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Novel lipid-modifying therapies addressing unmet needs in cardiovascular disease

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Abstract

Cardiovascular disease (CVD) remains a major cause of morbidity and mortality worldwide. Currently, it is well established that dyslipidemia is one of the major risk factors leading to the development of atherosclerosis and CVD. Statins remain the standard-of-care in the treatment of hypercholesterolemia and their use has significantly reduced cardiovascular morbidity and mortality. In addition, recent advances in lipid-modifying therapies, such as the development of proprotein convertase subtilisin/kexin type 9 inhibitors, have further improved cardiovascular outcomes in patients with hypercholesterolemia. However, despite significant progress in the treatment of dyslipidemia, there is still considerable residual risk of recurring cardiovascular events. Furthermore, in some cases, an effective therapy for the identified primary cause of a specific dyslipidemia has not been found up to date. Thus, a number of novel pharmacological interventions are under early human trials, targeting different molecular pathways of lipid formation, regulation and metabolism. This editorial aims to discuss the current clinical and scientific data on new promising lipid-modifying therapies addressing unmet needs in CVD, which may prove beneficial in the near future.

Key words: Lipid-modifying therapies; Cardiovascular disease; Dyslipidemia

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Core tip: Despite significant progress in the treatment of dyslipidemia, there is still considerable residual risk of recurring cardiovascular events. Ongoing research has led to the discovery of several different molecules involved in lipid homeostasis, which can serve as possible targets for new lipid-modifying therapies. Novel medications that have

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provided promising results in early human trials include inclisiran, bempedoic acid, seladelpar, CSL-112, apabetalone, volanesorsen, APO(a)-RX, and APO(a)-LRX. Furthermore, several other lipid-lowering agents are being evaluated in ongoing trials. Thus, there is optimism that use of these lipid-lowering medications may in the future lead to a reduction of the residual cardiovascular risk.

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INTRODUCTION

Cardiovascular disease (CVD) has consistently been the leading cause of death in the United States from 1950 through 2014^[1]. However, a significant decline in premature mortality due to heart disease is projected through 2030 in United States, attributed mainly to sustained declines in smoking, cholesterol and hypertension, which are major risk factors for CVD, as well as to presumed future advances in medical care and treatment^[2].

Undoubtedly, lipid-modifying therapies have played a crucial role in the prevention and treatment of major adverse CV events, improving the CV outcomes of patients with dyslipidemia. Statins are the standard-of-care for the treatment of hypercholesterolemia and their use is supported by extensive evidence demonstrating their effectiveness in lowering low density lipoprotein cholesterol (LDL-C) and in reducing CVD risk in both primary and secondary prevention^[3]. Furthermore, statins exert a number of pleiotropic cardioprotective effects, including improved endothelial function, reduced vascular inflammation, and reduced platelet adhesion and thrombosis, which also definitely contribute in the reduction of CVD risk^[4]. Another recent success story is the development of monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9), which cause a 54.0%-62.7% incremental reduction in LDL-C levels when administered on top of statins and are associated with a significant reduction of adverse CV events^[5,6]. Certainly, several other lipid-modifying therapies are currently being used in everyday clinical practice, such as fibrates, ezetimibe, bile acid sequestrants and niacin.

However, despite the significant progress made in the treatment of dyslipidemia, there is still considerable residual risk of recurring cardiovascular events^[7,8]. Our current pharmacological interventions are able to target a finite number of lipid pathways. For example, up to date, no specific therapy has been found, which would specifically and significantly improve high-density lipoprotein (HDL) functionality and cholesterol efflux capacity (CEC), leading to a reduction of CVD risk. Moreover, there are many rare, yet important, genetic diseases that cause dyslipidemia and hence premature CVD, for which a specific therapy has not yet been found. In addition, intolerance to certain lipid-lowering medications, especially statins, due to side effects (mostly myalgias and weakness), as well as inability to achieve the LDL-C goal despite use of maximally tolerated dose of statins, are factors that undoubtedly contribute to the residual CVD risk^[9].

