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REVIEW

Current pharmacotherapeutic options for primary dyslipidemia in adults

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ABSTRACT

Introduction: Atherosclerotic cardiovascular disease (ASCVD) and its clinical manifestations, remain a leading cause of death and disability worldwide. One of the major risk factors of ASCVD is dyslipidemia and all the available guidelines suggest the importance of strategies for lipid control in a remarkable proportion of the general population.

Areas covered: This review focuses on the therapeutic options available for the management of lipid disorders in adults.

Expert opinion: A large body of evidence supports that statins are still the first-line option for the management of hypercholesterolemia in a large percentage of patients. Statins should be given at the appropriate dose and considering the differences in lipid-lowering potency across the different medications. The main current challenge in the treatment of lipid disorders is the need of improving patient adherence and persistence to lipid-lowering treatments beyond the drug choice and the target lipid component. To achieve this goal, the best strategy would be to treat the patients by using the appropriate drugs given at adequate doses to reach the treatment target. We should also avoid drug interactions, monitor possible untoward side effects and promote adherence to treatment by tailoring treatment strategies to each patient.

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1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) and its clinical manifestations, such as myocardial infarction (MI), ischemic stroke (IS) and peripheral artery disease (PAD), are still the leading cause of morbidity and mortality in the developed countries [1]. The most important modifiable risk factors for ASCVD are arterial hypertension, lipid disorders, diabetes, obesity, and smoking habit and, probably, elevated serum uric acid [2].

Dyslipidaemia includes a wide range of abnormalities of lipid profile including increased levels of total cholesterol (TC) (≥200 mg/dL), low density lipoprotein cholesterol (LDL-C) (>100 mg/dL), triglyceride (TG) levels (>150 mg/dL) and lipoprotein(a) (Lp(a)) (>30 mg/dL) and/or a decrease of high density lipoprotein cholesterol (HDL-C) (<50 mg/dL or <40 mg/dL, respectively, for female and male subjects). Secondary causes of dyslipidemia include hypothyroidism, obstructive liver disease, nephrotic syndrome, chronic kidney disease (CKD), uncontrolled diabetes mellitus, tobacco or alcohol abuse, medications such as full dosed thiazide diuretics, old-generation β-blockers, cyclosporine, glucocorticoids, and oral estrogens. Abnormalities of the lipid profile can be strongly associated with genetics: the typical example is familial hypercholesterolemia (FH) and polygenic disease because of their significant incidence, strong association with premature ACSVD, and therapeutic issues [3].

Dyslipidemia, especially in the form of high LDL-C levels, has a strong impact in the pathophysiology of ASCVD. It has been extensively demonstrated that the accumulation of cholesterol-rich LDL (and in particular oxidized LDL) into the vascular walls leads to the formation and subsequent progression of the atherosclerotic lesions and vascular disease [4].

From the epidemiological perspective, several population-based studies, randomized clinical trials (RCTs), Mendelian randomization studies, and meta-analyses have demonstrated a consistent and linear association between the magnitude and the duration of the exposure to high LDL-C levels and the risk of developing ASCVD [5,6]. Furthermore, several meta-analyses and genetic studies have supported the additional role of high TG levels that can act as an independent risk factor for ASCVD [7–9]. On the contrary, the vasculoprotective role of high HDL-C levels has been recently questioned by Mendelian randomization studies whilst recent findings have suggested a possible negative role of HDL-C role in the atherogenic process, based on the presence of a dysfunctional HDL [10,11].

In terms of prevention, any strategy aimed at reducing the risk and the incidence of major cardiovascular events (MACE), should include appropriate lifestyle changes combined with drug therapy. According to the European and American guidelines [12–14], this strategy will be more favorable in patients with previous CV disease and in those at higher CV risk [15] including subjects in primary prevention that should be treated with the appropriate statin therapy in order to lower their LDL-C levels and probability of CV diseases. The addition of a non-statin drug (such as ezetimibe and/or PCSK9-inhibitors) should be considered if statin monotherapy fails because of insufficient LDL-C control or development of adverse events,

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Article highlights

- Dyslipidemia is largely prevalent in the adult populations and often requires pharmacological treatment.
- Dyslipidemia includes a range of abnormalities of lipid metabolism and may involve a combination of increased total cholesterol, low-density lipoprotein cholesterol, serum triglyceride, and lipoprotein(a) levels or a decrease in high-density lipoprotein cholesterol.
- The lipid-lowering drugs with proven efficacy for lipids control and cardiovascular risk reduction are statins, used as monotherapy or in combination with ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, fibrates, and PUFA.
- Statins reduce the synthesis of cholesterol by the liver, mainly by competitive inhibition with the activity of the HMG-CoA reductase, the rate-limiting enzyme responsible for the transformation of mevalonate into cholesterol.
- Lipid-lowering therapies are associated with an insufficient patient's compliance and persistence in treatment that can explain the unsatisfactory rate of attainment of desired LDL-Cholesterol and triglycerides levels.

This box summarizes the key points contained in the article.

Table 1. Mean effect of pharmacologic therapy on lipid panel [12,13,14].

