# STRATEGIES FOR THE USE OF NON-STATIN THERAPIES

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## Abstract

**Purpose of review**

Dyslipidaemias are a major risk factor for cardiovascular disease (CVD); in particular high levels of low density lipoprotein cholesterol (LDL-C) have been associated to a higher cardiovascular risk. Reducing LDL-C levels decreases the risk of coronary heart disease (CHD), and the greater the LDL-C reduction, the greater the cardiovascular risk decrease. Although statins represent the first line lipid-lowering therapy, many patients do not reach the recommended goals or exhibit adverse side effects leading to therapy discontinuation; in addition, a significant percentage of statin-treated patients continue to experience cardiovascular events even in the presence of well controlled LDL-C levels, due to alterations in other lipid/lipoprotein classes, including triglycerides and high-density lipoprotein cholesterol.

**Recent findings**

These conditions require further therapeutic interventions to achieve the recommended lipid goals. Several drugs have been developed to address these needs. Recent studies have shown that the association of ezetimibe with rosuvastatin or atorvastatin results in a better hypolipidaemic effect; beside this, PCSK9 inhibitors significantly reduce LDL-C levels and cardiovascular events.

**Summary**

For patients intolerant to statins or not able to reach the recommended LDL-C levels despite maximal tolerated dose of statin, or exhibiting additional lipid alterations, several drugs are available that can be used either in monotherapy or on top of the maximally tolerated dose of statins.

**Keywords**: dyslipidaemias; hypercholesterolaemia; LDL-C; triglycerides; statin-intolerance; ezetimibe; PCSK9 inhibitors

## Introduction

Dyslipidaemias, and in particular hypercholesterolaemia, represent a major risk factor for cardiovascular disease (CVD). Evidence from clinical trials, epidemiological and Mendelian randomization studies has established the causality for low density lipoprotein cholesterol (LDL-C) and/or triglyceride rich lipoproteins (TGRL) in atherosclerotic cardiovascular disease [1-3]. Data from meta-analyses of statin trials further proved that reducing LDL-C levels reduces the risk of coronary heart disease (CHD), and that the greater the LDL-C reduction, the greater the cardiovascular (CV) risk decrease [4-7].

Despite the established clinical efficacy of statin therapy, several statin-treated patients continue to experience cardiovascular events, even in the presence of well controlled LDL-C levels [8]. This observation suggests that an alteration in the plasma levels of other lipids (such as high triglycerides and/or low HDL-C plasma levels) may confer a residual risk [9, 10]. This may be the case of diabetic patients, who are characterized by the atherogenic dyslipidaemia (low HDL-C levels, high TG and small dense LDL levels) [11]. A causal association between elevated TG, TG-rich lipoproteins or their remnants and increased CVD risk has also been established, independent of LDL-C or HDL-C levels [3, 12-17]. Statins may affect TG and HDL-C levels: a dose-dependent TG reduction has been reported, ranging from 9 up to 25%, with greater reductions observed in patients with higher baseline TG values [18, 19]; in addition, all statins are able to increase HDL-C and apoA-I independently of LDL-C reduction but related to the baseline TG levels [20, 21].

Thus, statins might represent a reasonable approach also for the treatment of subjects with increased TG levels and increased CV risk. Many patients, however, do not reach the desired goal despite maximal tolerated statin therapy or experience side effects, particularly muscle-related adverse events, when taking statins. The incidence of statin-related side effects is further increased in subjects undergoing polytherapy, which increases the probability of drug-drug interactions and the appearance of adverse side-effects [22]. This may lead to therapy discontinuation and makes difficult the management of patients intolerant to statins, particularly those at high or very high CV risk, for whom high doses of high intensity statins are recommended.

Therefore, although statin therapy represents the first approach in the management of dyslipidaemias, there are patients that require further therapeutic interventions to achieve the recommended lipid goals or patients where statins are less effective. This review will focus on three categories of patients that include 1) statin-intolerant patients, 2) patients not at target and 3) patients with marked hypertriglyceridaemia (HTG).

**1) Patients with statin-intolerance**

Statin intolerance is defined as the inability to tolerate statins, independently on the type and dose [23]. Despite a possible causal association between statin use and myopathy, randomised controlled trials have suggested a small impact of statin therapy on less severe muscle pain (i.e., myalgia) or weakness [24]. In the clinical practice, such symptoms are commonly attributed to statins, as also suggested by the so-called nocebo effect, with an increased rate of muscle-related effects only after having been informed of the statin treatment compared with the blinded use [25]. The occurrence of statin-related side effects, which appears to be dose-dependent, may lead to therapy discontinuation, and therefore increases the CV risk of these patients. Thus, the availability of alternative non-statin lipid-lowering drugs (Figure 1), which include bile acid sequestrants, ezetimibe or PCSK9 inhibitors that may be used either as monotherapy or in combination with lower doses of statins (thus reducing the chance of statin-induced side effects), is essential to reduce the CV risk of statin-intolerant patients.

