Evolving Concepts in LDL-Lowering Strategies: Are We There?

Giovanni Cimmino 1, Francesco S Loffredo2, Giulia Arena1 and Paolo Golino1*

1Department of Cardio-Thoracic and Respiratory Sciences, Section of Cardiology, Second University of Naples, Naples, Italy
2Molecular Cardiology, International Centre for Genetic Engineering and Biotechnology, Trieste, Cardiovascular Department, Ospedale Riuniti and University of Trieste, Trieste, Italy

*Corresponding author: Paolo Golino, Department of Cardio-Thoracic and Respiratory Sciences, Section of Cardiology, Second University of Naples, via Leonardo Bianchi, 1 80131 Naples, Italy. Tel: +39-0823-306001; Fax: +39-0823-232395; E-mail: paolo.golino@unina2.it

Received date: September 02, 2016; Accepted date: October 10, 2016; Published date: October 17, 2016

Copyright: © 2016 Cimmino G, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

High plasma levels of low density lipoproteins (LDLs) represent one of the major risk factors for cardiovascular disease, as shown by many epidemiological studies. On the other hand, randomized trials designed to address the clinical impact of lipid lowering interventions, have clearly shown that reduction in LDL plasma levels lead to a significant decrease in major cardiovascular events. Based on these observations, pharmacological modulation of LDLs has been highly investigated. Statins, alone or in combination, represent the most powerful agents to date available to reach the LDLs levels suggested by the current guidelines. However, in some patients the recommended LDLs reduction is difficult to be achieved because of genetic background (familial hypercholesterolemia), side effects (statin intolerance), or simply because of a non-sufficient response. In the last few years, our understanding of the basic mechanisms involved in the lipoprotein metabolism has progressed significantly. The crucial role of proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged. The main characterized function of PCSK9 relates to the binding to LDL-C receptors (LDLR) in hepatocytes. However, PCSK9 does not interfere with the binding between LDL and its own receptor, but with the ability of the latest to return to the surface of the hepatocyte and bind new LDL molecules. Based on these observations, blocking PCSK-9 may reduce the LDLR clearance, thus increasing the ability of LDLR to remove circulating LDLs. Pharmacological inhibition of this protein has been proposed as new therapeutic approach. The clinical evidence available to date seem to fully support this hypothesis.

Keywords: Lipoproteins; Statin; PCSK9; Cardiovascular risk

Introduction

Several epidemiological studies have clearly shown the existence of a tight correlation between lipid levels in blood and atherosclerotic cardiovascular disease (CVD) [1]. The term hyperlipidemia refers to increased levels of lipids in the blood, including cholesterol and triglycerides. The main issue related to hyperlipidemia is that this condition does not cause symptoms, but it can silently and significantly increase the risk of developing CVD. The deposition of lipids is progressive and occurs in the arterial wall of almost all vascular district, such as vessels supplying the heart (coronary artery disease), brain (cerebrovascular disease), and limbs (peripheral vascular disease) [2]. Acute thrombus formation superimposed on a pre-existing plaque and the subsequent blood flow reduction is responsible for the conversion of atherosclerosis from a chronic disease to an acute medical emergency, such as acute coronary syndromes (ACS), stroke and related problems [3]. Because of this risk, treatment is highly recommended for people with hyperlipidemia [4]. Based on the current guidelines, dietary approach and weight loss is the first recommendation [5]. In case of failure, pharmacological modulation is indicated. Inhibition of the HMG-CoA reductase by statins, the enzyme involved in the first metabolic step of endogenous production of cholesterol, is one the most powerful treatment used. Clinical trials have shown the relevant impact of statins in reducing cardiovascular risk both in primary and secondary prevention [6-9]. However, despite of their power, alone or in combination with other lipid lowering medications, there are groups of patients in which statins are: 1) contraindicated for intolerance (such as muscle pain and/or liver dysfunction), 2) not powerful enough to achieve the recommended cholesterol value based on the risk stratification, 3) not efficient for unfavorable genetic background, such as in patients with heterozygous familial hypercholesterolemia (FH) or homozygous FH [10]. In the last fifteen years, our understanding of the basic mechanisms involved in the cholesterol metabolism has progressed significantly, thus identifying new possible pharmacological targets. The discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) in 2003 [11] opened a new molecular and therapeutical scenario. This protein is a crucial factor in the clearance pathway of low-density lipoproteins (LDLs) and its inhibition appears to be highly effective in reducing LDLs levels. This review will discuss the available data on the safety and effectiveness of PCSK9 inhibition starting from the biological mechanisms to its role in the clinical setting.