Pharmacologic class	LDL-C	HDL-C	TG
Statins	↓ 30–50%	↑ 4–10%	↓ 10–20%
Ezetimibe	↓ 15–25%	↑ ≈ 3%	↓ ≈13%
PCSK9-I	↓ 40–70%	↑ 4–9%	↓ 10–17%
Fibrates	↓ 10–30%	↑ 7–16%	↓ 25–50%
Niacin	↓ 5–28%	↑ 7–28%	↓ 9–50%
ω-3 PUFA	Non-significant	Non-significant	↓ 30–45%

PCSK9-I, proprotein convertase subtilisin/kexin type 9;
ω-3 PUFA = omega-3 polyunsaturated fatty acids.

particularly for those patients who bear a very high ASCVD risk. The use of fibrates should be considered in patients with high serum TG levels despite LDL-C control and in those with very high TG levels (>400 mg/dL) particularly in presence of diabetes or low-HDL levels [12]. Niacin failed to demonstrate any benefit in CV outcome trials. More recently some outcome studies have supported that adding eicosapentaenoic acid (EPA) to a statin treatment improves the cardiovascular outcome in patients with a residual TG level of 150–500 mg/dL [16]. This support the relevance of TG reduction in some specific sub-populations of patients where the complexity of the lipid profile strongly influenced by the interaction between TG-rich lipoproteins (VLDL, Chylomicrons) and LDL-C.

The mean effect of the different classes of available lipid-lowering drugs is summarized in Table 1.

2. LDL-C as the primary target of pharmacotherapy

2.1. Intervention strategies based on CV risk and LDL-C levels

According to the most recent international guidelines [12–14], the intensity of the preventive intervention in patients at risk of CV disease should be graduated according to the overall CV risk profile. The European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines [12], suggest that the global CV risk profile should be evaluated by the Systematic Coronary Risk Estimation (SCORE) system that only estimates the 10-year risk of a fatal cardiovascular event. In patients with lipid disorders, moderate risk is defined in the range of 1–5%; high risk between 5% and 10% or by the presence of concomitant familial dyslipidemia, uncontrolled arterial hypertension or diabetes mellitus. Finally, a very high risk is established in patients with a ≥10% risk of a fatal event, in diabetic or hypertensive patients with target organ damage, and in patients with a previous documented ASCVD. According to risk profile, ESC suggests a specific target of LDL-C level: <115 mg/dL for patients at moderate risk, <100 mg/dL for high-risk patients, and <70 mg/dL for very high-risk patients. The 2018 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines [14] strongly recommend to immediately start lipid-lowering treatment (without risk calculation), in patient with clinical ASCVD, in those with LDL-C ≥190 mg/dL, and in presence of diabetes. In all the other subjects, the treatment recommendations support a strategy based on the estimate of the global CV risk profile by using the 10-year Pooled Cohort Equations CV Risk Calculator. This scoring system considers four 10-year risk categories: low risk as less than 5%, borderline as 5% to 7.4%, intermediate as 7.5% to 19.9%, and high as 20% or higher. In the same Guidelines, the definition of the targets of treatment seems to be slightly different from those proposed by ESC guidelines [12], with a recommended reduction of LDL-C greater than 50% and 30% from baseline for secondary prevention or high-risk patients and for intermediate risk patients, respectively. [14].

These recommendations (summarized in Tables 1 and 2) are based on multiple evidence from large RCTs and meta-analyses supporting the importance of LDL-C lowering to prevent ASCVD in patients with lipid disorders [15]. In particular, they highlight the parallel and consistent decrease in CV risk in response to the reduction of TC and LDL-C levels, with a greater absolute benefit in patients with the higher initial LDL-C level and global CV risk. Furthermore, the recent trials involving PCSK9-inhibitors have shown that there is apparently no lower level for LDL-C in response to treatment, with a safe reduction of the CV events also in patients reaching LDL-C levels below 20 mg/dL [17–19]. Other guidelines are not 'treat to target' based but more practical and focused on phenotypical approaches or patient centered, but the ESC/EAS [12] and AHA/ACC [14] guidelines are currently the most acknowledged worldwide.

2.2. The central role of statins

Statins reduce the synthesis of cholesterol in the liver mainly by competitive inhibition of the activity of the HMG-CoA reductase, the rate-limiting enzyme that transforms mevalonate into cholesterol. By reducing the intracellular cholesterol synthesis, statins induce an increased uptake of LDL-C and other TG-rich lipoproteins from the blood. This, in turn, leads to a lower lipid plasma concentration, as a consequence of an increased expression of the LDL-receptor (LDL-R) on the hepatocytes membrane [20].

The effects of statins in patients at CV risk have been extensively reviewed in several meta-analyses of trials including large populations of patients and specific subgroups

Table 2. Guideline recommendations for primary prevention of ASCVD with LDL-C lowering treatment.

