and enhances lipid metabolism. Indeed, evidence suggests that ezetimibe attenuates lipogenesis in non-alcoholic fatty liver disease (NAFLD)

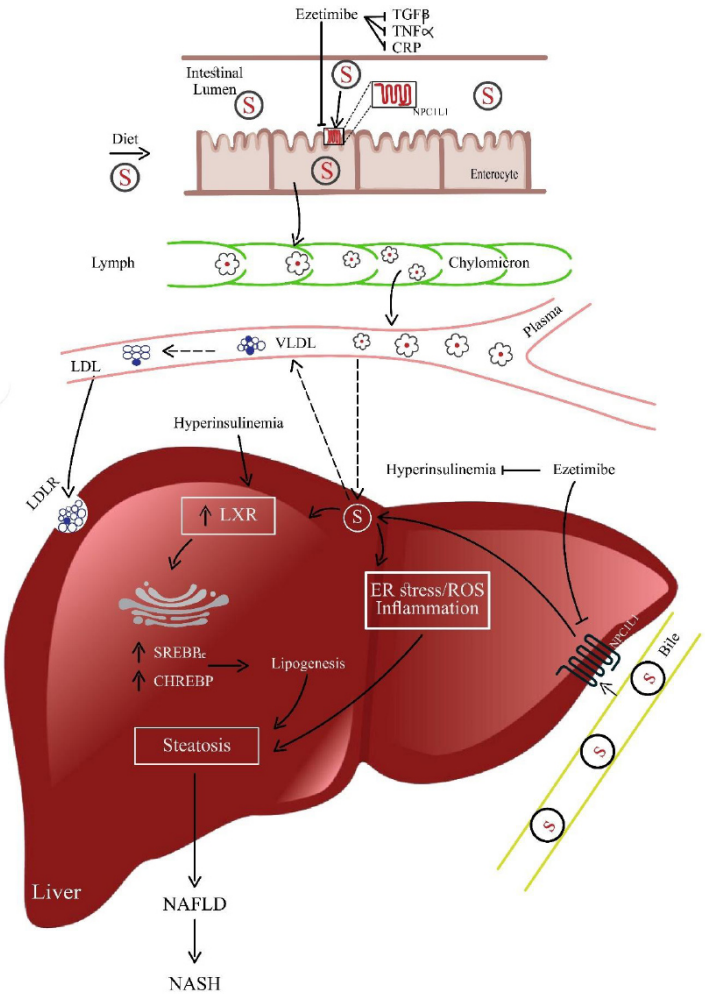

Fig. (2). Ezetimibe's Pleiotropic Effects. Ezetimibe attenuates the progression of NAFLD and NASH through exerting anti-inflammatory, anti-hyperinsulinimic and anti-hyperlipidemic effects. It decreases levels of cholesterol, VLDL and LDL by blocking intestinal and hepatic NPC1L1 cholesterol transporter. Accordingly, ezetimibe inhibits hypercholesterolemia-induced inflammation and subsequent steatosis via two mechanisms. The first pathway is through downregulating Liver X receptor (LXR) and its downstream players, sterol regulatory element-binding protein1c ($SREBP_{1C}$) and carbohydrate-responsive element-binding protein (CHREBP) respectively. The second pathway involves eliminating cholesterol-induced endoplasmic reticulum- (ER) generated ROS. In addition, ezetimibe revives insulin sensitivity and prevents hyperinsulinemia-induced inflammation and lipogenesis. Ezetimibe also decreases markers of inflammation (TGF-β, TNF-α and C-RP). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

[92, 93]. Nevertheless, results regarding the efficacy of ezetimibe in the treatment of both NAFLD and non-alcoholic steatohepatitis (NASH) are inconsistent and rather conflicting [94]. Interestingly, NPC1L1-knockout mice exhibit asignificant reduction in plasma cholesterol levels [91]. Contextually, ezetimibe reduces plasma LDL both directly and indirectly. It acts directly through blunting intestinal cholesterol absorption, thus lowering the amount of cholesterol entering the bloodstream. This decrease in blood cholesterol levels leads to a diminished amount of cholesterol delivered to the liver, which in turn triggers the upregulation of hepatic LDL receptors. These receptors serve as scavengers for circulating LDL; this being the indirect effect of ezetimibe.

Ezetimibe was first approved as monotherapy in the management of dyslipidemia for those who cannot tolerate statins [89]. It was shown to reduce LDL plasma levels by 10 to 18% and Apo-B by 11% [95]. However, when combined with other medications, ezetimibe appeared to further reduce LDL levels and minimize cardiovascular risk. In fact, the combination of ezetimibe with statins dramatically decreased LDL levels by 34 to 61% [96]. Moreover, combining ezetimibe with fenofibrate not only reduced LDL levels by 22% but also increased HDL levels [96]. Two clinical trials, SHARP and IMPROVE-IT, showed that combining moderate dose statins with ezetimibe was superior to statin dose-doubling in lowering LDL levels and the associated cardiovascular risk [97, 98]. Furthermore, ezetimibe monotherapy was associated with rare events of myopathies and rhabdomyolysis, as compared to high intensity statins. Similarly, the statin-ezetimibe combo is considered relatively safe [95]. Importantly, from a financial standpoint, the use of ezetimibe-statin mix is preferred over evolocumab-statin mix since treatment with the former combo was manifested to be more cost effective [99]. It is important to mention here that statins are still recommended as first-line therapy for atherosclerosis since they are associated with improved primary and secondary cardiovascular outcomes. The benefit of statins is attributed not only to their lipid-lowering effect but also to their "pleiotropic effect" which includes anti-thrombotic, anti-oxidant, and anti-inflammatory properties. Likewise, ezetimibe was described to have a "potential pleiotropic effect" [100, 101]. Evidence suggests that ezetimibe may decrease oxidative stress markers and exert an anti-inflammatory effect in subjects with hypercholesterolemia [100, 101]. Novel drugs that act on NPC1L1 or other cholesterol transporters like ABCG5/8 seem to be pharmacotherapeutically attractive; nonetheless, more investigation is warranted [102, 103].

3.4. PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that is mainly produced and secreted by hepatocytes [104]. PCSK9 binds to LDL-receptor (LDL-R), causing endocytosis of this complex and its degradation. Unlike LDL-LDLR binding, LDL-R-PCSK binding causes no recycling of the LDL-R [105]. This results in a decrease in the number of cell-bound LDL-R. As such, PCSK9 decreases the uptake of LDL by hepatocytes from the extracellular fluid; hence the importance of blocking PCSK9 as a treatment option for hypercholesterolemia [106]. PCSK9's action can be inhibited at multiple levels: gene silencing using siRNA or ASO, as well as by blocking and sequestering its molecules via monoclonal antibodies or small protein inhibitors Fig. (**3**) [107-109]. In addition, several preclinical endeavors currently aim to develop PCSK9 vaccines and CRISPR/CAS9 genome editing for a more sustained treatment that is independent of taking pills on a regular basis.

Several monoclonal antibodies were proposed and tested in phase 1 clinical trials; however, only three have reached phase 3: bococizumab, alirocumab and evolocumab. Although results with bococizumab were promising at first, trials were halted at phase 3 because of the production of anti-drug antibodies (ADAs) and neutralizing antibodies. Indeed, a year into the study, 48% of patients developed detectable ADAs, and 29% developed neutralizing antibodies. This is attributed to the fact that 3% of bococizumab 's sequence is of murine origin and thus it was antigenic [110].

In contrast, the sequence of the two other monoclonal antibodies is fully (100%) human, and thus shows rarer incidence of ADAs and neutralizing antibodies. Patients who took alirocumab had only 1.4% and 1.3% incidence in producing ADAs or neutralizing antibodies, respectively [111]. Patients on evolocumab had even better outcomes as cases of ADA incidence were rare and no neutralizing antibodies were reported [112].

A clinical trial involving alirocumab 's (Odyssey) demonstrated that for statin-intolerant individuals, alirocumab was significantly more efficient than ezitimibe in reducing LDL-Cholesterol (LDL-C) (45% vs 14.6% respectively) [113]. Studies have also shown that addition ofalirocumab to Atorvastatin (20 mg or 40 mg) results in significantly more reduction of LDL-C (44.1 or 54% respectively for the two statin doses) when compared to adding ezetimibe to statin or doubling atorvastatin [114]. Similar results were also obtained when the statin of choice was rosuvastatin for

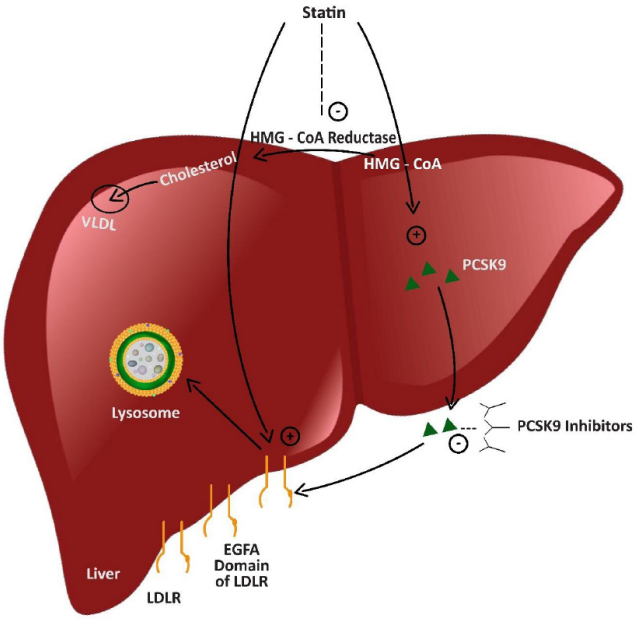

Fig. (3). Statin and PCSK9's synergistic effect. Statin is a classic hypercholesterolemia medication whose HMG-CoA reductase inhibition has been well described and established with positive clinical outcomes. Recently, PCSK9 was recognized as a promotor of lysosomal degradation of LDL-R by binding to its EGFA domain and activating its uptake to the hepatocytes. Moreover, an increase in serum level of PCSK9 was described in patients on statin. In order to operate around this relationship, and to have optimal reduction in LDL-C, increase in LDL-R and better clinical outputs, clinical trials have combined the use of statin along with a PCSK9 inhibitor. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

the 20 mg dosing but not the 40 mg [115]. In other trials, adding alirocumab to a maximally tolerated statin in high cardiovascular risk patients over 52 weeks was tested. Efficacy was tested by comparing change in LDL-C levels at week 24 to those at baseline. The group treated with alirocumab had 48.2% reduction in LDL-C, while the placebo reduced it by only 2.3% [116]. The safety level of alirocumab was promising since no significant difference in adverse effects between the experimental and the control groups was noted [116].