Specifically, bile acid sequestrants (cholestyramine, colestipol and more recently colesevelam) act by binding bile acids thus limiting their reabsorption; indirectly, this results in an increased expression of hepatic LDL receptor (LDLR) and increased LDL catabolism. These drugs reduce LDL-C by 18-25%, with an additional 10-20% reduction when added to a statin [26]. This effect translates into a reduction of CV events which is proportional to the degree of LDL-C lowering achieved [27, 28]. Bile acid sequestrants may be used also in patients intolerant to statins as well as in those who do not tolerate increasing dose of statins, and may be combined with other lipid-lowering drugs such as ezetimibe, resulting in a greater reduction of LDL-C levels compared with ezetimibe alone [29].

Ezetimibe reduces intestinal uptake of dietary and biliary cholesterol by inhibiting the interaction with the Niemann-Pick C1-like protein 1 (NPC1L1) [30]. Consequently, the delivery of diet cholesterol to the liver is reduced, thus favouring the increase of hepatic LDLR expression and reducing LDL-C plasma levels. The validity of this approach is confirmed by the fact that NPC1L1 inactivating mutations are associated with lower plasma LDL-C levels and reduced CV risk [31]. A pooled analysis of over 21,000 subjects from 27 clinical trials showed that combining ezetimibe with a statin induces a greater lipid-lowering effect than statin monotherapy [32]. The administration of ezetimibe in combination with low dose of simvastatin (10 mg) for 6 months significantly reduces LDL-C levels and a high percentage of patients achieves the therapeutic target; more importantly, no adverse events were reported during the study [33]. The effectiveness of this combination in reducing CV events has been confirmed by several clinical trials [34-36]. Additional benefits are achieved when ezetimibe is combined with atorvastatin or rosuvastatin [37-40]. Ezetimibe may also be combined with bile acid sequestrants, resulting in an additional reduction of LDL-C levels [29].

Proprotein convertase subtilisin kexin 9 (PCSK9) is a protein involved in the control of hepatic LDLR expression [41]; upon binding to the LDLR, it favours its targeting to the lysosome for degradation, thus resulting in a reduced LDLR expression and increased LDL-C levels. Reduced levels or function of this protein are associated with hypocholesterolaemia and reduced CV risk, suggesting it as a pharmacological target to reduce hypercholesterolaemia [42]. Two fully human monoclonal antibodies against PCSK9, alirocumab and evolocumab, which decrease LDL-C by up to 70%, have been approved for the treatment of patients with primary hypercholesterolaemia not at LDL-C goal despite maximal tolerated LLT as well as for statin-intolerant patients. A number of randomized clinical trials have evaluated the effect of evolocumab in statin-intolerant patients [43-45]. The GAUSS-3 study was designed as a two-phase trial to first identify patients with muscle-related adverse events during an atorvastatin rechallenge phase to proceed to the second phase of treatment with evolocumab or ezetimibe [45]. A greater reduction of LDL-C levels was reported in evolocumab-treated patients compared with ezetimibe after 24 weeks (treatment difference vs. ezetimibe ~-36%), with a good tolerability of both drugs [45]. Similar results were observed when alirocumab was compared to ezetimibe in statin-intolerant patients: the reduction of LDL-C levels was -45% with alirocumab and -14.6% with ezetimibe (mean treatment difference -30.4%); the incidence of muscle-related adverse events were lower when patients had evolocumab compared with the rechallenge phase with atorvastatin [46]. These data indicate a higher effectiveness of anti-PCSK9 mAbs in reducing LDL-C levels compared with ezetimibe in statin-intolerant hypercholesterolaemic patients. Furthermore, the recent data from the FOURIER trial show that inhibition of PCSK9 effectively reduces LDL-C levels and significantly reduces the risk of cardiovascular events [47], suggesting that this therapeutic approach could be effective in reducing the CV risk of patients intolerant to statins.