	ESC/EAS 2016	ACC/AHA 2018
Primary prevention of ASCVD with LDL-C lowering pharmacotherapy		
Patients	Age 40–65 years with LDL-C 70–190 mg/dL	Age 40–75 years with LDL-C 70–190 mg/dL
Risk estimator	SCORE risk (10-year risk of first fatal atherosclerotic event: MI, stroke, occlusive arterial disease or sudden cardiac death)	ASCVD risk estimator plus (10-year risk of fatal and nonfatal MI or stroke)
Risk predictors	Age, sex, smoke, SBP, TC, and HDL-C	Age, sex, race, SBP, DBP, TC, HDL-C, LDL-C, DM, smoke, treatment
Risk stratification	Very high risk = ≥10% SCORE risk, documented ASCVD High risk = 5–10% SCORE risk, elevated single risk factor Moderate risk = 1–5% SCORE risk Low risk = <1% SCORE risk	High risk = ≥20% 10-year risk Intermediate-risk = 7.5–20% 10-year risk Borderline risk = 5–7.5% 10-year risk Low risk = <5% 10-year risk
Treatment target	Very high risk = LDL-C ≤70 mg/dL or ↓ of 50% from baseline High risk = LDL-C ≤100 mg/dL or a ↓ of 50% from baseline Moderate/Low risk = LDL-C ≤115 mg/dL	High risk = LDL-C ≤70 mg/dL or a ↓ of 50% from baseline Intermediate risk = LDL-C ≤100 mg/dL or a ↓ of 50% from baseline Borderline/low risk = LDL-C ≤115 mg/dL
Treatment strategy	Maximally tolerated dose of statin to achieve target + ezetimibe to maximally tolerated statin therapy to achieve target + PCSK9-inhibitors on maximally tolerated statin and ezetimibe therapy	
Primary prevention in special groups		
Age 20–39 years	Consider statin if family history of premature ASCVD	Consider statin if family history of premature ASCVD and LDL-C ≥160 mg/dL
LDL-C ≥190 mg/dL	Treat as high risk	High intensity statin independent of risk assessment
Diabetes mellitus	Statin therapy if: - LDL-C ≥100 mg/dl - LDL-C 70–100 mg/dl AND organ damage OR 1 additional CV risk factor	Moderate intensity statin risk assessment to consider high-intensity statin
CKD	Treat as very high risk if severe CKD (GFR <30 mL/min) Treat as high risk if moderate CKD (GFR 30–60 ml/min)	In adults 40–75 years of age with LDL-C 70– 190 mg/dL who are at 10-year ASCVD risk of 7.5% or higher, CKD is a risk-enhancing factor and initiation of a moderate-intensity statin or statin + ezetimibe can be useful

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; MI, Myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[21,22]. In the Cholesterol Treatment Trialists (CTT) analysis data, 170'000 participants and 26 RCTs with statins were included. This large meta-analysis showed a significant and consistent reduction of all-cause mortality, CV death, coronary events, and IS (10%, 20%, 23%, and 17%, respectively) per 40 mg/dL of LDL-C reduction. The long-term benefit was similar in all the subgroups of patients, without any major safety concerns (there was no increased risk of death or other morbidity linked to statin therapy) [17].

The impact of statins on primary CV prevention has been investigated in some selected meta-analyses. In the largest one, that included 19 studies with different statins and different inclusion criteria, all-cause mortality was reduced by 14%, CV events by 27%, coronary events by 27%, and ischemic stroke by 22% per 40 mg/dL of LDL-C reduction. The relative risk reduction in primary prevention patients was similar to that observed in secondary prevention, with a significant reduction in absolute CV risk also in the groups with a lower baseline CV risk [23,24].

Available evidence has clarified that these clinical effects mostly depend on the extent of the LDL-C reduction rather than on type of statin prescribed, suggesting a class effect [25]. Each statin held a different potency and, despite the degree of the reduction is dose-dependent, there is a substantial inter-individual variability in response to treatment. This could be explained by a diverse genetic background, mainly involving genes implied in lipid and drug metabolism [26]. Despite one could expect a large variability of results in primary and secondary CV prevention trials that included women, a recent meta-analysis has reported a similar benefit in men and women that can be equally prescribed in all the patients with a specific indication [15].

2.3. Therapeutic issues with statins

2.3.1. Statin intolerance, adverse effects, and interactions

The definition of statin intolerance is still largely arbitrary and neither standardized diagnostic criteria nor a uniform definition have been officially proposed by the main drug regulatory agencies, namely: the European Medicine Agency (EMA) and Food and Drug Administration (FDA).

Statins are usually well tolerated, even if some adverse effects have to be considered since they can be responsible for poor adherence, arbitrary dose reduction, and therapy withdrawal [27]. The most frequent adverse effect is muscular pain and tenderness (statin-associated muscle symptoms or SAMS), that typically present without signs of myocyte necrosis (creatine kinase (CK) elevation) or major muscle functional loss. Less frequently reported side effects are headache, sleep disorders, dyspepsia, nausea, cutaneous rash, alopecia, erectile dysfunction, gynecomastia, and arthritis [28,29]. If SAMS represent the most commonly described adverse effects of statins, rhabdomyolysis is considered the most severe form of statin-induced myopathy. It is defined as diffuse muscle necrosis (at least 10 times CK elevation, often up to 40 times the upper limit of normal (ULN)) accompanied by severe muscular pain and myoglobinuria. Although it has been estimated to be an extremely rare condition (1–3 cases/100'000 patients/year) it can potentially lead to acute renal failure and death [29]. Despite the large number of studies and patients currently treated with statins the actual incidence of SAMS is still a matter of debate. In meta-analyses of RCTs, the rate of AEs wan not significantly increased in statin-treated groups. Conversely, the reported incidence of AEs varies between

10% and 15% in few observational studies [30,31]. A single study specifically designed to evaluate the incidence of muscle symptoms in statin-treated patients showed that the frequency of muscle-related AEs was about 5% [32].