Given the above, extensive research is being conducted for the development of new drugs that would reduce residual CV risk and address other unmet needs in CVD. Thus, this editorial aims to discuss the current clinical and scientific data on new promising lipid-modifying therapies addressing unmet needs in CVD, which may prove beneficial in the near future.

MEDICATIONS THAT DECREASE LDL CHOLESTEROL LEVELS

The direct association between plasma LDL-C concentration and the incidence of CVD has been unequivocally proven in many epidemiological studies. Inclisiran is a new, recently developed agent, which targets PCSK9 *via* a different route, as compared to PCSK9 monoclonal antibodies. Inclisiran, which is administered

subcutaneously, is a chemically synthesized small interfering RNA molecule, which targets the hepatic production of PCSK9, as it affects the degradation of mRNA post-transcription, thus preventing translation of PCSK9^[10]. ORION-1 was a phase 2, multicenter, double-blind, placebo-controlled, multiple ascending-dose trial of inclisiran, administered in patients at high risk for CVD with elevated plasma LDL-C concentration. Administration of a single or two doses of inclisiran was associated with marked declines in LDL-C and PCSK9 levels, as compared to placebo. The greatest LDL-C reduction (52.6%) was observed in association with the two-dose 300-mg regimen of inclisiran^[11]. An ongoing phase 3 clinical trial, ORION-11, is expected to provide more information about the cardioprotective properties of inclisiran and its long-term safety and efficacy. The results of this trial are expected to be available in late 2019^[12].

Undoubtedly, inclisiran is a new promising agent for further reduction of the residual cardiovascular risk in patients with elevated LDL-C. Furthermore, there is optimism that inclisiran only needs to be administered once every 3-6 mo, which would significantly improve compliance and comfort for the patients.

Another novel LDL-C targeting drug, which is currently under clinical trials, is ETC-1002 or bempedoic acid, a dual modulator of hepatic adenosine triphosphate-citrate lyase (ACL) and adenosine monophosphate-activated protein kinase (AMPK). Inhibition of ACL leads to reduced acetyl coenzyme A (CoA) and hence decreased 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which is the molecular target of statins. Adding to that, activation of AMPK leads to an inhibitory phosphorylation of HMG-CoA reductase and to improved glucose regulation^[9,13]. In a phase 2a clinical trial, ETC-1002 was shown to be safe and well tolerated and it significantly lowered LDL-C by up to 27% in a dose-dependent manner in patients with hypercholesterolemia^[13]. In another phase 2a clinical trial, ETC-1002 not only reduced LDL-C by 43% after 4 wk, but also decreased high sensitivity CRP (hsCRP) by 41% in patients with hypercholesterolemia and type 2 diabetes mellitus without worsening glycemic control^[14]. Moreover, ETC-1002 was shown to be effective, causing a significant reduction in LDL-C levels, when administered to patients with statin intolerance or when given as add-on therapy to statin- or ezetimibe-treated patients^[15-17].

The results of a phase 3 trial with bempedoic acid (CLEAR Wisdom Trial) were very recently presented at the American College of Cardiology 2019 Scientific Sessions. Bempedoic acid (ETC-1002), added to maximally tolerated statin therapy in patients with hypercholesterolemia and high risk for CVD, lowered LDL-C by 17.4% at 12 wk compared to placebo and maintained significant LDL-C reductions for 52 wk. In addition, bempedoic acid decreased hsCRP by 18.7%. There was no worsening of glycemic control in patients with a history of diabetes and the side effect profile of bempedoic acid was similar to that of placebo. No difference was noted for clinical outcomes, although the trial was not powered for this endpoint^[18]. Thus, further outcome studies are required to more definitely assess the role of bempedoic acid in reducing CV risk. Notwithstanding, bempedoic acid may in the future provide an additional therapeutic option to safely lower LDL-C in high CV risk patients with elevated LDL-C treated with maximally tolerated dose of statins and other lipid-modifying therapies.