Clinical trials of evolocumab showed similar effects. For statin-intolerant patients, evolocumab caused more reduction (54.4%) in LDL-C compared to ezetimibe (16.7%) [117]. This is further supported by findings of two-open, randomized trials which reported that after 11.1 months of adding evolocumab to standard therapy, LDL-C levels dropped by 61% compared to standard therapy alone [118]. The adjusted cumulative cardiovascular outcome (death, MI, ischemic attack, stroke, unstable angina, heart failure) also decreased by 53% when compared to control [118]. Most of the adverse effects occurred at similar rates between the two groups except for some non-significant increase (0.9 compared to 0.3%) in neurocognitive adverse events, like dementia delirium and mental impairment problems [118].

It is important to note that in the United States, alirocumab and evolocumab were approved to be taken in addition to statin for heterozygous familial hypercholesterolemia and CVD requiring aggresive LDL-C reduction [119]. In Europe, they were approved in conjunction to statin and diet monitoring for the treatment of primary hypercholesterolemia and mixed dyslipidemia and as a monotherapy for statin intolerant patients [119]. However, with the high market price, not all patients could opt for this new treatment.

Another mechanism by which PCSK9 could be modulated is via the siRNA inclisiran. A clinical trial (ORION) of inclisiran showed dose-dependent decrease in LDL-C and PCSK9 [120]. The most optimal results were obtained in the group of patients that received two doses of 300 mg ondays 1 and 90. This regimen caused 52.6% decrease in LDL-C levels after 6 months in phase 2 trials. Phase 3 trials showed that inclisiran significantly reduced levels of LDL-C in patients with heterozygous familial hypercholesterolemia [121] or other patients with atherosclerotic CVD [122].

It is important to mention that although its main role is involved in LDL-R regulation in hepatocytes, but PCSK9 is also expressed by other cells and thus has other roles than lipid homeostasis [104]. For instance, PCSK9 increases protease degradation and decreases exocytosis of epithelial sodium channels (ENaC) [123]. This prompted concern of blood pressure fluctuation; however, no such signs were noticed in the trials of PCSK9 inhibitors [123]. PCSK9 is also involved in the post-trauma regenerating of hepatocytes. Indeed, genetically engineered mice with silenced PCSK9 alleles showed slower liver regeneration, smaller regenerated liver and multiple necrotic lesions in the new liver [124]. Moreover, PCSK9 double knockout mice had chronic hyperglycemia and glucose intolerance [125]. Thus, it is warranted that these important potentially adverse effects be closely monitored in humans.

3.5. Evinacumab

Angiopoietin-like 3 (ANGPTL3) is a crucial player in the regulation of lipid metabolism. It acts by inhibiting both lipoprotein and endothelial lipases [126, 127]. Patients with a defective ANGPTL3 exhibit a hypolipi-

demic profile reflected by a significant decrease in LDL levels, independently of the LDL receptor [128]. In addition, a significant decrease in both triglycerides and HDL is observed in these patients. Despite the decline in HDL levels, this profile clinically translates into a 41% decrease in the incidence of coronary artery disease when compared to the general population [129]. Two current classes of medications are employed to regulate ANGPTL3. While evinacumab directly inhibits ANGPTL3, another approach utilizing antisense oligonucleotide (ASO) specific to hepatic ANGPTL3 mRNA is also employed to suppress the synthesis of ANGPTL3 [61].

Evinacumab has shown promising results in many clinical trials. A very recent phase 3 trial involved 65 patients with homozygous familial hypercholesterolemia maintained on lipid-lowering medications [130]. After 24 weeks, patients receiving intravenous (IV) evinacumab at a dose of 15mg/kg of body weight every 4 weeks had a 47.1% decrease compared to a1.9% increase in LDL in the IV placebo group ($P< 0.001$). The treatment group, however, had a 29.6% drop in HDL compared to a 0.8% increase in the control group ($p<0.001$) [130]. In terms of safety, the incidence of adverse events was 66.0% among the Evinacumab-treated group compared to 81.0% in the control group, with headache and nasopharyngitis being the most common complaints. Only two serious events, urosepsis and a suicide attempt were noted in the treatment group; the patients have since recovered [130]. Notably, in August 2020, the U.S. Food and Drug Administration (FDA) has accepted the priority review of the Biologics License Application of evinacumab as an adjunct therapy to patients with homozygous familial hypercholesterolemia. The final decision of FDA is expected on the 11th of February 2021 [131].

In phase 2 clinical trial, 272 patients with or without familial hypercholesterolemia, who had uncontrolled hypercholesterolemia were enrolled to receive subcutaneous or intravenous evinacumab at different doses or a placebo [132]. At week 16, patients who received subcutaneous treatment had a 47.2% or 44% drop in LDL for the groups receiving respectively 450 mg or 300 mg weekly, as compared to an 8.0% increase in LDL in the subcutaneous placebo ($p <0.001$ for both groups *versus* placebo). For the IV treatments, patients who received 15 mg/kg or 5 mg/kg of evinacumab exhibited a drop of 49.9% or 23.5% in LDL, respectively, compared to an increase of0.6% in the group receiving IV placebo [132].

Although these studies are limited by the short treatment period and the small sample size, they nonetheless show promising results. However, long-term safety profile and cardiovascular gain remain unestablished to this date. Interestingly, statins reduced the progression of atherosclerosis by 28% ($P < 0.001$) in mice fed a western-type diet for 13 weeks. Combined treatment with a statin and alirocumab completely blocked progression and diminished lesion severity. Impressively, triple treatment with a statin, alirocumab and evinacumab regressed the lesion size in the thoracic aorta by 50% and the aortic root by 36% [133]. Taken together, we suggest that the future of lipid control can dramatically benefit from novel medications like evinacumab. However, further larger and longer-term clinical studies are warranted before such a stand can be cemented.

3.6. Micro RNA (or miRNA)

MiRNAs are short sequences of single stranded non-coding RNA that are involved in regulating gene expression [134]. Recent studies have shownthe presence of circulating miRNA originating from dead cells or even secreted by cells as a mean of signaling [135]. A role for miRNAs in the various aspects of atherosclerosis has been highlighted. Indeed, miRNAs appear to modulate endothelial cell damage and dysfunction, monocyte adhesion and activation to macrophages, as well as proliferation of the vascular smooth muscle cells [136]. Some of the miRNAs involved in the progression of atherosclerosis include miR-21, 24, 26a, 29b, 31, 33, 34, 92a, 122,146a, 155, 204, 221, 222, 541, 663; while the ones involved in the suppression of this progression include miR-10, 19a, 22, 23, 27, 29, 96,126, 133, 137, 144,143/145, 181b, 195, 214, 223, 322, 409-3p, 424, 503, 633, 688 [137, 138].

The increasing evidence that supports a role for miRNAs in various hallmarks of atherosclerosis prompted the consideration of these molecules as therapeutic targets in the management or treatment of this disease. There was also a proposition of integrating miRNAs as diagnostic and prognostic markers. However, it appears that miRNAs possess inferior and rarely equal or superior diagnostic power over the traditional biomarkers used [139]. A special and important exception was the early phase of myocardial infarction, where detection of miR-208a/b precedes that of troponins and other cardiac enzymes that usually require more than three hours to be significant [140-142].

CONCLUSION

In conclusion, the era of statin monotherapy is slowly being substituted with combination therapies. Evidence confirms that adding non-statin lipid lowering agents like ezetimibe and PSCK9 inhibitors to statins

significantly reduces the CVD risk [143]. Ezetimibe, PCSK9 monoclonal antibodies, evinacumab, and microRNA inhibitors are only a glimpse of the atherosclerosis management renaissance.