Cholesterol Metabolism and Regulation

Endogenous and exogenous pathway

Despite the inverse correlation between plasma levels and free-events survival, cholesterol is an extremely important molecule for several biological processes. It has roles in membrane structure as well as being a precursor for the synthesis of the steroid hormones, the bile acids, and vitamin D [12]. Body cholesterol, derived from both the diet and de novo synthesis, because of its hydrophobic property, is transported through the circulation in lipoprotein particles. Two major lipoprotein vehicles have been identified and are inversely correlated to
cardiovascular risk: low-density lipoproteins (LDLs) or the so-called "bad" cholesterol, and high-density lipoproteins (HDLs) indicated as "good" cholesterol [13,14]. Due to its important role in membrane function, all cells express the enzymes of cholesterol biosynthesis. The first step in cholesterol production is the mitochondrial or cytosolic formation of acetyl-CoA from an oxidation reaction that involves fatty acids or pyruvate (in mitochondria) or ethanol (in cytosol). Acetyl-CoAs are converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) which, under the activity of the HMG-CoA reductase become mevalonate. Mevalonate is converted to the isoprene based molecule, isopentenyl pyrophosphate (IPP), with the concomitant loss of CO2. The IPP turned to squalene and then to cholesterol. Thus, HMG-CoA reductase is the rate-limiting enzyme in cholesterol synthesis [15].

Intestinal absorption of cholesterol begins with the formation of micelles containing bile acids, phospholipids, and hydrolytic products of triglycerides. This step is critical to allow diffusion across the unstirred water layer at the intestinal brush border membrane. The apexes of enterocytes express Niemann-Pick CI-Like 1 (NPC1L1) protein that has a crucial role in intestinal cholesterol absorption acting as a sterol transporter. After entering the enterocyte via a NPC1L1-dependent pathway, cholesterol is esterified in large amount and then incorporated into the nascent chylomicron, along with triglycerides, some non-esterified cholesterol, and apolipoprotein B48. These particles are then secreted into lymph across the basolateral membrane of enterocytes and are transported to the bloodstream via the lymphatic system. The remaining non-esterified quote of cholesterol may be transported to the basolateral membrane of the enterocyte for biogenesis of HDL mediated by ATP binding cassette type A1 (ABCA1) [16,17].

Circulating chylomicrons are target of the lipoprotein lipase that hydrolyzes triglycerides for utilization and storage by peripheral tissues such as fat and muscle. The majority of cholesterol in the chylomicron remnant is delivered to the liver [18,19].

Dietary cholesterol as well as any cholesterol synthesized by the liver is transported in the serum within LDLs if it exceeds hepatic needs. The liver synthesizes VLDLs and these are converted to LDLs through the action of endothelial cell-associated lipoprotein lipase (LPL). Cholesterol found in plasma membranes can be extracted by HDLs and esterified by the HDL-associated enzyme lecithin-cholesterol acyltransferase, LCAT. The cholesterol acquired from peripheral tissues by HDLs can then be transferred to VLDLs and LDLs via the action of cholesteryl ester transfer protein (CETP), which is associated with HDLs. Reverse cholesterol transport allows peripheral cholesterol to be returned to the liver in LDLs. Ultimately, cholesterol is excrated in the bile as free cholesterol or as bile salts following conversion to bile acids in the liver [20].

Based on the multiple steps required for cholesterol biosynthesis, pharmacological modulation may include two different strategies: lowering LDLs and increasing HDLs. Two major proteins have been identifying to address the first point: HMG-CoA reductase and NPC1L1, as summarized in Figure 1.

HDL increasing therapy, although potentially interesting, still remains an unmet clinical need as clinical studies using different pharmacological approaches leading to increase in HDL plasma levels have failed to demonstrate a reduction in CV events [21]; this approach will be not discussed in this review.