Peroxisome proliferator-activated receptors (PPARs) are molecular sensors that regulate diverse aspects of lipid metabolism, thus playing a crucial role in lipid homeostasis. Three isoforms of PPARs have been described: α (NR1C1), β/δ (NR1C2) and γ (NR1C3). Fibrates are classical PPAR α agonists, whereas thiazolidinediones are potent PPAR γ agonists. PPAR β/δ agonists are not currently used in clinical practice; however, they have shown promising results in early clinical trials^[19].

Seladelpar or MBX-8025 is a selective PPAR- δ agonist, which has emerged as a promising new agent for the treatment of mixed dyslipidemia. In a multicenter, randomized, double-blind, placebo-controlled study, MBX-8025 was administered to patients with mixed dyslipidemia, alone or in combination with atorvastatin, for 8 wk. In this study, MBX-8025 reduced LDL-C by 18%-43%, triglycerides by 26%-30% and hsCRP by 43%-72%, favorably affecting multiple metabolic parameters. The administration of MBX-8025 was safe and generally well-tolerated^[20]. Moreover, MBX-8025 produced substantial reductions in small and very small LDL particles, which translated to reversal of the small dense LDL phenotype in the vast majority of participants^[21]. Although these initial results with the use of MBX-8025 appear very promising, further large clinical studies are required to definitely ascertain that the use of MBX-8025 (or another PPAR β/δ agonist) will be truly associated with a reduction in CV risk.

MEDICATIONS THAT INCREASE HDL CHOLESTEROL LEVELS AND/OR FUNCTIONALITY

The inverse association of HDL cholesterol (HDL-C) with future risk of CVD has been unequivocally demonstrated in several epidemiological studies. Although the concept of developing a drug that would raise HDL-C levels and subsequently reduce CV risk exists for many years, no selective HDL-C-raising medication has proven its atheroprotective properties in previous clinical trials. In fact, our current knowledge indicates that HDL functionality plays a much more crucial role in atheroprotection than circulating HDL-C levels^[22].

A reconstituted infusible human apolipoprotein A-I (ApoA-I), CSL-112, is under early human trials. In a phase 2a, randomized, double-blind, multicenter, dose-ranging trial, a single intravenous infusion of CSL-112 in patients with stable atherosclerotic disease was shown to be safe and well tolerated. It produced marked and rapid dose-dependent increases in ApoA-I levels (up to 145% increase in the 6.8-g group after 2 h from the time of administration). In addition, total CEC, a key metric of HDL functionality was increased up to 3.1-fold, as compared with placebo^[23]. In another phase 2b trial, 4 consecutive weekly infusions of CSL-112, administered to patients with a recent acute myocardial infarction, induced an increase in ApoA-I levels, HDL-C levels, as well as CEC, and preferentially ATP-binding cassette transporter A1 (ABCA1)-dependent CEC, in a dose-dependent manner and with no significant side effects^[24]. Given the above, CSL-112 appears to be a very promising new therapeutic intervention for patients with CVD and currently a phase 3 trial is ongoing to assess the potential benefit of CSL-112 in reducing major adverse CV events in patients with acute coronary syndrome. The results of this trial are expected to be available in 2022^[25].