Interestingly, patients who claim to be statin-intolerant can frequently tolerate the same drugs when given in double-blind conditions, indicating the unlikely pharmacological basis of intolerance. When symptoms are mild without any objective evidence of myopathy, a possible explanation is the nocebo effect. It results from the expectation of a potential harm, and it is driven by a warning about the possible adverse effects (physicians, RCPs or media information, reported personal negative experience with the same drugs.) After excluding the nocebo effect, the diagnosis of SAMS is based on the clinical observation and whether or not symptoms disappear after discontinuation of statins and develop again with statin re-challenge. In patients with a high risk for CVD, a correct diagnosis of statin-related AEs it is crucial before excluding the patient from the benefits of statin treatment [33].

The risk of side effects with statins can be also dependent on drug-to-drug interactions [29,34]. Indeed, many statins (such as atorvastatin, simvastatin, and lovastatin) are metabolized via cytochrome P450 isoenzymes (especially CYP3A4) so their plasma level and toxicity can increase when co-administered with other drugs undergoing the same extensive hepatic metabolism (typically azole antifungals, macrolides, antivirals, cyclosporine, amiodarone, and non-dihydropyridine calcium channel blockers). Additional pharmacological interactions with some influence on the efficacy and toxicity of statins are: a decrease in oral bioavailability when given with bile acid sequestrant (statins should be taken at least 1 h before or 4–6 h later), a decreased concentration and activity of endogenous steroid hormones during treatment with mineralocorticoid receptor antagonist (MRA), an increase in fluvastatin and a decrease in atorvastatin and rosuvastatin blood level with antacids drugs (cimetidine, ranitidine, and PPIs), and a more rapid statin excretion with rifampicin. Finally, the anticoagulant activity of warfarin may increase if administered with fluvastatin, lovastatin, rosuvastatin, or simvastatin [35].

Practical management of muscular symptoms is suggested by the most recent guidelines based on the identification of a cause–effect relationship [12–14]. In presence of a causal relationship between muscle symptoms and statin therapy, the statin administration should be stopped and re-started after a period of washout of 2 to 6 weeks (according to symptoms severity, CK levels, and kidney involvement), especially if the patients have a high or very high CV risk or if the symptoms persist (maybe not due to statin therapy). Since the target LDL-C reduction need to be achieved, the re-challenge might consider: a reduction of the dose of the same statin, a different statin with the same potency or a statin with longer half-life and minor hepatic metabolism (rosuvastatin, pravastatin, and fluvastatin) that can be taken any other day or twice weekly [36]. At present, despite no available results from clinical trials reporting the impact of these strategies on major CV outcomes, we have to consider this approach at least in high-risk patients who do not tolerate daily doses of a specific statin [29,37]. Otherwise, If no causal relationship can be demonstrated between the muscle symptoms and the use of statins, the original drug at the given or lower dose can be prescribed again to the patient [12–14].

In the safety area, an asymptomatic alteration of liver function tests (LFTs) is another possible adverse effect during statin therapy, though the incidence of significative elevated aminotransferase activity (>3 times of the ULN) is low and acute hepatic failure is an extremely uncommon event [12–14]. A report of *The National Lipid Association* [38] *focused* on the safety of statins concluded that adverse hepatic consequences of statin therapy are rare and their incidence is comparable to that in non-statin treated individuals. Thus, the actual recommendation is to check liver function tests at baseline and to avoid systematic monitoring of transaminase that is not necessary. If symptomless LFTs abnormalities develop during statin therapy, the patient should be actively monitored to verify that the elevation of liver enzymes is transient and self-limiting. Most important, no down-titration of the dose or interruption of the statin therapy is required unless a diagnostic workup has been completed to clarify the cause of LFT abnormalities [12–14].

Finally, statin therapy has been associated with an increased risk of new onset diabetes mellitus (NOD) and this association has been observed with all the statins (hydrophilic or lipophilic), thus representing a possible class effect [39]. A great debate focused on the clinical implication of this finding has started a few years ago after the publication of a meta-analysis, which revealed a higher incidence of NOD in patients undergoing statin treatment [40]. Recently, a new meta-analysis has demonstrated that the risk of diabetes is largely encompassed by the beneficial effects of statins in terms of CV outcomes (DM = 2/498 treated patients per year; CV events prevented = 1/155 patients treated per year) [41]. The overall net benefit of statin therapy has been also observed in the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study [42]. In primary prevention participants, with or without risk factors for diabetes, the beneficial effect of statin therapy on CV events was again greater than the risk of developing NOD (almost 2.5-fold), and this effect was confirmed also in a lower-risk primary-prevention subpopulation.

2.3.2. Subjects not achieving LDL-C target despite statin treatment

Besides the patients intolerant or experiencing mild to severe adverse effects, there is a considerable proportion of adequately treated patients that fail to achieve the recommended LDL-C targets in response to statins [18,43]. The results of a multicentric European cross-sectional study (EUROASPIRE IV) showed that less than 20% of very high-risk patients with known coronary artery disease actually attain the LDL-C goal indicated by the guidelines [44].