Figure 1: Schematic view of cholesterol metabolism (endogenous and exogenous pathway) and regulation. It is highlighted the modulation by the available drugs (inhibitors of HMG-CoA reductase, inhibitors of intestinal cholesterol absorption and inhibitors of PCSK9).

Discovery of PCSK9 and its biological role in cholesterol homeostasis

In 2003, proprotein convertase subtilisin/kexin type 9 (PCSK9) was discovered [11]. Since this first report, several other data have been published highlighting the key regulatory role of this protein in LDL receptor homeostasis [22]. Genetic studies have confirmed that according the type of mutations of PCSK9 (loss of function [LOF] or gain of function [GOF]) patients may have hypocholesterolemia or hypercholesterolemia [23,24]. Based on the results of these observations pharmacological modulation of PCSK9 has been explored as a promising therapeutic approach to decrease LDL cholesterol levels.

Once secreted, PCSK9 binds to the LDL receptor on the surface of cells and the complex PCSK9-LDL receptor is internalized [25]. Interestingly, the binding of PCSK9 to the LDL receptor results in the redistribution of LDL receptors from the cell surface to lysosomes. The acidic environment of the endosome increases the affinity of this binding by nearly 150-fold. The internalized complex undergoes to degradation in lysosomes, thus preventing LDL receptors from recycling to cells surface with the final event to increase circulating LDLs [26]. This effect may explain the low LDL cholesterol levels associated with the LOF mutation and high LDL cholesterol levels correlated with the GOF mutants. It has been postulated that the binding of PCSK9 induces conformational modifications in the LDL receptor that renders it incapable of being sorted to recycling endosomes. Alternatively, the PCSK9-LDL receptor complex could be actively recognized and directed toward lysosomes. Therefore, if PCSK9 is blocked, more LDL receptors will be present on the surface of liver cells and will remove more LDLs from the blood, thus lowering blood cholesterol levels.
Cholesterol Lowering Therapy and Cardiovascular Risk Reduction

Inhibition of HMG-CoA reductase and role of statins

Several epidemiological studies have confirmed and expanded the first observation by the FRAMINGHAM study in the 1959s [27,28], establishing a firm correlation between high plasma cholesterol levels and cardiovascular mortality [29]. Based on these data, an intensive research began, in the attempt to find a pharmacological compound able to reduce cholesterol blood levels.

Discovery of inhibitors of HMG-CoA reductase came out during intense studies performed on antibiotics. The main hypothesis was that antibiotics were able to inhibit many different kinds of enzymes, like HMG-CoA reductase to fight against other microbes that required sterols or other isoprenoids for growth [30]. From these studies the first HMG-CoA reductase inhibitor was isolated, the compactin [30]. Despite of its efficacy in lowering blood levels of cholesterol, compactin was discontinued in 1980 because of a report showing correlation with lymphoma in dogs receiving this compound [30]. From that moment, intensive research began on HMG-CoA reductase inhibitors, leading to the discovery and clinical use of Lovastatin in 1986. That was the first commercial statin available for clinical use. Since its introduction, 6 statins, including 2 semi-synthetic statins (simvastatin and pravastatin) and 4 synthetic statins (fluvastatin, atorvastatin, rosuvastatin and pitavastatin) have been discovered and released to the market. Efficacy of statins has been tested in many large-scale clinical trials, involving thousands of subjects and concluding that treatment with statins lowers plasma LDL levels by 25–35% and reduces the frequency of heart attacks by 25–30%. This effect was even higher, in terms of percentage reduction in coronary events, if the treatment were longer and statin therapy were started earlier, and more powerful if intermediate or high dose was given [7,8,14,31-33]. Since the discovery of statins, several randomized clinical trials have been performed enrolling thousands of patients. In a couple of year three mega-trials came out. The Scandinavian Simvastatin Survival Study (45) [34], the WOSCOPS [35], and the CURE [36], showing the benefits of statin therapy in primary and secondary prevention. The results of these three trials were confirmed by two later study, the LIPID (addressing the role of statin therapy in secondary prevention) [37] and the AFCAPS/TexCAPS trial (a primary prevention study emphasizing that lipid lowering intervention in patients at higher risk will bring a bigger impact at lower cost) [38].