Apabetalone or RVX-208 is an orally active small molecule, which increases ApoA-I transcription through an epigenetic mechanism that is mediated by bromodomain and extra-terminal domain (BET) protein 4 (BRD4)^[26]. In a multicenter, randomized, double-blind, placebo-controlled study, RVX-208 was administered at varying doses twice daily for 12 wk to statin-treated patients with stable coronary artery disease (CAD). In this study, administration of RVX-208 led to a significant, dose-dependent increase of ApoA-I levels by up to 5.6%. HDL-C levels were also increased by 3.2% to 8.3%, with increasing doses of RVX-208. In addition, there was an increase of the large HDL particles. Transient and reversible elevations in liver transaminases, but with no associated increase in bilirubin levels, were observed in some patients treated with RVX-208^[27]. Another study, which retrospectively analyzed the clinical data from two randomized, double-blind, placebo-controlled, similarly designed phase 2b clinical trials of RVX-208 treatment over 6 mo in patients with CAD (SUSTAIN and ASSURE trials), demonstrated a statistically significant increase in HDL-C, ApoA-I, large HDL particles, and average HDL particle size of 7.69%, 10.3%, 30.7%, and 1.16%, respectively, versus placebo. Moreover, a post-hoc analysis showed lower instances of major adverse cardiac events in patients receiving RVX-208^[28]. In addition, there is evidence suggesting that RVX-208 may exert some protective effects against the development of type 2 diabetes^[29]. Notwithstanding, further studies will be required to better define the role of RVX-208 in the reduction of the risk for CVD.

MEDICATIONS THAT DECREASE TRIGLYCERIDE LEVELS

ApoC-III is another molecule that plays an important regulative role in lipoprotein metabolism. ApoC-III raises plasma triglycerides through inhibition of lipoprotein lipase (LPL), an enzyme essential for the hydrolysis and distribution of triglyceride-rich lipoproteins (TRLs) to extrahepatic tissues, as well as through stimulation of very low-density lipoprotein secretion and *via* prevention of the hepatic clearance of TRL-remnants by the LDL receptor^[30]. Elevated plasma triglyceride levels are associated with CVD and clinical studies have clearly shown that non-fasting triglyceride levels are strongly predictive of ischemic events and all-cause mortality, even when differences in plasma HDL-C are taken into account^[30]. Epidemiological evidence shows that carriers of loss-of-function mutations of the ApoC-III gene have 39% lower triglycerides, 22% higher HDL-C, and 16% lower LDL-C plasma concentrations. More importantly, their risk of coronary heart disease is reduced by 40%^[31].

Given the above, reduction of ApoC-III plasma levels has emerged as a promising therapeutic strategy to decrease risk for CVD. This has led to the development of volanesorsen or ISIS 304801, which is a human antisense oligonucleotide (ASO) that binds to mRNA of the ApoC-III gene and blocks its expression. In a randomized, double-blind, placebo-controlled, dose-ranging, phase 2 study, ISIS 304801,

administered as a single agent to patients with hypertriglyceridemia, produced dose-dependent mean reductions in APOC-III levels of up to 79.6% and reductions in triglycerides of up to 70.9%. No safety concerns related to the use of ISIS 304801 were identified in this study^[32]. In another study, volanesorsen (ISIS 304801), administered to patients with hypertriglyceridemia, including familial chylomicronemia syndrome, uniformly lowered ApoC-III on ApoB-100, lipoprotein (a) [Lp(a)] and ApoA-I. Thus, it was suggested that volanesorsen may be a potent agent to reduce triglycerides and CV risk mediated by ApoC-III^[33]. In addition, there is evidence that volanesorsen may be an especially useful treatment option for patients with hypertriglyceridemia and type 2 diabetes mellitus, as it improves glucose disposal, insulin sensitivity and various integrative markers of diabetes after short treatment^[34]. Given the above, volanesorsen appears to be a novel promising therapy for hypertriglyceridemia, which may also decrease the burden associated with certain genetic diseases causing hypertriglyceridemia, such as the familial chylomicronemia syndrome^[35]. Notwithstanding, further investigation on the long-term efficacy and safety of volanesorsen is warranted.