A very high baseline levels or a large distance from LDL-C target, dramatically reduce the capacity of statin monotherapy to effectively reduce the CV risk [45]. A typical example is the patients with familial hypercholesterolemia (FH) that is the result of an autosomal dominant genetic mutation, affecting the expression or the function of LDL-R, PCSK9 or apolipoprotein-B (APO-B) that eventually leads to altered LDL-C

metabolism with a consequent marked elevation in TC and LDL-C from birth [46]. Heterozygous FH (HeFH) is associated with LDL-C levels of 200 to 450 mg/dL and it is relatively common, affecting approximately 1 out of 250 subjects, while homozygous FH (HoFH), associated with much higher LDL-C levels (450 to >1000 mg/dL), is a rare condition, affecting about 1 out of 300,000 to 1,000,000 people [47]. Underdiagnosis, lifetime exposure to a very high level of LDL-C, and resistance to the lipid-lowering therapy represent the major problems in patients with FH, that may experience an ACVSD at a very young age [48–51] despite the use of high-intensity statin (atorvastatin, and rosuvastatin) in combination with other lipid-lowering drugs [52,53].

Given these unmet needs, researchers have focused their attention on the development of novel effective and well-tolerated drugs able to lower LDL-C levels below the threshold reached by statins monotherapy. Although the treatment with the highest tolerable dose of statin should be considered as first-line, for patients who do not respond adequately or for those who are intolerant, there are other effective non-statin therapies approved such as cholesterol absorption inhibitors and PCSK9 inhibitors [12–14,54]. European and American guidelines have a slightly different approach to patients in primary (Table 2) and secondary CV prevention (Table 3) [12–14]. An integrated flow-chart to the treatment of dyslipidaemic patients has been proposed in Figure 1.

2.3.3. Ezetimibe

Ezetimibe is a pro-drug that once rapidly absorbed is extensively metabolized to pharmacologically active ezetimibe glucuronide. The active metabolite inhibits the intestinal uptake of dietary and biliary cholesterol by interfering with the activity of the Niemann-Pick C1-like protein 1 (NPC1L1) expressed in the intestinal brush border. A lower amount of cholesterol absorbed and delivered to the liver determines an upregulation of the LDL-R expression, which in turn promotes the clearance of LDL-C from the blood. Unlike statins, ezetimibe exhibits a favorable pharmacokinetic profile, with no clinically relevant implications for age, sex or ethnicity. It also does not deserve any dose adjustment in patients with mild hepatic impairment and/or mild to severe renal failure. So far, no major adverse effects have been reported with ezetimibe and the most frequently complained are mild musculoskeletal and gastrointestinal disorders. Myalgia was the most common musculoskeletal adverse event, followed by arthralgia and involuntary muscle contractions. From the gastrointestinal point of view, nausea is the most common adverse event (19%), followed by diarrhea and abdominal pain [55].

Data from multiple clinical trials demonstrated that ezetimibe in monotherapy reduces LDL-C in hypercholesterolemic patients, a beneficial effect that was supported also by genetic studies of NPC1L1 loss-of-function (LOF) mutations. Ezetimibe in combination with statins reduces mean LDL-C levels significantly more than either statin or ezetimibe alone [56–58]. Furthermore, the combination of ezetimibe with statins is effective also in reducing CV events in primary and secondary prevention [59]. Recently, the results of two randomized clinical trials (IMPROVE-IT and PRECISE-IVUS) have indicated that the combination of statin plus ezetimibe improved overall CV outcomes in patients after acute coronary syndrome (ACS, simvastatin) and contributes to ezetimibe coronary plaque regression (atorvastatin) [60,61].

At present, no RCT has demonstrated a reduction of the incidence of MACE with ezetimibe monotherapy that for this reason is considered as second-line therapy either alone or in combination with the maximally tolerated dose of statin, especially when the therapeutic goal is not achieved or the patient appears intolerant [12–14,54].

2.3.4. PCSK9 inhibitors

PCSK9 is a proprotein convertase produced by the liver and secreted into the circulation where it binds to the LDL-R promoting the internalization and the intracellular degradation of the ligand-receptor complex [62]. Genetic studies identified PCSK9 gain-of-function (GOF) mutations of as a rare cause of FH, with a similar atherosclerotic burden to that observed with the more traditional mutations in the LDL-R and APO-B [63,64]. On the opposite, several PCSK9 LOF mutations were found to be associated with lower plasma LDL-C and lower prevalence of coronary artery disease, suggesting the inhibition of PCSK9 as a possible treatment option for patients with uncontrolled LDL-C and high CV risk [65]. Alirocumab and evolocumab are two fully human monoclonal antibodies that can selectively target and inhibit circulating

Table 3 Guideline recommendations for secondary prevention of ASCVD with LDL-C lowering treatment.