LIST OF ABBREVIATIONS

CVD	=	Cardiovascular Disease
WHO	=	World Health Organization
IHD	=	Ischemic Heart Disease
LDL	=	Low Density Lipoprotein
HDL	=	High Density Lipoprotein
CT	=	Computed Tomography
PET	=	Positron Emission Tomography
MRI	=	Magnetic Resonance Imaging
EKG	=	Electrocardiogram
LDL-R	=	Low Density Lipoprotein-receptor
SR-B1	=	Scavenger Receptor B1
ApoB-100	=	Apoprotein B-100
DOCK-4	=	Dedicator of Cytokinesis 4
ROS	=	Reactive Oxygen Species
ICAM-1	=	Intercellular Adhesion Molecule-1
VCAM-1	=	Vascular Cells Adhesion Molecule-1
TLR	=	Toll-like Receptor
CD	=	Cluster of Differentiation
TGF-β	=	Tumor Growth Factor-β
ATP	=	Adenosine Triphosphate
PDGF	=	Platelet-derived Growth Factor
FGF	=	Fibroblast Growth Factor
VSMC	=	Vascular Smooth Muscle Cell
VLDL	=	Very Low Density Lipoprotein
MTP	=	Microsomal Transfer Protein
ASO	=	Antisense Oligonucleotide
ANGPTL3	=	Angiopoietin-like 3
Pcsk 9	=	Proprotein Convertase Subtilisin/Kexin Type 9
NO	=	Nitric Oxide
CHREBP	=	Carbohydrate-responsive Element-binding Protein
eNOS	=	Endothelial Nitric Oxide Synthase
IL	=	Interleukin
Mcp1	=	Monocyte Chemoattractant Protein-1
MHC	=	Major Histocompatibility Complex
Hmg-coA	=	3-Hydroxy-3-methylglutaryl Coenzyme A
PPARα	=	Proliferator-activated Receptor Alpha
ABCA1	=	ATP-binding Cassette A1 Transporter
LPL	=	Lipoprotein Lipase
TNF	=	Tumor Necrosis Factor
PAI-1	=	Plasminogen Activator Inhibitor-1
NPC1L1	=	Niemann-pick C1 like1
NAFLD	=	Non-alcoholic Fatty Liver Disease
NASH	=	Non-alcoholic Steatohepatitis
ER	=	Endoplasmic Reticulum
SREBP1C	=	Sterol Regulatory Element-binding Protein1c
CHREBP	=	Carbohydrate-responsive Element-binding Protein
LXR	=	Liver X Receptor
LDL-C	=	Low Density Lipoprotein-cholesterol
CRISPR/CAS9	=	Clustered Regularly Interspaced Short Palindromic Repeats/ CRISPR-associated Protein 9
ADA	=	Anti-drug Antibodies
ENaC	=	Epithelial Sodium Channel
FDA	=	Food and Drug Administration
miRNA	=	Micro Ribonucleic Acid
mg	=	Milligram

AUTHOR'S CONTRIBUTIONS

AHE conceived the idea of the paper. NY and AHA wrote most of the first draft of the manuscript. All authors contributed to the first and the subsequent drafts. RA and FS lead the production of the artwork. All authors edited the final version.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

[1] Bentzon, J.F.; Otsuka, F.; Virmani, R.; Falk, E. Mechanisms of plaque formation and rupture. *Circ. Res.,* **2014**, *114*(12), 1852-1866. http://dx.doi.org/10.1161/CIRCRESAHA.114.302721 PMID: 24902970

[2] *WHO Cardiovascular diseases (CVDs).,* https://www.who.int/cardiovascular_diseases/en/2019 25-March;

[3] Liew, S.M.; Abdullah, A.; Abdullah, N.; Chia, Y.C. Health innovation in cardiovascular diseases. *Australas. Med. J.,* **2013**, *6*(1), 67-69. PMID: 23423184

[4] *National Heart, L., and Blood Institute (NHLBI), Atherosclerosis.,*

[5] Herrington, W.; Lacey, B.; Sherliker, P.; Armitage, J.; Lewington, S. Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease. *Circ. Res.,* **2016**, *118*(4), 535-546. http://dx.doi.org/10.1161/CIRCRESAHA.115.307611 PMID: 26892956

[6] Chen, Y.C.; Huang, A.L.; Kyaw, T.S.; Bobik, A.; Peter, K. Atherosclerotic Plaque Rupture: Identifying the Straw That Breaks the Camel's Back. *Arterioscler. Thromb. Vasc. Biol.,* **2016**, *36*(8), e63-e72. http://dx.doi.org/10.1161/ATVBAHA.116.307993 PMID: 27466619

[7] Zmysłowski, A.; Szterk, A. Current knowledge on the mechanism of atherosclerosis and pro-atherosclerotic properties of oxysterols. *Lipids Health Dis.,* **2017**, *16*(1), 188. http://dx.doi.org/10.1186/s12944-017-0579-2 PMID: 28969682

[8] Yu, X.H.; Zheng, X.L.; Tang, C.K. Nuclear Factor-κB Activation as a Pathological Mechanism of Lipid Metabolism and Atherosclerosis. *Adv. Clin. Chem.,* **2015**, *70*, 1-30. http://dx.doi.org/10.1016/bs.acc.2015.03.004 PMID: 26231484

[9] Si-Tayeb, K.; Idriss, S.; Champon, B.; Caillaud, A.; Pichelin, M.; Arnaud, L.; Lemarchand, P.; Le May, C.; Zibara, K.; Cariou, B. Urine-sample-derived human induced pluripotent stem cells as a model to study PCSK9-mediated autosomal dominant hypercholesterolemia. *Dis. Model. Mech.,* **2016**, *9*(1), 81-90. http://dx.doi.org/10.1242/dmm.022277 PMID: 26586530

[10] Wehbe, Z.; Nasser, S.A.; El-Yazbi, A.; Nasreddine, S.; Eid, A.H. Estrogen and Bisphenol A in Hypertension. *Curr. Hypertens. Rep.,* **2020**, *22*(3), 23. http://dx.doi.org/10.1007/s11906-020-1022-z PMID: 32114652

[11] Fardoun, M.; Dehaini, H.; Shaito, A.; Mesmar, J.; El-Yazbi, A.; Badran, A.; Beydoun, E.; Eid, A.H. The hypertensive potential of estrogen: An untold story. *Vascul. Pharmacol.,* **2020**, *124*, 106600. http://dx.doi.org/10.1016/j.vph.2019.106600 PMID: 31629918

[12] Dehaini, H.; Fardoun, M.; Abou-Saleh, H.; El-Yazbi, A.; Eid, A.A.; Eid, A.H. Estrogen in vascular smooth muscle cells: A friend or a foe? *Vascul. Pharmacol.,* **2018**, *111*, 15-21. http://dx.doi.org/10.1016/j.vph.2018.09.001 PMID: 30227233

[13] Ross, R. Atherosclerosis--an inflammatory disease. *N. Engl. J. Med.,* **1999**, *340*(2), 115-126. http://dx.doi.org/10.1056/NEJM199901143400207 PMID: 9887164

[14] Nasser, S.A.; Afify, E.A.; Kobeissy, F.; Hamam, B.; Eid, A.H.; El-Mas, M.M. Inflammatory basis of atherosclerosis: modulation by sex hormones. *Curr. Pharm. Des.,* **2021**. http://dx.doi.org/10.2174/1381612827666210122142811 PMID: 33480335

[15] Patel, B.B.; Raad, M.; Sebag, I.A.; Chalifour, L.E. Lifelong exposure to bisphenol a alters cardiac structure/function, protein expression, and DNA methylation in adult mice. *Toxicol. Sci.,* **2013**, *133*(1), 174-185. http://dx.doi.org/10.1093/toxsci/kft026 PMID: 23418087

[16] Tabas, I. Macrophage death and defective inflammation resolution in atherosclerosis. *Nat. Rev. Immunol.,* **2010**, *10*(1), 36-46. http://dx.doi.org/10.1038/nri2675 PMID: 19960040

[17] Kwak, B.R.; Back, M.; Bochaton-Piallat, M.L.; Caligiuri, G.; Daemen, M.J.; Davies, P.F.; Hoefer, I.E.; Holvoet, P.; Jo, H.; Krams, R.; Lehoux, S.; Monaco, C.; Steffens, S.; Virmani, R.; Weber, C.; Wentzel, J.J.; Evans, P.C. Biomechanical factors in atherosclerosis: mechanisms and clinical implications. *Eur Heart J,* **2014**, *35*(43), 3013-3020. 3020a-3020d. http://dx.doi.org/10.1093/eurheartj/ehu353

[18] Zhang, X.; Sessa, W.C.; Fernández-Hernando, C. Endothelial Transcytosis of Lipoproteins in Atherosclerosis. *Front. Cardiovasc. Med.,* **2018**, *5*, 130. http://dx.doi.org/10.3389/fcvm.2018.00130 PMID: 30320124

[19] Huang, L.; Chambliss, K.L.; Gao, X.; Yuhanna, I.S.; Behling-Kelly, E.; Bergaya, S.; Ahmed, M.; Michaely, P.; Luby-Phelps, K.; Darehshouri, A.; Xu, L.; Fisher, E.A.; Ge, W.P.; Mineo, C.; Shaul, P.W., Sr SR-B1 drives endothelial cell LDL transcytosis *via* DOCK4 to promote atherosclerosis. *Nature,* **2019**, *569*(7757), 565-569. http://dx.doi.org/10.1038/s41586-019-1140-4 PMID: 31019307

[20] Wu, M.Y.; Li, C.J.; Hou, M.F.; Chu, P.Y. New Insights into the Role of Inflammation in the Pathogenesis of Atherosclerosis. *Int. J. Mol. Sci.,* **2017**, *18*(10), E2034. http://dx.doi.org/10.3390/ijms18102034 PMID: 28937652

[21] Weber, C.; Noels, H. Atherosclerosis: current pathogenesis and therapeutic options. *Nat. Med.,* **2011**, *17*(11), 1410-1422. http://dx.doi.org/10.1038/nm.2538 PMID: 22064431

[22] Zeibig, S.; Li, Z.; Wagner, S.; Holthoff, H.P.; Ungerer, M.; Bültmann, A.; Uhland, K.; Vogelmann, J.; Simmet, T.; Gawaz, M.; Münch, G. Effect of the oxLDL binding protein Fc-CD68 on plaque extension and vulnerability in

atherosclerosis. *Circ. Res.,* **2011**, *108*(6), 695-703. http://dx.doi.org/10.1161/CIRCRESAHA.111.240515 PMID: 21293004

[23] Hansson, G.K. Inflammatory mechanisms in atherosclerosis. *J. Thromb. Haemost.,* **2009**, *7*(Suppl. 1), 328-331. http://dx.doi.org/10.1111/j.1538-7836.2009.03416.x PMID: 19630827