**2) Hypercholesterolaemic patients not at target despite maximized statin therapy**

Despite the established efficacy of statin therapy in reducing LDL-C levels and CV events, a considerable proportion of patients do not achieve the LDL-C levels recommended by guidelines based on their CV risk [48]. There are specific groups of patients in whom this proportion is significantly higher, such as patients with familial hypercholesterolaemia (FH) or patients with established CVD or very high CV risk, thus indicating the need of additional lipid-lowering therapies (Figure 1).

Due to the lifelong exposure to high levels of cholesterol, FH patients are at high CV risk; although statin therapy represents always the first approach also in these patients, the effectiveness of statins is strictly related to the presence of a functional LDLR, due to the mechanism of action of this class of drugs. Thus, FH patients on statin therapy are often far from the recommended LDL-C levels [49] and need to be treated with lipid-lowering drugs with a mechanism of action differing from that of statins. The addition of ezetimibe to a statin in FH patients results in an additional 10-15% LDL-C reduction [50-52], which may translate into a further reduction of CV risk. Heterozygous FH patients are the principle candidates for the therapy with anti-PCSK9 mAbs. Several clinical trials have in fact reported a robust benefit in HeFH patients following the addition of an anti-PCSK9 mAb to their current lipid-lowering therapy (maximally tolerated statin with/without other lipid-lowering therapy) [53-59]. Both alirocumab and evolocumab significantly decrease LDL-C levels by -42.5% up to -67.9% in HeFH under different clinical settings, with higher proportion of patients under anti-PCSK9 mAb therapy reaching the recommended LDL-C levels based on their CV risk [53-59]. The LDL-C lowering effect persists over time and after 78 weeks the LDL-C levels are still significantly low; similarly, the proportion of patients reaching their goal is maintained up to 78 weeks [60]. A pooled analysis of safety data for alirocumab in HeFH patients showed that rates of treatment-emergent adverse events (TEAEs) as well as TEAEs leading to discontinuation are similar in alirocumab and placebo groups [60]. These findings suggest that PCSK9 inhibitors represent a major opportunity for these difficult-to-treat patients to reach the recommended LDL-C levels and, as a consequence, to reduce their high CV risk.

Patients with established CVD may benefit from the addition of ezetimibe to a statin. As reported by the IMPROVE-IT trial, the addition of ezetimibe to simvastatin not only results in a greater reduction of LDL-C levels compared with simvastatin monotherapy, but also reduces the incidence of cardiovascular events in patients with a recent acute coronary syndrome [34]. The absolute benefit deriving from the combination therapy is small, but significant, thus confirming that lower LDL-C levels always associate with lower CV risk. Ezetimibe thus represents a second line of therapy that can be added to the current statin therapy to achieve the therapeutic goal; this may be of special relevance in patients at high CV risk who cannot reach the LDL-C target with the maximal tolerated dose of statins [48]. The FOURIER trial showed that evolocumab added to a statin therapy significantly reduced LDL-C levels (mean percentage reduction 59% as compared with placebo) and reduced the risk of cardiovascular events (hazard ratio, 0.85; $p<0.001$) in patients with atherosclerotic cardiovascular disease and LDL-C >70 mg/dL (1.81 mmol/L) [47]. A secondary analysis of the FOURIER trial showed that patients who achieved progressively lower LDL-C levels at 4 weeks exhibited progressively a lower rate of cardiovascular events, with adjusted hazard ratios of 0.69 for the primary endpoint and 0.59 for key secondary endpoints in the group with LDL-C <10 mg/dL or 0.26 mmol/L at 4 weeks [61]; no serious adverse events or adverse events leading to drug discontinuation were observed in patients achieving such very low LDL-C levels, thus suggesting that lower LDL-C levels (<0.5 mmol/L) can be safely considered for high risk patients. In addition, evolocumab added to a moderate or high-intensity statin therapy induced atherosclerotic plaque regression compared with placebo in patients with angiographic coronary disease [62]. Similarly, alirocumab significantly reduced LDL-C plasma levels compared with either placebo (difference -45.9%) or ezetimibe (difference: -29.8%) in high risk patients on maximally tolerated doses of statins; accordingly, a higher proportion of patients on alirocumab achieved the recommended LDL-C levels [63, 64].

**3) Patients with hypertriglyceridaemia**

For the purpose of this review, we discuss exclusively data about patients with mild-to-moderate hypertriglyceridaemia (150-880 mg/dL, 1.7-10 mmol/L); we did not include patients with severe hypertriglyceridaemia (>880 mg/dL, >10 mmol/L), typically associated with a high risk of pancreatitis and determined by monogenic mutations, who require a different therapeutic approach [15].