	Secondary Prevention of ASCVD with LDL-C lowering treatment	
2016 ESC/EAS	Maximally tolerated dose of statin to achieve LDL-C ≤ 70 mg/dL (or a ↓ of 50% from baseline)	
2018 AHA/ACC	**Very high risk for future ASCVD events** *Major ASCVD events* Recent ACS (within the past 12 months)History of MI (other than recent ACS)History of ischemic strokeSymptomatic peripheral arterial disease (or revascularization or amputation) *High risk conditions* Age ≥ 65 years, HeFH, history of CABG or PCI, DM, hypertension, CKD (eGFR 15-60 ml/min), current smoking, LDL-C ≥ 100 mg/dL despite maximally tolerated lowering therapy, HF	High intensity or maximal statin + ezetimibe if on maximal statin and LDL-C ≥ 70 mg/dL + PCSK9-I if on maximal LDL-C lowering therapy and LDL-C ≥ 70 mg/dL
	Non very high risk for future ASCVD events	High intensity statin (goal ↓ 50% of LDL-C) or Moderate intensity statin if not tolerated + ezetimibe if on maximal statin and LDL-C ≥ 70 mg/dL

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; ACS, acute coronary syndrome; MI, myocardial infarction; HeFH, heterozygous familial hypercholesterolemia; CABG, coronary artery by-pass graft; PCI, percutaneous coronary intervention; HF, heart failure.

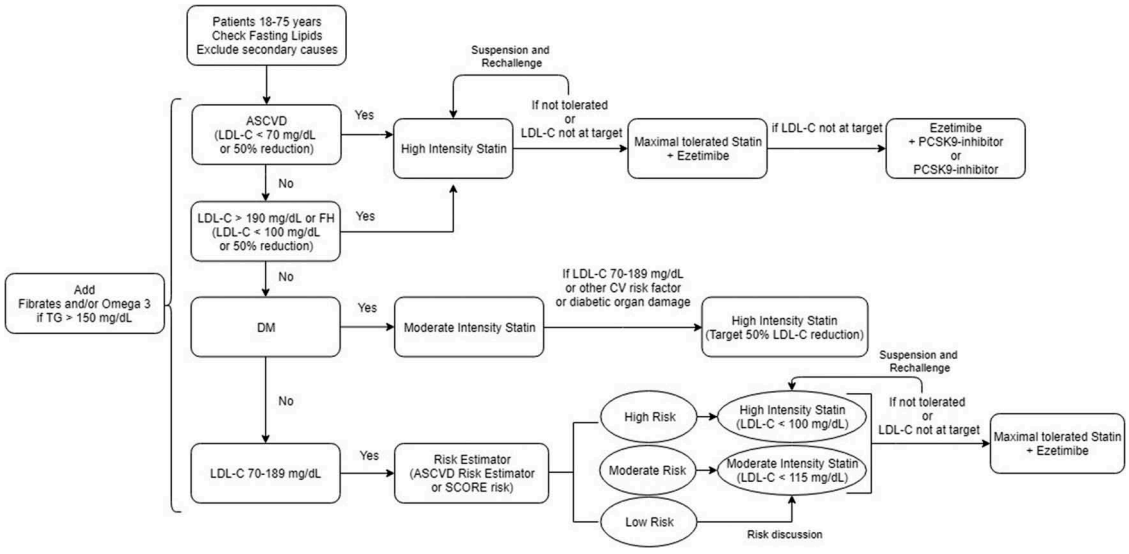

Figure 1. Tentative integrated flow-chart to the treatment of dyslipidemic patients based on their clinical characteristics.

PCSK9. The efficacy of these PSCK9 inhibitors to reduce LDL-C has been extensively investigated in several phase II trials [66–70]. Both molecules were associated with a significant, dose-dependent reduction in LDL-C limited by a plateau effect, suggesting a system saturation (i.e. complete binding of circulating PCSK9). Interestingly, no difference in the amount or duration of LDL-C reduction was observed between FH and non-FH patients, meaning that PCSK9 inhibition was able to compensate for the adverse functional effects of the genetic mutation of the LDL-R in FH patients. Similarly, the reduction in LDL-C was not different between patients who were already on a statin, a clear evidence of a powerful synergistic effect. In phase III RCTs in high-risk hypercholesterolemic patients, Alirocumab and evolocumab, alone or in combination with other LDL-C lowering drugs, demonstrated significant and persistent efficacy in reducing LDL-C with a favorable safety profile [71–76]. From the clinical point of view, the initial result of the post-hoc analysis of the ODYSSEY LONG TERM trial showed a lower rate of MACE with alirocumab versus placebo [77]. Similar results were also observed in an exploratory analysis carried out on evolocumab data, where the rate of CV events at 1 year was significantly reduced versus standard therapy [78].