Because of other “pleiotropic effects” of statins beyond cholesterol lowering, such as improving endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response [39], other clinical trials have evaluated these properties using high dose of statin: the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study [40] and the Atorvastatin Versus Revascularization Treatment (AVERT) study [41]. The Heart Protection Study (HPS) firmly established the benefit of statin therapy (based on simvastatin) in preventing adverse events, such as total mortality, major coronary events, strokes and revascularization procedures in high risk patients for atherosclerotic disease, regardless of initial lipid levels [42]. However, some studies raised serious issues about the correlation of statin use with cancer and diabetes. In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial new cancer diagnoses were more frequent in the pravastatin-treated patients [43]. However, a meta-analysis performed by the authors of previous statin trials showed no overall increase in cancer occurrence whether patients were on pravastatin or other statin drugs. In 2010 another report linked the use of statin with diabetes [44]. However, although the risk of diabetes mellitus is higher in patients receiving statins, people with established heart disease or risk factors for heart disease can get major cardiac benefit compare to the risk to develop diabetes. It is common believed that statins may simply unmask patients already at high risk to develop diabetes. Five more studies (PROVE-IT, A to Z trial, REVERSAL, ALLIANCE, TNT), support the use of higher-dose ‘aggressive’ statin therapy in high-risk patients to get more benefits.

Based on the trials published to date, no more doubts exist on the benefit of statin treatment. In secondary prevention the mean number needed to treat (NNT) to reduce a primary end-point is 38 (range 19–56), compared to a mean NNT of 85 (31–250) in the primary prevention. Thus, risk stratification for future cardiovascular events will be crucial to identify patients that can benefit of the statin therapy beyond the plasma lipid levels.

Inhibition of intestinal cholesterol absorption as “add-on” therapy

Clinical trials on statin therapy have clearly shown that the more aggressive the lipid lowering treatment is, the more benefits the high risk cardiovascular patient will get. Thus, a combination therapy to lower cholesterol has been proposed. The discovery of NPC1L1 protein and its pharmacological modulation by a new drug, namely ezetimibe, has offered a new opportunity for this combination treatment. Ezetimibe is a selective and potent inhibitor of NPC1L1, thus reducing intestinal cholesterol absorption. This effect stimulates, in turn, upregulation of LDL receptors in the liver [45]. In 2015 the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) has been published, confirming that the addition of ezetimibe to simvastatin in patients presenting with ACS, resulted in further lowering of LDLs, as compared with simvastatin alone, with an associated improvement in cardiovascular outcomes, defined as cardiovascular death, nonfatal myocardial infarction (MI), unstable angina requiring rehospitalization, coronary revascularization, or nonfatal stroke [46]. The average LDL cholesterol level during this study was 53.7 mg/dL in combination group and 69.5 mg/dL in statin group alone [46]. Two main messages come out for the IMPROVE-IT: first, combination therapy may further lower the LDL cholesterol levels up to 50 mg/dL; second, lowering LDL cholesterol even below 70 mg/dL adds a greater cardiovascular protection, thus redefining the previous LDL target established by the guidelines. These findings were further supported by the PRECISE-IVUS (Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial, in which combination therapy based on atorvastatin plus ezetimibe, showed greater regression of coronary plaques as compared with statin therapy alone [47].

Based on these results, the values of ezetimibe finally appear established. The subgroups analysis performed in several clinical trials (PROVE-IT-TIMI 22, JUPITER, GREACE) [31,48,49] and the meta-analyses by Boekholdt et al. looking at all the patients with LDL levels below 70 mg/dL [50] seems definitely confirm the hypothesized approach “lower is better”.

Inhibition of PCSK9: is the future now?