[24] Martinet, W.; Schrijvers, D.M.; De Meyer, G.R. Necrotic cell death in atherosclerosis. *Basic Res. Cardiol.,* **2011**, *106*(5), 749-760. http://dx.doi.org/10.1007/s00395-011-0192-x PMID: 21611880

[25] Khyzha, N.; Alizada, A.; Wilson, M.D.; Fish, J.E. Epigenetics of Atherosclerosis: Emerging Mechanisms and Methods. *Trends Mol. Med.,* **2017**, *23*(4), 332-347. http://dx.doi.org/10.1016/j.molmed.2017.02.004 PMID: 28291707

[26] Badimon, L.; Vilahur, G. Thrombosis formation on atherosclerotic lesions and plaque rupture. *J. Intern. Med.,* **2014**, *276*(6), 618-632. http://dx.doi.org/10.1111/joim.12296 PMID: 25156650

[27] Allahverdian, S.; Chaabane, C.; Boukais, K.; Francis, G.A.; Bochaton-Piallat, M.L. Smooth muscle cell fate and plasticity in atherosclerosis. *Cardiovasc. Res.,* **2018**, *114*(4), 540-550. http://dx.doi.org/10.1093/cvr/cvy022 PMID: 29385543

[28] Wang, Y.; Dubland, J.A.; Allahverdian, S.; Asonye, E.; Sahin, B.; Jaw, J.E.; Sin, D.D.; Seidman, M.A.; Leeper, N.J.; Francis, G.A. Smooth Muscle Cells Contribute the Majority of Foam Cells in ApoE (Apolipoprotein E)-Deficient Mouse Atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.,* **2019**, *39*(5), 876-887. http://dx.doi.org/10.1161/ATVBAHA.119.312434 PMID: 30786740

[29] Pryma, C.S.; Ortega, C.; Dubland, J.A.; Francis, G.A. Pathways of smooth muscle foam cell formation in atherosclerosis. *Curr. Opin. Lipidol.,* **2019**, *30*(2), 117-124. http://dx.doi.org/10.1097/MOL.0000000000000574 PMID: 30664015

[30] Allahverdian, S.; Chehroudi, A.C.; McManus, B.M.; Abraham, T.; Francis, G.A. Contribution of intimal smooth muscle cells to cholesterol accumulation and macrophage-like cells in human atherosclerosis. *Circulation,* **2014**, *129*(15), 1551-1559. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.005015 PMID: 24481950

[31] Saleh Al-Shehabi, T.; Iratni, R.; Eid, A.H. Anti-atherosclerotic plants which modulate the phenotype of vascular smooth muscle cells. *Phytomedicine,* **2016**, *23*(11), 1068-1081. http://dx.doi.org/10.1016/j.phymed.2015.10.016 PMID: 26776961

[32] Fardoun, M.; Al-Shehabi, T.; El-Yazbi, A.; Issa, K.; Zouein, F.; Maaliki, D.; Iratni, R.; Eid, A.H. *Ziziphus nummularia* Inhibits Inflammation-Induced Atherogenic Phenotype of Human Aortic Smooth Muscle Cells. *Oxid. Med. Cell. Longev.,* **2017**, *2017*, 4134093. http://dx.doi.org/10.1155/2017/4134093 PMID: 28593025

[33] Badran, A.; Nasser, S.A.; Mesmar, J.; El-Yazbi, A.F.; Bitto, A.; Fardoun, M.M.; Baydoun, E.; Eid, A.H. Reactive Oxygen Species: Modulators of Phenotypic Switch of Vascular Smooth Muscle Cells. *Int. J. Mol. Sci.,* **2020**, *21*(22), E8764. http://dx.doi.org/10.3390/ijms21228764 PMID: 33233489

[34] Fardoun, M.; Iratni, R.; Dehaini, H.; Eid, A.; Ghaddar, T.; El-Elimat, T.; Alali, F.; Badran, A.; Eid, A.H.; Baydoun, E. 7-*O*-methylpunctatin, a Novel Homoisoflavonoid, Inhibits Phenotypic Switch of Human Arteriolar Smooth Muscle Cells. *Biomolecules,* **2019**, *9*(11), E716. http://dx.doi.org/10.3390/biom9110716 PMID: 31717401

[35] Weber, C.; Badimon, L.; Mach, F.; van der Vorst, E.P.C. Therapeutic strategies for atherosclerosis and atherothrombosis: Past, present and future. *Thromb. Haemost.,* **2017**, *117*(7), 1258-1264. http://dx.doi.org/10.1160/TH16-10-0814 PMID: 28594053

[36] Valanti, E.; Tsompanidis, A.; Sanoudou, D. Pharmacogenomics in the development and characterization of atheroprotective drugs. *Methods Mol. Biol.,* **2014**, *1175*, 259-300. http://dx.doi.org/10.1007/978-1-4939-0956-8_11 PMID: 25150873

[37] Kuk, M.; Ward, N.C.; Dwivedi, G. Extrinsic and Intrinsic Responses in the Development and Progression of Atherosclerosis. *Heart Lung Circ.,* **2021**, S1443-9506(20)31552-3. PMID: 33468387

[38] Alali, F.Q.; El-Elimat, T.; Khalid, L.; Hudaib, R.; Al-Shehabi, T.S.; Eid, A.H. Garlic for Cardiovascular Disease: Prevention or Treatment? *Curr. Pharm. Des.,* **2017**, *23*(7), 1028-1041. http://dx.doi.org/10.2174/1381612822666161010124530 PMID: 27748188

[39] Shouk, R.; Abdou, A.; Shetty, K.; Sarkar, D.; Eid, A.H. Mechanisms underlying the antihypertensive effects of garlic bioactives. *Nutr. Res.,* **2014**, *34*(2), 106-115. http://dx.doi.org/10.1016/j.nutres.2013.12.005 PMID: 24461311

[40] Fardoun, M.M.; Maaliki, D.; Halabi, N.; Iratni, R.; Bitto, A.; Baydoun, E.; Eid, A.H. Flavonoids in adipose tissue inflammation and atherosclerosis: one arrow, two targets. *Clin. Sci. (Lond.),* **2020**, *134*(12), 1403-1432. http://dx.doi.org/10.1042/CS20200356 PMID: 32556180

[41] Maaliki, D.; Shaito, A.A.; Pintus, G.; El-Yazbi, A.; Eid, A.H. Flavonoids in hypertension: a brief review of the underlying mechanisms. *Curr. Opin. Pharmacol.,* **2019**, *45*, 57-65. http://dx.doi.org/10.1016/j.coph.2019.04.014 PMID: 31102958

[42] Hu, D.; Wang, Z.; Wang, Y.; Liang, C. Targeting Macrophages in Atherosclerosis. *Curr. Pharm. Biotechnol.,* **2021**. http://dx.doi.org/10.2174/1389201022666210122142233 PMID: 33480337

[43] Chen, J.; Zhang, X.; Millican, R.; Sherwood, J.; Martin, S.; Jo, H.; Yoon, Y.S.; Brott, B.C.; Jun, H.W. Recent advances in nanomaterials for therapy and diagnosis for atherosclerosis. *Adv. Drug Deliv. Rev.,* **2021**, *170*, 142-199. http://dx.doi.org/10.1016/j.addr.2021.01.005 PMID: 33428994

[44] Tabaei, S.; Tabaee, S.S. Implications for MicroRNA involvement in the prognosis and treatment of atherosclerosis. *Mol. Cell. Biochem.,* **2021**. http://dx.doi.org/10.1007/s11010-020-03992-4 PMID: 33389489

[45] Yvan-Charvet, L.; Cariou, B. Poststatin era in atherosclerosis management: lessons from epidemiologic and genetic studies. *Curr. Opin. Lipidol.,* **2018**, *29*(3), 246-258. http://dx.doi.org/10.1097/MOL.0000000000000505 PMID: 29553996

[46] Okopień, B.; Buldak, L.; Bołdys, A. Fibrates in the man-

agement of atherogenic dyslipidemia. *Expert Rev. Cardiovasc. Ther.,* **2017**, *15*(12), 913-921. http://dx.doi.org/10.1080/14779072.2017.1408410 PMID: 29183206

[47] Rader, D.J.; Kastelein, J.J. Lomitapide and mipomersen: two first-in-class drugs for reducing low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. *Circulation,* **2014**, *129*(9), 1022-1032. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.001292 PMID: 24589695

[48] Tomkin, G.H.; Owens, D. Investigational therapies for the treatment of atherosclerosis. *Expert Opin. Investig. Drugs,* **2014**, *23*(10), 1411-1421. http://dx.doi.org/10.1517/13543784.2014.922950 PMID: 24857672

[49] Gouni-Berthold, I.; Berthold, H.K. Mipomersen and lomitapide: Two new drugs for the treatment of homozygous familial hypercholesterolemia. *Atheroscler. Suppl.,* **2015**, *18*, 28-34. http://dx.doi.org/10.1016/j.atherosclerosissup.2015.02.005 PMID: 25936301

[50] Kumar, S.; Kim, C.W.; Simmons, R.D.; Jo, H. Role of flow-sensitive microRNAs in endothelial dysfunction and atherosclerosis: mechanosensitive athero-miRs. *Arterioscler. Thromb. Vasc. Biol.,* **2014**, *34*(10), 2206-2216. http://dx.doi.org/10.1161/ATVBAHA.114.303425 PMID: 25012134