Of course, these preliminary findings based on post-hoc analysis required some confirmation from major prospective randomized clinical trials. The impact of alirocumab on CV risk has been recently confirmed by the results of the ODYSSEY Outcomes trial whose primary endpoint was a composite of death from coronary heart disease, non-fatal MI, fatal or non-fatal IS, or unstable angina requiring hospitalization. In the study, patients with a history of ACS within the previous 12 months and a residual LDL-C levels ≥70 mg/dL, non-HDL-C ≥100 mg/dL or apolipoprotein B ≥80 mg/dL despite intensive or maximally tolerated high-intensity statin therapy (atorvastatin or rosuvastatin) were randomized to receive either subcutaneous injections of alirocumab or placebo. After a median follow-up of 2.8 years, the mean LDL-C levels were 53.3 mg/dL in the alirocumab group compared with 101.4 mg/dL in the placebo group, for a mean absolute reduction of 54.7%. The incidence of the composite primary end-point was significantly lower in the alirocumab group (hazard ratio, 0.85; 95% confidence interval [CI], 0.78 to 0.93; P < 0.001), with greater absolute benefit among patients who had a baseline LDL-C of 100 mg/dL or more and a similar rate of adverse events in the two groups, with the exception of local injection-site reactions (3.8% in the alirocumab group vs. 2.1% in the placebo group) [79]. The clinical efficacy of Evolocumab was tested in the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) study by evaluating similar endpoints (composite of CV death, MI, IS, hospitalization for unstable angina, or coronary revascularization) in a different population of patients with stable CV disease. This randomized, placebo-controlled trial included patients with atherosclerotic CVD and LDL-C levels ≥70 mg/dL already receiving background statin therapy. At 48 weeks, evolocumab significantly reduced LDL-C levels from a median baseline value of 92 mg/dL to 30 mg/dL, with a mean percentage reduction of 59%, as compared with placebo. After a median follow-up of 2.2 years, evolocumab treatment significantly reduced the risk of the primary endpoint (hazard ratio, 0.85; 95%CI, 0.79 to 0.92; P < 0.001). The results were consistent across subgroups, including the prespecified subgroup of patients with the lowest baseline LDL-C levels, patients with recent myocardial infarction and with multivessels disease. These favorable effects of evolocumab were also confirmed in patients with PAD, with a significant reduction in the incidence of major cardiovascular events and peripheral vascular complications [80,81]. The safety analysis showed no significant difference between the study groups with regard to major adverse events (including new-onset diabetes), with only a higher rate of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%) [82].

2.4. Non-HDL-C, HDL-C, and TG as a secondary target

One of the main problems in the treatment of patients with lipid disorders is that, regardless of the efficacy of cholesterol-lowering treatment on LDL-C, the residual risk of ASCVD

remains significantly high in a large proportion of patients. Such situation is thought to be a direct consequence of the persistent high concentrations of other atherogenic particles involved in the atherosclerotic process. Non-HDL cholesterol (non-HDL-C), that is calculated as the difference of TC minus HDL-C, is a reliable estimate of the total amount of atherogenic lipoproteins circulating in the plasma (VLDL, VLDL remnants, intermediate-density lipoproteins (IDL), LDL, Lp(a)) [12]. The role of non-HDL-C in predicting ASCVD is well defined: it has been found that any increase in the levels of baseline non-HDL-C of 1 mg/dL corresponds to a 5% increase in the risk of cardiovascular death [83]. Furthermore, the European Prospective Investigation into Cancer and Nutrition (EPIC) study proved that, in the group of patients considered to be on target for LDL-C levels (<100 mg/dL), the presence of high levels of non-HDL-C (>130 mg/dL) were responsible for increased incidence of CHD compared to the ones with lower non-HDL-C [84] Given the impact of elevated TG levels in the calculation of LDL-C with the Friedewald formula and in order to reach a more accurate assessments of CHD risk in those subjects with plasma triglycerides (TGs) in the range 200–499 mg/dL, the use of non-HDL-C has been advocated as a secondary target of therapy. A significant reduction of non-HDL-C has been found to be an important marker of lower CHD risk [85]. A meta-analysis by Robinson et al. showed that different strategies of intervention mainly based on the reduction of non-HDL-C levels (e.g. diet rich in PUFAs, several pharmacological treatments, ileal bypass) resulted in a linear decrease of CHD risk. This evidence suggests that non-HDL-C, along with LDL, could be considered both a marker and a target of cardiovascular prevention [86].

Low levels of HDL-C have shown to be a strong and independent ASCVD risk factor in several studies. In fact, it is included in most of the tools available for the assessment of CV risk [9]. The strong inverse correlation between plasma HDL-C concentrations and CHD and has generally supported the concept that increasing the plasma levels of HDL-C by pharmacological agents would contribute to the prevention of CHD. However, recent genetic analysis/Mendelian randomization studies) and a number of clinical trials carried out with the CETP-inhibitors, have actually failed to demonstrate a significant benefit and to support a causal role for HDL-C in patients with CHD, supporting a marginal and probably secondary role of HDL-C in atherosclerotic disease [87].

While the popularity of HDL-C as CV risk factor progressively declined, the importance of serum TGs as a causal risk factor for ASCVD got the stage. The epidemiological evidence connecting serum TG levels and CHD risk has progressively increased beyond the causative role of LDL-C: high TGs levels are often associated with low HDL-C, and a high concentration of small dense LDL particles and this combination results in an elevated atherogenic capacity [88]. The role of serum TGs and Triglycerides Rich Lipoproteins (TRLs) as causal risk factor for CHD is also supported by genetic studies [87]. An interesting paper published by Do et al. in *Nature Genetic*, clearly discriminated the primary effects of TGs on CHD risk from those of elevated LDL-C [89]. On the other side, the evidence of the clinical benefits of lowering high TGs levels is still debated and largely based on metanalysis, subgroups or post-hoc analyses of large trials [12]. In the PROVE IT-TIMI 22 trial, involving patients hospitalized for an ACS and effectively treated with statins, a reduced risk of recurrent coronary events was observed in presence of serum TGs levels below 1.7 mmol/L (150 mg/dL) [90]. Accordingly, a pooled analysis of the TNT and IDEAL trials have reported a 63% higher risk of new cardiovascular events in patients in the highest quintile of TGs compared to the lowest quintile [91].