Since its discovery in 2003, the crucial role of PCSK9 in cholesterol metabolism and regulation has been highlighted. Thus, research has progressed rapidly to identify compounds able to modulate the biological activity of this protein and ultimately, to evaluate its efficacy in reducing major cardiovascular events. The lesson from patients affected by mutations in PCSK9 (LOF or GOF) have defined the clinical relevance of this therapeutic approach. Thus, several strategies have been already tested and some others are currently under investigation for PCSK9 inhibition. At the moment, monoclonal antibodies to block PCSK9 activity are available. Previously published clinical trials have clearly indicated a greater efficacy of these drugs than statin therapy for decreasing LDLs. This is of great importance especially for patients who tend to discontinue the statins due to their adverse effects and/or resistance towards these drugs [51]. Combination therapy of atorvastatin (at different dose) plus PCSK9 inhibitor caused a significantly greater decrease in LDL cholesterol compared to statin alone [52]. It has been reported that administration of statins (independently of the type of statin prescribed) and even more the use of fenofibrate result in a significant PCSK9 upregulation, thereby decreasing their effectiveness [53,54].

However, even if the chance of adverse reaction is low, toxicity may occur due to individual pharmacological activity of the mAbs, interaction with the target molecule, or a reaction within the targeted tissue [55]. However, even if the chances of adverse reaction are low, toxicity may occur due to individual pharmacological activity of the mAbs, interaction with the target molecule, or a reaction within the targeted tissue [55]. Based on the current available data, the PCSK9 inhibitors appear to be well tolerated, but long-term safety is still to be confirmed. A possible disadvantage is the subcutaneous injection every two weeks.

Combination therapy of statins plus PCSK9: a marriage of convenience?

As reported above, statins and fenofibrate increase PCSK9, with a resultant decrease in LDL receptor density [56]. Increased PCSK9 may just be a response to decreased LDL receptors resulting from the statin treatment and, thus, the combination of statins and PCSK9 inhibitors seems appropriate. Moreover, it has been shown that this may also occur in diabetic patients. However, controversial data are available on the correlations among circulating PCSK9, insulin and glucose levels [57-60].

Clinical impact of PCSK9 inhibitors

In the last decade, a considerable amount of data on the clinical use of PCSK9 inhibitors has been published. In two recent meta-analysis, including up to 25 randomized controlled trials, the significant effect of PCSK9 inhibitors in decreasing LDL cholesterol with a good safety and tolerability profile has been confirmed [61,62]. At the time of this review, two mAbs against PCSK9 have been approved for clinical use: Alirocumab and Evelocumab.

Alirocumab was the first United States of America Food and Drug Administration (US FDA)-approved PCSK9 inhibitor, evaluated in several trials at various doses and different administration schedules. Independently of that, injection of alirocumab, in monotherapy as well as in combination with statins and/or ezetimibe, resulted in a strong and significant LDL cholesterol reduction [63] achieved with comparable minimal adverse events in both groups [64]. The role of alirocumab in the clinical scenario has been evaluated in a series of 13 trials involving up to 23000 patients under the name of ODYSSEY program. The major findings of these studies will be briefly discussed. In the ODYSSEY MONO, alirocumab has been shown to be more powerful than ezetimibe in reducing LDL cholesterol (47% vs. 16%) in 103 hypercholesterolemic patients with cardiovascular disease [65]. In the ODYSSEY COMBO I (52 weeks follow-up) and II (104 weeks follow-up), alirocumab has been combined with a statin at its maximum tolerated dose and its safety and efficacy has been confirmed in a high cardiovascular risk population [66-68]. In the ODYSSEY LONG TERM (Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy), high cardiovascular risk patients receiving alirocumab on top of statin therapy for 78 weeks showed an occurrence of a MACE significantly less (1.7%) than placebo (3.3%), adding for the first time significant outcomes data on the use of PCSK9 inhibitors [69].

The power of alirocumab therapy has been confirmed also in patients with familial hypercholesterolemia (FH) in the ODYSSEY FH I and II, at a population at high risk of cardiovascular events because of a genetic disorder of lipid metabolism. In both trials, patients affected by heterozygous FH (HeFH) might reduce LDL cholesterol levels up to 48% the baseline value [70].

The second monoclonal antibody inhibitor of PCSK9 which has also received FDA approval is evolocumab. As for alirocumab, this mAb has been also intensively tested in the clinical scenario. The primary analysis has been reported in the DESCARTES (Durable Effect of PCSK9 Antibody Compared with placebo Study), in which was reported a reduction in LDL cholesterol up to 57% in patients receiving evolocumab compared to 48% in patients who received atorvastatin 80 mg/day plus ezetimibe 10 mg/day in a 52 weeks period [71].