[51] Loyer, X.; Potteaux, S.; Vion, A.C.; Guérin, C.L.; Boulkroun, S.; Rautou, P.E.; Ramkhelawon, B.; Esposito, B.; Dalloz, M.; Paul, J.L.; Julia, P.; Maccario, J.; Boulanger, C.M.; Mallat, Z.; Tedgui, A. Inhibition of microRNA-92a prevents endothelial dysfunction and atherosclerosis in mice. *Circ. Res.,* **2014**, *114*(3), 434-443. http://dx.doi.org/10.1161/CIRCRESAHA.114.302213 PMID: 24255059

[52] Lu, H.; Daugherty, A. Atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.,* **2015**, *35*(3), 485-491. http://dx.doi.org/10.1161/ATVBAHA.115.305380 PMID: 25717174

[53] Charo, I.F.; Taub, R. Anti-inflammatory therapeutics for the treatment of atherosclerosis. *Nat. Rev. Drug Discov.,* **2011**, *10*(5), 365-376. http://dx.doi.org/10.1038/nrd3444 PMID: 21532566

[54] van Diepen, J.A.; Berbée, J.F.; Havekes, L.M.; Rensen, P.C. Interactions between inflammation and lipid metabolism: relevance for efficacy of anti-inflammatory drugs in the treatment of atherosclerosis. *Atherosclerosis,* **2013**, *228*(2), 306-315. http://dx.doi.org/10.1016/j.atherosclerosis.2013.02.028 PMID: 23518178

[55] Bäck, M.; Hansson, G.K. Anti-inflammatory therapies for atherosclerosis. *Nat. Rev. Cardiol.,* **2015**, *12*(4), 199-211. http://dx.doi.org/10.1038/nrcardio.2015.5 PMID: 25666404

[56] McKenney, J.M. Understanding PCSK9 and anti-PCSK9 therapies. *J. Clin. Lipidol.,* **2015**, *9*(2), 170-186. http://dx.doi.org/10.1016/j.jacl.2015.01.001 PMID: 25911073

[57] Urban, D.; Pöss, J.; Böhm, M.; Laufs, U. Targeting the proprotein convertase subtilisin/kexin type 9 for the treatment of dyslipidemia and atherosclerosis. *J. Am. Coll. Cardiol.,* **2013**, *62*(16), 1401-1408. http://dx.doi.org/10.1016/j.jacc.2013.07.056 PMID: 23973703

[58] Allard, D.; Amsellem, S.; Abifadel, M.; Trillard, M.; Devillers, M.; Luc, G.; Krempf, M.; Reznik, Y.; Girardet, J.P.; Fredenrich, A.; Junien, C.; Varret, M.; Boileau, C.; Benlian, P.; Rabès, J.P. Novel mutations of the PCSK9 gene cause variable phenotype of autosomal dominant hypercholesterolemia. *Hum. Mutat.,* **2005**, *26*(5), 497. http://dx.doi.org/10.1002/humu.9383 PMID: 16211558

[59] Abifadel, M.; Varret, M.; Rabès, J.P.; Allard, D.; Ouguerram, K.; Devillers, M.; Cruaud, C.; Benjannet, S.; Wickham, L.; Erlich, D.; Derré, A.; Villéger, L.; Farnier, M.; Beucler, I.; Bruckert, E.; Chambaz, J.; Chanu, B.; Lecerf, J.M.; Luc, G.; Moulin, P.; Weissenbach, J.; Prat, A.; Krempf, M.; Junien, C.; Seidah, N.G.; Boileau, C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat. Genet.,* **2003**, *34*(2), 154-156. http://dx.doi.org/10.1038/ng1161 PMID: 12730697

[60] Mabuchi, H.; Nohara, A.; Noguchi, T.; Kobayashi, J.; Kawashiri, M.A.; Inoue, T.; Mori, M.; Tada, H.; Nakanishi, C.; Yagi, K.; Yamagishi, M.; Ueda, K.; Takegoshi, T.; Miyamoto, S.; Inazu, A.; Koizumi, J.; Hokuriku, F.H.S.G. Hokuriku FH Study Group. Genotypic and phenotypic features in homozygous familial hypercholesterolemia caused by proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function mutation. *Atherosclerosis,* **2014**, *236*(1), 54-61. http://dx.doi.org/10.1016/j.atherosclerosis.2014.06.005 PMID: 25014035

[61] Geladari, E.; Tsamadia, P.; Vallianou, N.G. ANGPTL3 Inhibitors□- Their Role in Cardiovascular Disease Through Regulation of Lipid Metabolism. *Circulation journal : official journal of the Japanese Circulation Society,* **2019**, *83*(2), 267-273..

[62] Collins, R.; Reith, C.; Emberson, J.; Armitage, J.; Baigent, C.; Blackwell, L.; Blumenthal, R.; Danesh, J.; Smith, G.D.; DeMets, D.; Evans, S.; Law, M.; MacMahon, S.; Martin, S.; Neal, B.; Poulter, N.; Preiss, D.; Ridker, P.; Roberts, I.; Rodgers, A.; Sandercock, P.; Schulz, K.; Sever, P.; Simes, J.; Smeeth, L.; Wald, N.; Yusuf, S.; Peto, R. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet,* **2016**, *388*(10059), 2532-2561. http://dx.doi.org/10.1016/S0140-6736(16)31357-5 PMID: 27616593

[63] DiNicolantonio, J.J.; Lavie, C.J.; Serebruany, V.L.; O'Keefe, J.H. Statin wars: the heavyweight match--atorvastatin versus rosuvastatin for the treatment of atherosclerosis, heart failure, and chronic kidney disease. *Postgrad. Med.,* **2013**, *125*(1), 7-16. http://dx.doi.org/10.3810/pgm.2013.01.2620 PMID: 23391667

[64] Singh, M.; Bedi, U.S. Is atherosclerosis regression a realistic goal of statin therapy and what does that mean? *Curr. Atheroscler. Rep.,* **2013**, *15*(1), 294. http://dx.doi.org/10.1007/s11883-012-0294-4 PMID: 23250630

[65] Ferrières, J. A paradigm shift in the treatment of atherosclerosis. *Arch. Cardiovasc. Dis.,* **2015**, *108*(6-7), 337-339. http://dx.doi.org/10.1016/j.acvd.2015.05.007 PMID: 26148633

[66] Bergheanu, S.C.; Bodde, M.C.; Jukema, J.W. Pathophysiology and treatment of atherosclerosis : Current view and future perspective on lipoprotein modification treatment. *Neth. Heart J.,* **2017**, *25*(4), 231-242. http://dx.doi.org/10.1007/s12471-017-0959-2 PMID: 28194698

[67] Valacchi, G.; Sticozzi, C.; Lim, Y.; Pecorelli, A. Scavenger receptor class B type I: a multifunctional receptor.

Ann. N. Y. Acad. Sci., **2011**, *1229*, E1-E7. http://dx.doi.org/10.1111/j.1749-6632.2011.06205.x PMID: 22239457

[68] Badimon, L.; Vilahur, G. LDL-cholesterol versus HDL-cholesterol in the atherosclerotic plaque: inflammatory resolution versus thrombotic chaos. *Ann. N. Y. Acad. Sci.,* **2012**, *1254*, 18-32. http://dx.doi.org/10.1111/j.1749-6632.2012.06480.x PMID: 22548566

[69] Annema, W.; von Eckardstein, A.; Kovanen, P.T. HDL and atherothrombotic vascular disease. *Handb. Exp. Pharmacol.,* **2015**, *224*, 369-403. http://dx.doi.org/10.1007/978-3-319-09665-0_11 PMID: 25522995

[70] P., B. The role of HDL-cholesterol in preventing atherosclerotic disease. *Eur Hear J Suppl.,* **2005**.

[71] Wang, C.Y.; Liu, P.Y.; Liao, J.K. Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. *Trends Mol. Med.,* **2008**, *14*(1), 37-44. http://dx.doi.org/10.1016/j.molmed.2007.11.004 PMID: 18068482

[72] Davignon, J. Pleiotropic effects of pitavastatin. *Br. J. Clin. Pharmacol.,* **2012**, *73*(4), 518-535. http://dx.doi.org/10.1111/j.1365-2125.2011.04139.x PMID: 22053916

[73] Morikawa, S.; Takabe, W.; Mataki, C.; Kanke, T.; Itoh, T.; Wada, Y.; Izumi, A.; Saito, Y.; Hamakubo, T.; Kodama, T. The effect of statins on mRNA levels of genes related to inflammation, coagulation, and vascular constriction in HUVEC. Human umbilical vein endothelial cells. *J. Atheroscler. Thromb.,* **2002**, *9*(4), 178-183. http://dx.doi.org/10.5551/jat.9.178 PMID: 12226549

[74] Bea, F.; Blessing, E.; Shelley, M.I.; Shultz, J.M.; Rosenfeld, M.E. Simvastatin inhibits expression of tissue factor in advanced atherosclerotic lesions of apolipoprotein E deficient mice independently of lipid lowering: potential role of simvastatin-mediated inhibition of Egr-1 expression and activation. *Atherosclerosis,* **2003**, *167*(2), 187-194. http://dx.doi.org/10.1016/S0021-9150(02)00387-8 PMID: 12818400

[75] Owens, A.P., III; Byrnes, J.R.; Mackman, N. Hyperlipidemia, tissue factor, coagulation, and simvastatin. *Trends Cardiovasc. Med.,* **2014**, *24*(3), 95-98. http://dx.doi.org/10.1016/j.tcm.2013.07.003 PMID: 24016468

[76] Adhyaru, B.B.; Jacobson, T.A. Safety and efficacy of statin therapy. *Nat. Rev. Cardiol.,* **2018**, *15*(12), 757-769. http://dx.doi.org/10.1038/s41569-018-0098-5 PMID: 30375494

[77] Fitchett, D.H.; Hegele, R.A.; Verma, S. Cardiology patient page. Statin intolerance. *Circulation,* **2015**, *131*(13), e389-e391. http://dx.doi.org/10.1161/CIRCULATIONAHA.114.013189 PMID: 25825402

[78] Toth, P.P.; Patti, A.M.; Giglio, R.V.; Nikolic, D.; Castellino, G.; Rizzo, M.; Banach, M. Management of Statin Intolerance in 2018: Still More Questions Than Answers. *Am. J. Cardiovasc. Drugs,* **2018**, *18*(3), 157-173. http://dx.doi.org/10.1007/s40256-017-0259-7 PMID: 29318532

[79] Roberts, W.C. The rule of 5 and the rule of 7 in lipid-lowering by statin drugs. *Am. J. Cardiol.,* **1997**, *80*(1), 106-107. http://dx.doi.org/10.1016/S0002-9149(97)00298-1 PMID: 9205036

[80] J-C, F. Peroxisome proliferator-activated receptor-alpha (PPARα): At the crossroads of obesity, diabetes and cardiovascular disease. *Atherosclerosis,* **2009**.