MEDICATIONS THAT DECREASE LIPOPROTEIN (a) LEVELS

There is extensive clinical evidence demonstrating that elevated Lp(a) levels is an independent causative risk factor for CVD and aortic stenosis. Current treatments that are being used to decrease Lp(a) include nicotinic acid, aspirin and, in more severe cases, lipoprotein apheresis. Statins may raise Lp(a) by 10%-20% but are also being used in patients with elevated Lp(a) levels only to decrease LDL-C levels and reduce CVD risk. PCSK9 inhibitors have also been shown to reduce Lp(a) levels by approximately 30%, but up to date they have not been approved for the treatment of high Lp(a) levels^[36]. The causality of the relation between Lp(a) and CVD is considered significant and hence the concept of developing drugs that effectively reduce Lp(a) exists for many years. However, it is difficult to target Lp(a), as it has no enzymatic activity and it cannot be feasibly targeted with small molecules or monoclonal antibodies. RNA therapeutics, and specifically ASOs, represent an elegant method to reduce circulating Lp(a). Thus, APO(a)-Rx and APO(a)-LRx were developed, which are ASOs that are administered subcutaneously, inhibiting the synthesis of the atherogenic Apo(a), which is primarily synthesized in the liver^[37].

In a randomised, double-blind, placebo-controlled, phase 1 clinical study, participants were treated with a single subcutaneous injection or with six injections of APO(a)-Rx at varying doses. The single injection regimen did not provide any reduction in Lp(a) plasma levels. However, the six injections of APO(a)-Rx resulted in dose-dependent decreases in plasma Lp(a) levels with the highest administered dose of 300 mg being the most effective treatment, as it produced a 77.8% reduction in Lp(a) levels from baseline. Similar reductions were observed in the amount of oxidized phospholipids associated with ApoB-100 and Apo(a). The treatment with APO(a)-Rx was safe and generally well-tolerated, as the most common adverse events were mild injection site reactions^[38]. In a phase 2 trial of APO(a)-Rx, which was administered subcutaneously once a week for 12 wk in an ascending-dose design, similar reductions in Lp(a) levels of 66.8%-71.6% were observed^[39]. In a phase 1/2a trial of the other developed agent, APO(a)-LRx, the highest administered dose of 40 mg provided a decrease of 92% in Lp(a) levels after six doses in healthy human volunteers. Both agents were also safe^[39]. Thus, these new agents targeting the synthesis of Apo(a) may assist clinicians to effectively diminish Lp(a)-mediated cardiovascular risk.

A summary of the mechanisms of action of the aforementioned novel lipid-modifying therapies is shown in [Table 1](#). In addition, the molecular pathways of action and effects of the aforementioned novel lipid-modifying therapies are shown in [Figure 1](#).

ON THE HORIZON

Liver X receptors (LXRs) are members of the nuclear receptor superfamily of DNA-binding transcription factors and act as sensors of cholesterol homeostasis. LXRs mediate physiological responses to cellular and systemic cholesterol overload, including the upregulation of the reverse cholesterol transport (RCT), thus having cardioprotective effects against atherosclerosis. The development of drugs that stimulate LXRs have emerged as a new promising therapeutic intervention^[40,41]. There are two isoforms of LXRs; LXR α and LXR β . XL-652 or BMS-779788 is a partial LXR agonist with LXR β selectivity. When tested in nonhuman primates, XL-652 appears to

Table 1 Mechanisms of action of novel lipid-modifying therapies addressing unmet needs in cardiovascular disease

| Novel pharmacological agent | Mechanism of action |
|-----------------------------|---|
| Inclisiran | Small interfering RNA targeting the hepatic synthesis of PCSK9 |
| Bempedoic Acid | Inhibition of hepatic ACL and activation of AMPK |
| Seladelpar | Selective PPAR- δ agonist |
| CSL-112 | Reconstituted infusible human ApoA-I |
| Apabetalone | Increase of ApoA-I transcription acting on bromodomain and extra-terminal domain (BET) protein 4 (BRD4) |
| Volanesorsen | Human ASO inhibiting the expression of mRNA of the ApoC-III gene |
| APO(a)-Rx and APO(a)-LRx | ASOs inhibiting the synthesis of the apolipoprotein (a) |
| XL-652 | Partial LXR agonist with LXR β selectivity |
| Allicin | Upregulation of ABCA1 expression in macrophage-derived foam cells |
| ACP-501 | Recombinant human LCAT |