Mendelian randomization studies have reported a correlation between both high non-fasting TG levels and remnant cholesterol (i.e. the cholesterol of TG-rich lipoproteins) and increased risk of CV events and all-cause mortality [16, 17]. Despite this, the final evidence of benefits of lowering TG levels is still lacking. To date, no large clinical trials addressing specific clinical outcomes have been completed in which subjects were recruited based on their elevated levels of TG or TG-rich lipoproteins, and thus, the evidence to support TG-lowering therapies is less robust than for LDL-C. Thus, although clinical trials investigating the effects of TG-lowering drugs on cardiovascular outcomes have reported conflicting results, a recent meta-analysis reported an overall modest CV risk reduction (12%), which however was more consistent in specific subject subgroups, such as those with high TG (18% risk reduction) and even more in subjects with high TG and low HDL-C (29% risk reduction) [65].

Beside these considerations, it is worth noting that many patients treated with statins still exhibit high levels of non-HDL-C, which reflects an increase in TG-rich lipoprotein cholesterol [66, 67], suggesting the need of additional therapies able to lower specifically TG levels. The available pharmacological interventions that substantially reduce TG and TG-rich lipoprotein cholesterol include fibrates and n-3 PUFAs.

Fibrates are agonists of peroxisome proliferator-activated receptor-$\alpha$ (PPAR-$\alpha$), which act by regulating various steps in lipid and lipoprotein metabolism, resulting in reduced fasting TG levels, post-prandial TG and TG-rich lipoprotein remnant particles. Contrasting results have been reported from meta-analyses of fibrates clinical trials; in fact, while some meta-analyses did not observe any cardiovascular benefit [68, 69], others reported a reduction of CV events in specific group of patients with high TG levels associated with low HDL-C [70-72]. Thus, although overall these results may be suggestive of a clinical benefit in subgroups of high CV risk patients, specific clinical trials are essential to substantiate this hypothesis. The novel selective PPAR$\alpha$ modulator pemafibrate is currently under investigation in diabetic patients to evaluate the effect of TG-lowering on cardiovascular outcomes (PROMINENT, NCT03071692). N-3 fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) efficiently reduce TG levels by several mechanisms [73]. The recommended doses of EPA+DHA is 2-4 g/day, which translate into a 25-30% reduction of TG levels [73]. Whether this relevant reduction of plasma TG levels may also translate into a clinical benefit is still debated. In fact, although some studies reported significant reduction of CV outcomes following the treatment with omega-3 fatty acids [74, 75], other studies failed to observe any kind of protection [76]. A large systematic review including data from 20 clinical trials reported that omega-3 fatty acids protected against vascular death (RR=0.96, P=0.03) but overall there was no effect on composite cardiovascular events coronary events (RR=0.96, P=0.24) [77]. Two ongoing randomized placebo-controlled trials (REDUCE-IT, NCT01492361 and STRENGTH, NCT02104817) are evaluating the effect of omega-3 fatty acids on CVD outcomes in subjects with high TG levels.

## CONCLUSIONS

The reduction of LDL cholesterol is one of the pillars in the prevention of CVD. Statins are the first line therapy as suggested by the major guidelines and the benefit is directly proportional to the absolute LDL-C level decrease and the absolute CV risk of the patient. Yet there are circumstances under which either the hypolipidaemic response is deemed as insufficient (especially in patients with the so-called statin intolerance) or patients are affected of other forms of dyslipidaemia that confer additional CV risk. The size of these populations varies widely from survey to survey but certainly account for a relatively large part of the high and very high risk population and other non statin treatment represent a powerful tool in the armamentarium of the physician to provide the best CV protection possible.

**KEY POINTS**

- Despite the clinical efficacy of statin therapy, several patients still need further drugs to reduce their CV risk
- Statin-intolerant patients require alternative non-statin therapies to manage their CV risk, which may include bile acid sequestrants, ezetimibe in combination with low doses of statins, and PCSK9 inhibitors, which seem to represent a valid approach to reduce LDL-C levels and CV risk
- Specific groups of patients such as those with FH or with established cardiovascular disease, who are at high CV risk, often require additional drugs for the management of their CV risk, which may include PCSK9 inhibitors or ezetimibe in association with a statin
- Patients with severe HTG have an increased CV risk, and may be treated with fibrates or omega-3 fatty acids, although the final proof of their ability to reduce the CV risk in these patients is still debated.
- Here we discuss the recent findings on newest hypolipidaemic drugs as well as findings from drugs previously used for the management of these specific groups of patients