[81] Hafiane, A.; Kellett, S.; Genest, J. Treatment options for low high-density lipoproteins. *Curr. Opin. Endocrinol. Diabetes Obes.,* **2014**, *21*(2), 134-139. http://dx.doi.org/10.1097/MED.0000000000000049 PMID: 24535232

[82] Tenenbaum, A.; Fisman, E.Z. Fibrates are an essential part of modern anti-dyslipidemic arsenal: spotlight on atherogenic dyslipidemia and residual risk reduction. *Cardiovasc. Diabetol.,* **2012**, *11*, 125. http://dx.doi.org/10.1186/1475-2840-11-125 PMID: 23057687

[83] Seth Loomba, R.; Arora, R. Fibrates: where are we now? *Ther. Adv. Cardiovasc. Dis.,* **2009**, *3*(1), 91-96. http://dx.doi.org/10.1177/1753944708096281 PMID: 19144670

[84] Chinetti-Gbaguidi, G.; Fruchart, J.C.; Staels, B. Pleiotropic effects of fibrates. *Curr. Atheroscler. Rep.,* **2005**, *7*(5), 396-401. http://dx.doi.org/10.1007/s11883-005-0053-x PMID: 16105484

[85] Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, K.; Leitersdorf, E.; Fruchart, J.C. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation,* **1998**, *98*(19), 2088-2093. http://dx.doi.org/10.1161/01.CIR.98.19.2088 PMID: 9808609

[86] Tziomalos, K.; Athyros, V.G.; Karagiannis, A.; Mikhailidis, D.P. Anti-inflammatory effects of fibrates: an overview. *Curr. Med. Chem.,* **2009**, *16*(6), 676-684. http://dx.doi.org/10.2174/092986709787458416 PMID: 19199931

[87] Ginsberg, H.N.; Elam, M.B.; Lovato, L.C.; Crouse, J.R., III; Leiter, L.A.; Linz, P.; Friedewald, W.T.; Buse, J.B.; Gerstein, H.C.; Probstfield, J.; Grimm, R.H.; Ismail-Beigi, F.; Bigger, J.T.; Goff, D.C., Jr; Cushman, W.C.; Simons--Morton, D.G.; Byington, R.P.; Byington, R.P. ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N. Engl. J. Med.,* **2010**, *362*(17), 1563-1574. http://dx.doi.org/10.1056/NEJMoa1001282 PMID: 20228404

[88] Zhu, L.; Hayen, A.; Bell, K.J.L. Legacy effect of fibrate add-on therapy in diabetic patients with dyslipidemia: a secondary analysis of the ACCORDION study. *Cardiovasc. Diabetol.,* **2020**, *19*(1), 28. http://dx.doi.org/10.1186/s12933-020-01002-x PMID: 32138746

[89] Jellinger, P.S.; Handelsman, Y.; Rosenblit, P.D.; Bloomgarden, Z.T.; Fonseca, V.A.; Garber, A.J.; Grunberger, G.; Guerin, C.K.; Bell, D.S.H.; Mechanick, J.I.; Pessah-Pollack, R.; Wyne, K.; Smith, D.; Brinton, E.A.; Fazio, S.; Davidson, M. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. *Endocr. Pract.,* **2017**, *23*(Suppl. 2), 1-87. http://dx.doi.org/10.4158/EP171764.APPGL PMID: 28437620

[90] Davis, H.R., Jr; Altmann, S.W. Niemann-Pick C1 Like 1 (NPC1L1) an intestinal sterol transporter. *Biochim. Biophys. Acta,* **2009**, *1791*(7), 679-683. http://dx.doi.org/10.1016/j.bbalip.2009.01.002 PMID:

19272334

[91] Kosoglou, T.; Statkevich, P.; Johnson-Levonas, A.O.; Paolini, J.F.; Bergman, A.J.; Alton, K.B. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin. Pharmacokinet.,* **2005**, *44*(5), 467-494. http://dx.doi.org/10.2165/00003088-200544050-00002 PMID: 15871634

[92] Ahmed, M.H.; Byrne, C.D. Modulation of sterol regulatory element binding proteins (SREBPs) as potential treatments for non-alcoholic fatty liver disease (NAFLD). *Drug Discov. Today,* **2007**, *12*(17-18), 740-747. http://dx.doi.org/10.1016/j.drudis.2007.07.009 PMID: 17826687

[93] Nomura, M.; Ishii, H.; Kawakami, A.; Yoshida, M. Inhibition of hepatic Niemann-Pick C1-like 1 improves hepatic insulin resistance. *Am. J. Physiol. Endocrinol. Metab.,* **2009**, *297*(5), E1030-E1038. http://dx.doi.org/10.1152/ajpendo.00343.2009 PMID: 19654286

[94] Nakade, Y.; Murotani, K.; Inoue, T.; Kobayashi, Y.; Yamamoto, T.; Ishii, N.; Ohashi, T.; Ito, K.; Fukuzawa, Y.; Yoneda, M. Ezetimibe for the treatment of non-alcoholic fatty liver disease: A meta-analysis. *Hepatol. Res.,* **2017**, *47*(13), 1417-1428. http://dx.doi.org/10.1111/hepr.12887 PMID: 28257594

[95] Vavlukis, M.; Vavlukis, A. Adding ezetimibe to statin therapy: latest evidence and clinical implications. *Drugs Context,* **2018**, *7*, 212534. http://dx.doi.org/10.7573/dic.212534 PMID: 30023003

[96] Ansquer, J.C.; Bekaert, I.; Guy, M.; Hanefeld, M.; Simon, A.; Study, I. Study Investigators. Efficacy and safety of coadministration of fenofibrate and ezetimibe compared with each as monotherapy in patients with type IIb dyslipidemia and features of the metabolic syndrome: a prospective, randomized, double-blind, three-parallel arm, multicenter, comparative study. *Am. J. Cardiovasc. Drugs,* **2009**, *9*(2), 91-101. http://dx.doi.org/10.1007/BF03256580 PMID: 19331437

[97] Baigent, C.; Landray, M.J.; Reith, C.; Emberson, J.; Wheeler, D.C.; Tomson, C.; Wanner, C.; Krane, V.; Cass, A.; Craig, J.; Neal, B.; Jiang, L.; Hooi, L.S.; Levin, A.; Agodoa, L.; Gaziano, M.; Kasiske, B.; Walker, R.; Massy, Z.A.; Feldt-Rasmussen, B.; Krairittichai, U.; Ophascharoensuk, V.; Fellström, B.; Holdaas, H.; Tesar, V.; Wiecek, A.; Grobbee, D.; de Zeeuw, D.; Grönhagen-Riska, C.; Dasgupta, T.; Lewis, D.; Herrington, W.; Mafham, M.; Majoni, W.; Wallendszus, K.; Grimm, R.; Pedersen, T.; Tobert, J.; Armitage, J.; Baxter, A.; Bray, C.; Chen, Y.; Chen, Z.; Hill, M.; Knott, C.; Parish, S.; Simpson, D.; Sleight, P.; Young, A.; Collins, R.; Investigators, S. SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet,* **2011**, *377*(9784), 2181-2192. http://dx.doi.org/10.1016/S0140-6736(11)60739-3 PMID: 21663949

[98] Cannon, C.P.; Blazing, M.A.; Giugliano, R.P.; McCagg, A.; White, J.A.; Theroux, P.; Darius, H.; Lewis, B.S.; Ophuis, T.O.; Jukema, J.W.; De Ferrari, G.M.; Ruzyllo, W.; De Lucca, P.; Im, K.; Bohula, E.A.; Reist, C.; Wiviott, S.D.; Tershakovec, A.M.; Musliner, T.A.; Braunwald, E.; Califf, R.M. IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N. Engl. J. Med.,* **2015**, *372*(25), 2387-2397. http://dx.doi.org/10.1056/NEJMoa1410489 PMID: 26039521

[99] Arbel, R.; Hammerman, A.; Azuri, J. Usefulness of Ezetimibe Versus Evolocumab as Add-On Therapy for Secondary Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus. *Am. J. Cardiol.,* **2019**, *123*(8), 1273-1276. http://dx.doi.org/10.1016/j.amjcard.2019.01.021 PMID: 30711247

[100] Kostapanos, M.S.; Spyrou, A.T.; Tellis, C.C.; Gazi, I.F.; Tselepis, A.D.; Elisaf, M.; Liberopoulos, E.N. Ezetimibe treatment lowers indicators of oxidative stress in hypercholesterolemic subjects with high oxidative stress. *Lipids,* **2011**, *46*(4), 341-348. http://dx.doi.org/10.1007/s11745-011-3539-z PMID: 21359598