In RUTHERFORD-2 (Reduction of LDL-C with PCSK9 Inhibition in the Heterozygous Familial Hypercholesterolemia Disorder Study-2), evolocumab has been evaluated in HeFH patients showing a rapid LDL cholesterol decrease up to 60% compared with placebo [72]. Another important result came for the TESLA (Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities) study, enrolling homozygous FH (HoFH) patients (the most severe of all hypercholesterolemias), in which evolocumab treated group achieved a 30.9% decrease of LDL cholesterol at 12 weeks [73]. The OSLER (Open-label Study of Long-term Evaluation Against LDL-C) trial has attempted to investigate the long term efficacy of evolocumab. Patients in combination group (evolocumab plus standard therapy) reach an LDL cholesterol reduction up to 61% after 11 months of use vs. standard therapy alone with a safety profile [74]. Moreover, in the MENDEL-2 (Monoclonal Antibody against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2) trial, evolocumab confirmed its power in lipid lowering, demonstrating an LDL cholesterol decrease from baseline of 55–57% more than placebo and 38–40% more than ezetimibe [75]. Similar or even greater effectiveness was noted in the LAPLACE-2 (LDL-C Assessment w/PCSK9 Monoclonal Antibody Inhibition Combined with Statin Therapy-2). However, more adverse events were described in the evolocumab group, with an average rate of about 2% [76]. Regarding outcomes with evolocumab, the first report from the OSLER was positive. A specific trial, addressing cardiovascular events in high risk patients treated with evolocumab is currently ongoing (FOURIER [Further Cardiovascular Outcomes Research with PCSK9...
Inhibition in Subjects with Elevated Risk], enrolling approximately 27500 patients. Results are expected no later than 2017.

Another PCSK9 inhibitor is actually under development, namely Bococizumab, and patients are being recruited for SPIRE- (The Evaluation of Bococizumab (PF-04950615; RN316) in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects) study. Another interesting drug seems to be the ALN-PCScs based on the RNAI therapeutic strategy. Preliminary data have been presented during the European annual meeting of Cardiology in 2015, achieving an average reduction in LDL cholesterol of 44% with single 300 mg doses in a treatment program.

Lower is better for the heart but is it safe for the body?

The IMPROVE-IT trial has clearly showed that decreasing LDL cholesterol as low as 50 mg/dL resulted in a significant reduction in MACE. Statins, inhibitors of cholesterol absorption and inhibitors of PCSK9 alone or in combination give the opportunity to achieve strong target even below 50 mg/dL. However, a major warning raised by some meta-analyses is the correlation with the neurocognitive impairment [77-79]. Although the use of PCSK9 has emphasized the risk of cognitive decline correlated with lipid lowering agents, the first alert has been published in 2003 [79]. In the meta-analyses of observational studies performed by Emirin et al. lipid-lowering drugs, in particular the statins, were associated to lower odds of developing cognitive impairment [79]. A recent report, exploring the impact of PCSK9 inhibitors in cardiovascular outcome indicates a higher rate of neurocognitive adverse events in patients receiving the PCSK9 drug [77]. However other analysis seem to not confirm this correlation [78,80,81]. Specific study, such as EBINGHAUS (Evaluating PCSK9 Binding antibody Influence on cognitive Health in High cardiovascular Risk Subjects) will shed more light on this issue.

Conclusion

The entry of PCSK9 inhibitors in the clinical scenario is offering new and exciting opportunity for a better management of cardiovascular disease, especially in patients considered at high risk. Statins remain the cornerstone in the treatment of hypercholesterolemia and atherosclerotic disease, alone or in combination with inhibitors of cholesterol absorption as shown in Figure 1. However, the PCSK9 inhibitors appear to be a promising strategy especially to achieve the restricted LDL cholesterol levels in high-risk cardiovascular patients. Actually, the cost of this therapy may limit its use in patient at high risk in whom conventional therapies fail to meet the target. New strategies are on the way and most probably, in a close future, “lower” LDL cholesterol levels will be easier to achieve, making our dream become true.

References