PCSK9: Proprotein convertase subtilisin/kexin type 9; ACL: Adenosine triphosphate-citrate lyase; AMPK: Adenosine monophosphate-activated protein kinase; PPAR: Peroxisome proliferator-activated receptor; ApoA-I: Apolipoprotein A-I; ASO: Antisense oligonucleotide; LXR: Liver X receptor; ABCA1: ATP-binding cassette transporter A1; LCAT: lecithin-cholesterol acyltransferase.

have decreased lipogenic potential, as compared with a full pan agonist, but with similar potency in the induction of genes known to stimulate RCT^[42]. XL-652 has also been proven to be safe enough to continue with clinical trials^[19].

Another important molecule involved in lipid homeostasis is ABCA1, which has a critical role in modulating efflux of tissue cholesterol and phospholipids into the RCT pathway, thus clearing excess cholesterol from macrophages and preventing atherosclerosis. There is a clinical entity, known as Tangier disease, which is caused by mutations of the ABCA1 gene leading to ABCA1 deficiency^[43]. Allicin is a novel anti-atherosclerotic molecule with anti-oxidant and anti-inflammatory properties, which can be extracted from garlic. Allicin has been shown to reduce lipid accumulation through the upregulation of ABCA1 expression in macrophage-derived foam cells^[44]. Furthermore, in a randomized, placebo-controlled, clinical trial, the oral administration of a garlic powder tablet, containing 1200 mg of allicin, twice daily for 3 mo, was shown to be superior to placebo in the prevention of carotid intima-media thickness progression in patients with CAD^[45]. Another novel promising molecule, which has also been shown in animal studies to up-regulate ABCA1-mediated cholesterol efflux and retard atherosclerosis, is apigenin, a natural flavonoid compound^[46]. Thus, given the above, allicin (and possibly apigenin) may be proven useful in the future for the management of CVD and may also potentially have a place in the treatment of patients with Tangier disease with some residual ABCA1 activity.

Lecithin-cholesterol acyltransferase (LCAT) is a key enzyme for the esterification of cholesteryl esters in plasma, promoting also the formation of HDL and enhancing RCT. Mutations in the human LCAT gene underlie either familial LCAT deficiency (FLD) or fish-eye disease (FED)^[47]. In this regard, the infusion of recombinant human LCAT is a promising therapeutic option that remains to be explored. In a phase 1b, open-label, single-dose escalation study, a single intravenous infusion of a recombinant human LCAT (ACP-501) had an acceptable safety profile and led to significant dose-proportional increases of both LCAT and HDL-C, as well as to a favorable modification of HDL metabolism. The results of this study provide support for the use of recombinant human LCAT in future clinical trials in patient with CHD and/or FLD^[48]. In a first-in-human treatment with enzyme replacement in FLD, ACP-501 infusion therapy improved the anemia, stabilized the renal function, transiently normalized plasma lipids, and favorably modified HDL metabolism. Moreover, ACP-501 therapy was safe and well-tolerated^[49]. Hence, the results of these studies are encouraging and support continued development of the recombinant human LCAT therapy.

Last but not least, it should be noted that many other novel lipid-modifying therapies are being currently tested in ongoing trials. These therapies include medications that target protein asialoglycoprotein receptor 1, angiopoietin-related protein 4, desmocollin 1 and many other molecules playing significant roles in lipid homeostasis^[50,51].