[101] Qin, L.; Yang, Y.B.; Yang, Y.X.; Zhu, N.; Li, S.X.; Liao, D.F.; Zheng, X.L. Anti-inflammatory activity of ezetimibe by regulating NF-κB/MAPK pathway in THP-1 macrophages. *Pharmacology,* **2014**, *93*(1-2), 69-75. http://dx.doi.org/10.1159/000357953 PMID: 24557496

[102] Chiba, T.; Sakurada, T.; Watanabe, R.; Yamaguchi, K.; Kimura, Y.; Kioka, N.; Kawagishi, H.; Matsuo, M.; Ueda, K.; Fomiroid, A. Fomiroid A, a novel compound from the mushroom Fomitopsis nigra, inhibits NPC1L1-mediated cholesterol uptake *via* a mode of action distinct from that of ezetimibe. *PLoS One,* **2014**, *9*(12), e116162. http://dx.doi.org/10.1371/journal.pone.0116162 PMID: 25551765

[103] Molusky, M.M.; Hsieh, J.; Lee, S.X.; Ramakrishnan, R.; Tascau, L.; Haeusler, R.A.; Accili, D.; Tall, A.R. Metformin and AMP Kinase Activation Increase Expression of the Sterol Transporters ABCG5/8 (ATP-Binding Cassette Transporter G5/G8) With Potential Antiatherogenic Consequences. *Arterioscler. Thromb. Vasc. Biol.,* **2018**, *38*(7), 1493-1503. http://dx.doi.org/10.1161/ATVBAHA.118.311212 PMID: 29853564

[104] Shimada, Y.J.; Cannon, C.P. PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors: past, present, and the future. *Eur. Heart J.,* **2015**, *36*(36), 2415-2424. http://dx.doi.org/10.1093/eurheartj/ehv174 PMID: 25971287

[105] Poirier, S.; Mayer, G.; Poupon, V.; McPherson, P.S.; Desjardins, R.; Ly, K.; Asselin, M-C.; Day, R.; Duclos, F.J.; Witmer, M.; Parker, R.; Prat, A.; Seidah, N.G. Dissection of the endogenous cellular pathways of PCSK9-induced low density lipoprotein receptor degradation: evidence for an intracellular route. *J. Biol. Chem.,* **2009**, *284*(42), 28856-28864. http://dx.doi.org/10.1074/jbc.M109.037085 PMID: 19635789

[106] Norata, G.D.; Tibolla, G.; Catapano, A.L. Targeting PCSK9 for hypercholesterolemia. *Annu. Rev. Pharmacol. Toxicol.,* **2014**, *54*(1), 273-293. http://dx.doi.org/10.1146/annurev-pharmtox-011613-140025 PMID: 24160703

[107] Chan, J.H.; Lim, S.; Wong, W.S. Antisense oligonucleotides: from design to therapeutic application. *Clin. Exp. Pharmacol. Physiol.,* **2006**, *33*(5-6), 533-540. http://dx.doi.org/10.1111/j.1440-1681.2006.04403.x PMID: 16700890

[108] van Poelgeest, E.P.; Hodges, M.R.; Moerland, M.; Tessier, Y.; Levin, A.A.; Persson, R.; Lindholm, M.W.; Dumong Erichsen, K.; Ørum, H.; Cohen, A.F.; Burggraaf, J. Anti-

sense-mediated reduction of proprotein convertase subtilisin/kexin type 9 (PCSK9): a first-in-human randomized, placebo-controlled trial. *Br. J. Clin. Pharmacol.,* **2015**, *80*(6), 1350-1361. http://dx.doi.org/10.1111/bcp.12738 PMID: 26261033

[109] Shan, L.; Pang, L.; Zhang, R.; Murgolo, N.J.; Lan, H.; Hedrick, J.A. PCSK9 binds to multiple receptors and can be functionally inhibited by an EGF-A peptide. *Biochem. Biophys. Res. Commun.,* **2008**, *375*(1), 69-73. http://dx.doi.org/10.1016/j.bbrc.2008.07.106 PMID: 18675252

[110] Ridker, P.M.; Tardif, J-C.; Amarenco, P.; Duggan, W.; Glynn, R.J.; Jukema, J.W.; Kastelein, J.J.P.; Kim, A.M.; Koenig, W.; Nissen, S.; Revkin, J.; Rose, L.M.; Santos, R.D.; Schwartz, P.F.; Shear, C.L.; Yunis, C. SPIRE Investigators. Lipid-Reduction Variability and Antidrug-Antibody Formation with Bococizumab. *N. Engl. J. Med.,* **2017**, *376*(16), 1517-1526. http://dx.doi.org/10.1056/NEJMoa1614062 PMID: 28304227

[111] Roth, E.M.; Goldberg, A.C.; Catapano, A.L.; Torri, A.; Yancopoulos, G.D.; Stahl, N.; Brunet, A.; Lecorps, G.; Colhoun, H.M. Antidrug Antibodies in Patients Treated with Alirocumab. *N. Engl. J. Med.,* **2017**, *376*(16), 1589-1590. http://dx.doi.org/10.1056/NEJMc1616623 PMID: 28304229

[112] Sabatine, M.S.; Giugliano, R.P.; Keech, A.C.; Honarpour, N.; Wiviott, S.D.; Murphy, S.A.; Kuder, J.F.; Wang, H.; Liu, T.; Wasserman, S.M.; Sever, P.S.; Pedersen, T.R. FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N. Engl. J. Med.,* **2017**, *376*(18), 1713-1722. http://dx.doi.org/10.1056/NEJMoa1615664 PMID: 28304224

[113] Moriarty, P.M.; Thompson, P.D.; Cannon, C.P.; Guyton, J.R.; Bergeron, J.; Zieve, F.J.; Bruckert, E.; Jacobson, T.A.; Kopecky, S.L.; Baccara-Dinet, M.T.; Du, Y.; Pordy, R.; Gipe, D.A. ODYSSEY ALTERNATIVE Investigators. Efficacy and safety of alirocumab *vs* ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J. Clin. Lipidol.,* **2015**, *9*(6), 758-769. http://dx.doi.org/10.1016/j.jacl.2015.08.006 PMID: 26687696

[114] Bays, H.; Gaudet, D.; Weiss, R.; Ruiz, J.L.; Watts, G.F.; Gouni-Berthold, I.; Robinson, J.; Zhao, J.; Hanotin, C.; Donahue, S. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. *J. Clin. Endocrinol. Metab.,* **2015**, *100*(8), 3140-3148. http://dx.doi.org/10.1210/jc.2015-1520 PMID: 26030325

[115] Farnier, M.; Jones, P.; Severance, R.; Averna, M.; Steinhagen-Thiessen, E.; Colhoun, H.M.; Du, Y.; Hanotin, C.; Donahue, S. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial. *Atherosclerosis,* **2016**, *244*, 138-146. http://dx.doi.org/10.1016/j.atherosclerosis.2015.11.010 PMID: 26638010

[116] Kereiakes, D.J.; Robinson, J.G.; Cannon, C.P.; Lorenzato, C.; Pordy, R.; Chaudhari, U.; Colhoun, H.M. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. *American heart journal,* **2015**, *169*(6), 906-915. e913..

[117] Nissen, S.E.; Stroes, E.; Dent-Acosta, R.E.; Rosenson, R.S.; Lehman, S.J.; Sattar, N.; Preiss, D.; Bruckert, E.; Ceška, R.; Lepor, N.; Ballantyne, C.M.; Gouni-Berthold, I.; Elliott, M.; Brennan, D.M.; Wasserman, S.M.; Somaratne, R.; Scott, R.; Stein, E.A. GAUSS-3 Investigators. Efficacy and tolerability of evolocumab *vs* ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA,* **2016**, *315*(15), 1580-1590. http://dx.doi.org/10.1001/jama.2016.3608 PMID: 27039291

[118] Sabatine, M.S.; Giugliano, R.P.; Wiviott, S.D.; Raal, F.J.; Blom, D.J.; Robinson, J.; Ballantyne, C.M.; Somaratne, R.; Legg, J.; Wasserman, S.M.; Scott, R.; Koren, M.J.; Stein, E.A. Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N. Engl. J. Med.,* **2015**, *372*(16), 1500-1509. http://dx.doi.org/10.1056/NEJMoa1500858 PMID: 25773607

[119] Chaudhary, R.; Garg, J.; Shah, N.; Sumner, A. PCSK9 inhibitors: A new era of lipid lowering therapy. *World J. Cardiol.,* **2017**, *9*(2), 76-91. http://dx.doi.org/10.4330/wjc.v9.i2.76 PMID: 28289523

[120] Ray, K.K.; Landmesser, U.; Leiter, L.A.; Kallend, D.; Dufour, R.; Karakas, M.; Hall, T.; Troquay, R.P.; Turner, T.; Visseren, F.L.; Wijngaard, P.; Wright, R.S.; Kastelein, J.J. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N. Engl. J. Med.,* **2017**, *376*(15), 1430-1440. http://dx.doi.org/10.1056/NEJMoa1615758 PMID: 28306389

[121] Raal, F.J.; Kallend, D.; Ray, K.K.; Turner, T.; Koenig, W.; Wright, R.S.; Wijngaard, P.L.J.; Curcio, D.; Jaros, M.J.; Leiter, L.A.; Kastelein, J.J.P.; Investigators, O. ORION-9 Investigators. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. *N. Engl. J. Med.,* **2020**, *382*(16), 1520-1530. http://dx.doi.org/10.1056/NEJMoa1913805 PMID: 32197277