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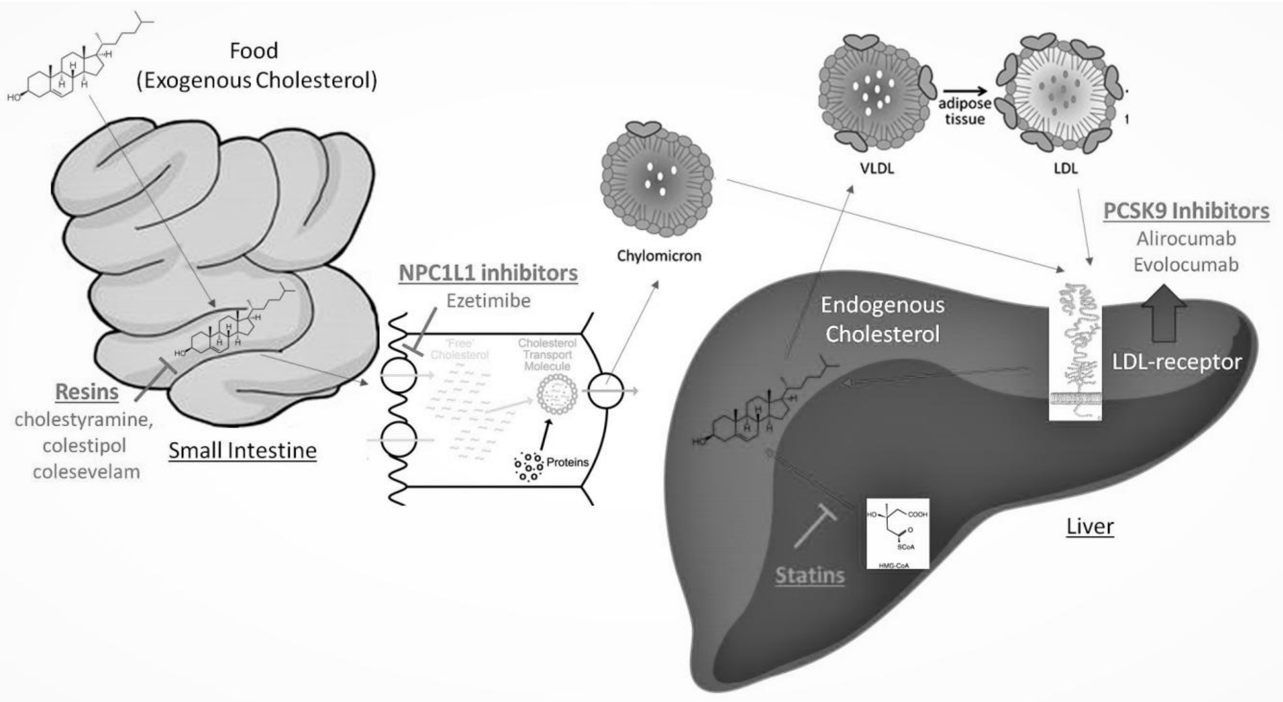
**Legend to the figure**

Figure 1. Sites of action of statins and other lipid-lowering drugs



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**STRATEGIES FOR THE USE OF NON-STATIN THERAPIES**

Current Opinion in Lipidology

**<u>Reviewers' comments:</u>**

Excellent overview, containing all relevant information
Some suggestions

1. overall: please perform one more thorough spell and grammar check:
Examples: pg 3: ipolipemic should read: hypolipemic; pg 6: a little effect should preferably read a small impact on etc

**We performed spelling and grammar check; the corrections are now highlighted in the text**

2. page 9: Just prior to topic 3 (hyperTG), consider to add the reference to the publication which will be online next week August 28th) in Lancet, describing benefit of LDLc reduction in Fourier to levels < 0.2 mmol/l! That makes sense to add a short sentence at the end of topic 2, in order to emphasize the relevance of extremely low LDLc in very high risk subjects? Just a suggestion! (first author: Giugliano)

**Thank you for this suggestion. The indicated paper has been discussed in the text and added as reference**

3. page 11: before getting into the topic of severe HTG, consider to add 1 sentence reading that this does not include the extreme HTGs (>10 mmol/l?): for these patients, usually with monogenetic severe causes and severely elevated pancreatitis risk, other modalities should be considered (reference to eg. apoCIIIas paper?). Severe range for this topic: 3-10 mmol/l?

**As suggested, in the indicated topic we added a sentence specifying that we only considered mild-to-moderate HTG patients and excluded severe HTG from the discussion as it was beyond the purpose of this review**