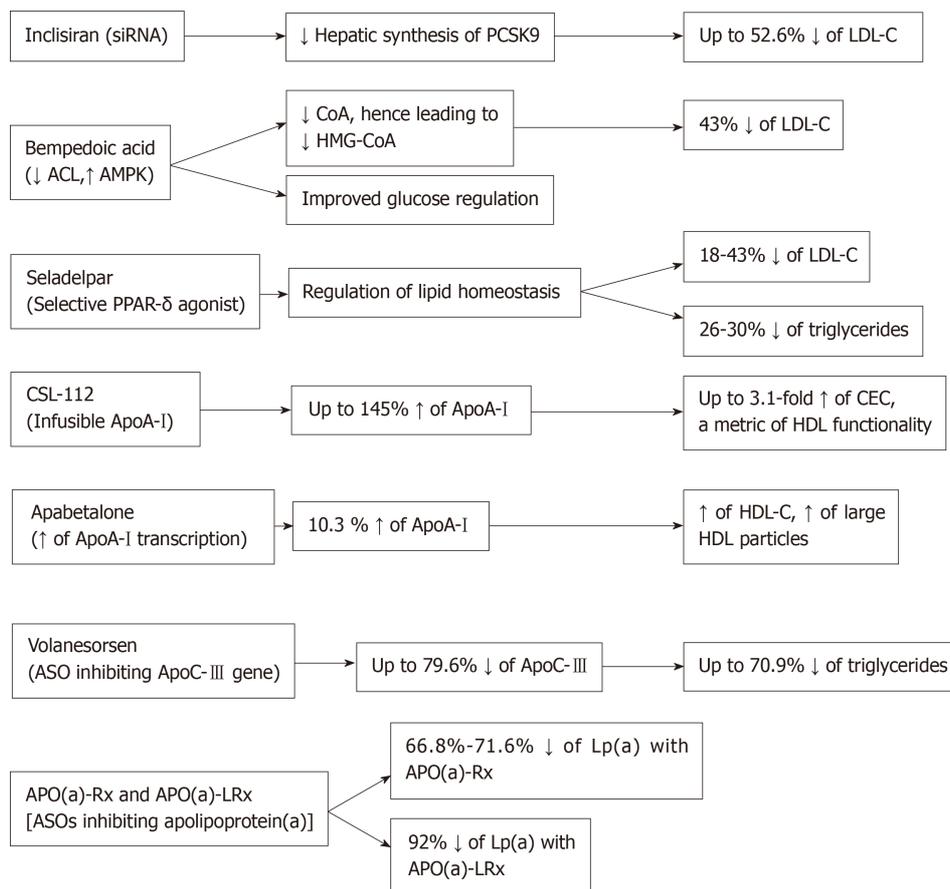


Figure 1 Molecular pathways of action and effects of novel lipid-modifying therapies addressing unmet needs in cardiovascular disease. siRNA: Small interfering RNA; ACL: Adenosine triphosphate-citrate lyase; AMPK: Adenosine monophosphate-activated protein kinase; PPARs: Peroxisome proliferator-activated receptors; Apo: Apolipoprotein; ASO: Antisense oligonucleotide; PCSK9: Proprotein convertase subtilisin/kexin type 9; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA; Lp(a): Lipoprotein (a); LXRs: Liver X receptors; LDL-C: Low-density lipoprotein cholesterol; CEC: Cholesterol efflux capacity.

CONCLUSION

It has been well established that despite the significant progress made in the management of CVD, there are still several unmet needs to be addressed. Currently, various lipid-modifying therapies are being evaluated in ongoing trials, targeting a number of different molecules involved in lipid homeostasis. There is optimism that some of these lipid-modifying therapies will be proven clinically beneficial and will eventually enter everyday clinical practice, hence enhancing the armamentarium for the optimal management of CV risk in dyslipidemic patients. Even if some of these drugs do not succeed in future trials, undoubtedly, we will still be a step forward towards a better understanding of the pathogenesis of atherosclerosis and to creating a better future for our patients, decreasing the risk of CVD.

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