[122] Ray, K.K.; Wright, R.S.; Kallend, D.; Koenig, W.; Leiter, L.A.; Raal, F.J.; Bisch, J.A.; Richardson, T.; Jaros, M.; Wijngaard, P.L.J.; Kastelein, J.J.P. ORION-10 and ORION-11 Investigators. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N. Engl. J. Med.,* **2020**, *382*(16), 1507-1519. http://dx.doi.org/10.1056/NEJMoa1912387 PMID: 32187462

[123] Sharotri, V.; Collier, D.M.; Olson, D.R.; Zhou, R.; Snyder, P.M. Regulation of epithelial sodium channel trafficking by proprotein convertase subtilisin/kexin type 9 (PCSK9). *J. Biol. Chem.,* **2012**, *287*(23), 19266-19274. http://dx.doi.org/10.1074/jbc.M112.363382 PMID: 22493497

[124] Zaid, A.; Roubtsova, A.; Essalmani, R.; Marcinkiewicz, J.; Chamberland, A.; Hamelin, J.; Tremblay, M.; Jacques, H.; Jin, W.; Davignon, J.; Seidah, N.G.; Prat, A. Proprotein convertase subtilisin/kexin type 9 (PCSK9): hepatocyte-specific low-density lipoprotein receptor degradation and critical role in mouse liver regeneration. *Hepatology,* **2008**, *48*(2), 646-654. http://dx.doi.org/10.1002/hep.22354 PMID: 18666258

[125] Mbikay, M.; Sirois, F.; Mayne, J.; Wang, G-S.; Chen, A.;

Dewpura, T.; Prat, A.; Seidah, N.G.; Chretien, M.; Scott, F.W. PCSK9-deficient mice exhibit impaired glucose tolerance and pancreatic islet abnormalities. *FEBS Lett.,* **2010**, *584*(4), 701-706. http://dx.doi.org/10.1016/j.febslet.2009.12.018 PMID: 20026049

[126] Tikka, A.; Jauhiainen, M. The role of ANGPTL3 in controlling lipoprotein metabolism. *Endocrine,* **2016**, *52*(2), 187-193. http://dx.doi.org/10.1007/s12020-015-0838-9 PMID: 26754661

[127] Wu, L.; Soundarapandian, M.M.; Castoreno, A.B.; Millar, J.S.; Rader, D.J. LDL-Cholesterol Reduction by ANGPTL3 Inhibition in Mice Is Dependent on Endothelial Lipase. *Circ. Res.,* **2020**, *127*(8), 1112-1114. http://dx.doi.org/10.1161/CIRCRESAHA.120.317128 PMID: 32808882

[128] Kersten, S. Bypassing the LDL Receptor in Familial Hypercholesterolemia. *N. Engl. J. Med.,* **2020**, *383*(8), 775-776. http://dx.doi.org/10.1056/NEJMe2023520 PMID: 32813955

[129] Dewey, F.E.; Gusarova, V.; Dunbar, R.L.; O'Dushlaine, C.; Schurmann, C.; Gottesman, O.; McCarthy, S.; Van Hout, C.V.; Bruse, S.; Dansky, H.M.; Leader, J.B.; Murray, M.F.; Ritchie, M.D.; Kirchner, H.L.; Habegger, L.; Lopez, A.; Penn, J.; Zhao, A.; Shao, W.; Stahl, N.; Murphy, A.J.; Hamon, S.; Bouzelmat, A.; Zhang, R.; Shumel, B.; Pordy, R.; Gipe, D.; Herman, G.A.; Sheu, W.H.H.; Lee, I.T.; Liang, K.W.; Guo, X.; Rotter, J.I.; Chen, Y.I.; Kraus, W.E.; Shah, S.H.; Damrauer, S.; Small, A.; Rader, D.J.; Wulff, A.B.; Nordestgaard, B.G.; Tybjærg-Hansen, A.; van den Hoek, A.M.; Princen, H.M.G.; Ledbetter, D.H.; Carey, D.J.; Overton, J.D.; Reid, J.G.; Sasiela, W.J.; Banerjee, P.; Shuldiner, A.R.; Borecki, I.B.; Teslovich, T.M.; Yancopoulos, G.D.; Mellis, S.J.; Gromada, J.; Baras, A. Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease. *N. Engl. J. Med.,* **2017**, *377*(3), 211-221. http://dx.doi.org/10.1056/NEJMoa1612790 PMID: 28538136

[130] Raal, F.J.; Rosenson, R.S.; Reeskamp, L.F.; Hovingh, G.K.; Kastelein, J.J.P.; Rubba, P.; Ali, S.; Banerjee, P.; Chan, K.C.; Gipe, D.A.; Khilla, N.; Pordy, R.; Weinreich, D.M.; Yancopoulos, G.D.; Zhang, Y.; Gaudet, D.; Investigators, E.H. ELIPSE HoFH Investigators. Evinacumab for Homozygous Familial Hypercholesterolemia. *N. Engl. J. Med.,* **2020**, *383*(8), 711-720. http://dx.doi.org/10.1056/NEJMoa2004215 PMID: 32813947

[131] José Manuel dos Santos Pereira, de Moura; Patrícia Filipa Afonso, Pais Pacheco Mendes; Catarina Peliz, Reigota New drugs coming up in the field of lipid control. *European Society of Cardiology- eJournal of Cardiology Practice,* **2020**, *19*(8)

[132] Rosenson, R.S.; Burgess, L.J.; Ebenbichler, C.F.; Baum, S.J.; Stroes, E.S.G.; Ali, S.; Khilla, N.; Hamlin, R.; Pordy, R.; Dong, Y.; Son, V.; Gaudet, D. Evinacumab in Patients with Refractory Hypercholesterolemia. *N. Engl. J. Med.,* **2020**, *383*(24), 2307-2319. http://dx.doi.org/10.1056/NEJMoa2031049 PMID: 33196153

[133] Pouwer, M.G.; Pieterman, E.J.; Worms, N.; Keijzer, N.; Jukema, J.W.; Gromada, J.; Gusarova, V.; Princen, H.M.G. Alirocumab, evinacumab, and atorvastatin triple therapy regresses plaque lesions and improves lesion composition in mice. *J. Lipid Res.,* **2020**, *61*(3), 365-375. http://dx.doi.org/10.1194/jlr.RA119000419 PMID: 31843957

[134] Chen, K.; Rajewsky, N. The evolution of gene regulation by transcription factors and microRNAs. *Nat. Rev. Genet.,* **2007**, *8*(2), 93-103. http://dx.doi.org/10.1038/nrg1990 PMID: 17230196

[135] Turchinovich, A.; Samatov, T.R.; Tonevitsky, A.G.; Burwinkel, B. Circulating miRNAs: cell-cell communication function? *Front. Genet.,* **2013**, *4*, 119. http://dx.doi.org/10.3389/fgene.2013.00119 PMID: 23825476

[136] Papageorgiou, N.; Tousoulis, D.; Charakida, M.; Briasoulis, A.; Androulakis, E.; Tentolouris, C.; Siasos, G.; Stefanadis, C. Prognostic role of miRNAs in coronary artery disease. *Curr. Top. Med. Chem.,* **2013**, *13*(13), 1540-1547. http://dx.doi.org/10.2174/15680266113139990103 PMID: 23745806

[137] Economou, E.K.; Oikonomou, E.; Siasos, G.; Papageorgiou, N.; Tsalamandris, S.; Mourouzis, K.; Papaioanou, S.; Tousoulis, D. The role of microRNAs in coronary artery disease: From pathophysiology to diagnosis and treatment. *Atherosclerosis,* **2015**, *241*(2), 624-633. http://dx.doi.org/10.1016/j.atherosclerosis.2015.06.037 PMID: 26117399

[138] Maguire, E.M.; Xiao, Q. Noncoding RNAs in vascular smooth muscle cell function and neointimal hyperplasia. *FEBS J.,* **2020**, *287*(24), 5260-5283. http://dx.doi.org/10.1111/febs.15357 PMID: 32367680

[139] Navickas, R.; Gal, D.; Laucevičius, A.; Taparauskaitė, A.; Zdanytė, M.; Holvoet, P. Identifying circulating microRNAs as biomarkers of cardiovascular disease: a systematic review. *Cardiovasc. Res.,* **2016**, *111*(4), 322-337. http://dx.doi.org/10.1093/cvr/cvw174 PMID: 27357636

[140] Wang, G-K.; Zhu, J-Q.; Zhang, J-T.; Li, Q.; Li, Y.; He, J.; Qin, Y-W.; Jing, Q. Circulating microRNA: a novel potential biomarker for early diagnosis of acute myocardial infarction in humans. *Eur. Heart J.,* **2010**, *31*(6), 659-666. http://dx.doi.org/10.1093/eurheartj/ehq013 PMID: 20159880

[141] Katus, H.A.; Remppis, A.; Neumann, F.J.; Scheffold, T.; Diederich, K.W.; Vinar, G.; Noe, A.; Matern, G.; Kuebler, W. Diagnostic efficiency of troponin T measurements in acute myocardial infarction. *Circulation,* **1991**, *83*(3), 902-912. http://dx.doi.org/10.1161/01.CIR.83.3.902 PMID: 1999039

[142] Li, L.M.; Cai, W.B.; Ye, Q.; Liu, J.M.; Li, X.; Liao, X.X. Comparison of plasma microRNA-1 and cardiac troponin T in early diagnosis of patients with acute myocardial infarction. *World J. Emerg. Med.,* **2014**, *5*(3), 182-186. http://dx.doi.org/10.5847/wjem.j.issn.1920-8642.2014.03.004 PMID: 25225581

[143] Wilson, P.W.F.; Polonsky, T.S.; Miedema, M.D.; Khera, A.; Kosinski, A.S.; Kuvin, J.T. Systematic Review for the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. *Circulation,* **2018**, CIR0000000000000626. PMID: 30586775