2.4.1. Pharmacological interventions

In terms of treatment, statins have a limited efficacy in improving serum TG levels and atherogenic dyslipidemia. The same is for PCSK9 inhibitors that have demonstrated an interesting capacity to improve the Lp(a) profile. The most effective drugs improving serum TG and atherogenic dyslipidemia are unquestionably fibrates and ω-3 polyunsaturated fatty acids (PUFAs)

2.4.2. Fibrates

Fibrates are synthetic ligands for peroxisome proliferator-activated receptor-α (PPAR-α), whose activation leads to β-oxidation of free fatty acids in the liver and reduces the availability of these molecules for VLDL-C synthesis. The hallmark of fibrate therapy is a substantial decrease of plasma TG levels (ranging from 30% to 50%), and a moderate increase of HDL-C levels (ranging from 5% to 15%) [92]. The results of the studies and meta-analyses on cardiovascular effects of fibrates are controversial: while some studies suggest a lack of benefit in the general population [93,94], other evidence has reported demonstrating a reduction in major CVD events (especially coronary) in patients with high TGs and low HDL-C [95,96]. In the Bezafibrate Infarction Prevention (BIP) and the Lower Extremity Arterial Disease Event Reduction (LEADER) secondary prevention trials, patients the treatment with 400 mg/day of bezafibrate, an agonist of all PPARs subtypes (PPARα, PPARγ, and PPARδ), failed to reduce the rate of fatal or non-fatal AMI [97]. Comparable results were obtained by treating with bezafibrate patients in primary CVD prevention [98]. Conversely, in the VA-HIT study, the administration of 1200 mg/day of gemfibrozil to male patients with a history of CHD, resulted in a 22% reduction of CHD events after 5 years follow-up. These findings have not been confirmed by other studies and meta-analysis [97]. In the diabetic population of the ACCORD-lipid trial, the treatment with fenofibrate on top of statin therapy reduced the rate of major CV events only in patients with hypertriglyceridemia and low HDL-C [99]. These results have been confirmed after an extended follow-up of the study [100]. A recent Cochrane review summarizing the effects of fibrates in monotherapy or in combination with other lipid-modifying has shown a reduction of 16% in the risk of combined outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in comparison to placebo or usual care. The benefits of fibrate therapy may no longer be relevant in the presence of background therapy with statins [98]. As a consequence, the International Atherosclerosis Society (IAS) and the European Society for Atherosclerosis (EAS) suggest that the addition of a fibrate should be considered [12,101] I patients where non-HDL-C and triglycerides remain elevated when the LDL-C goal is achieved [98].

New members of the fibrates family are currently under investigation and the most promising is Pemafibrate, with selective activity towards PPARα, that demonstrated an interesting capacity of modifying the lipid profile with a reduced incidence of side effects compared to fenofibrate [102]. However, it clinical evidence is still preliminary.

Fibrates are generally well tolerated with mild adverse effects: gastrointestinal symptoms and skin rash have been reported in <5% and 2% of patients, respectively. Myopathy, liver enzyme elevations and cholelithiasis represent other possible adverse effects [103]. The risk of myopathy is greater in patients with CKD, and it differs with different fibrates, especially when they are used in combination with statins. The interaction between fibrates and statins can be explained by the pharmacological effects of fibrates on the metabolic pathway of the statins. For instance, Gemfibrozil inhibits the glucuronidation of statins hence leading to a significant increase in their plasma concentrations. Since fenofibrate and gemfibrozil follow different pharmacokinetic pathways, the risk of myopathy is much less frequent when statins are combined with fenofibrate [103]. Fibrates can also raise serum levels of creatinine and homocysteine. Data from a recently published meta-analysis suggest that the reduction in calculated glomerular filtration rate (GFR) does not indicate any adverse effects on kidney function and is entirely reversible by discontinuing the fibrates administration. High homocysteine levels have been considered to have some prothrombotic effect without any clear-cut causative association between the increase in homocysteine induced by fibrates and the venous thromboembolic events. In particular, the increased trend for deep vein thrombosis that was seen in the FIELD study was actually correlated with pre-treatment homocysteine levels [104].

2.4.3. Nicotinic acid

Nicotinic acid has a broad, dose-dependent, lipid-modulating effect that involves an increase in HDL-C (up to 25%) and a reduction of LDL-C (up to 15–18%) and TGs (up to 20–40%) [105]. This effect, at least in part, seems to be mediated by its action on hormone-sensitive lipase in adipose tissue. In the liver, nicotinic acid inhibits diacylglycerol acyltransferase-2, ensuing in decreased secretion of VLDL particles; this is also reflected by the reductions in both IDL and LDL particles. Nicotinic acid increases HDL-C primarily by the stimulation of apoA1 production in the liver [106].

The impact of niacin therapy on cardiovascular outcome was the object of a meta-analysis published in 2010 that included 11 randomized controlled trials. In these studies, the use of niacin, mainly in combination with other lipid-lowering strategies, led to a significant reduction in major coronary events (25% reduction), as well as a reduction in stroke by 26%, and all cardiovascular events by 27%. Unfortunately, the absence of appropriately powered studies did not allow any definite conclusion about the effects of niacin monotherapy on major CV events [105]. More recently the results of the HPS2-THRIVE [107] and the AIM-HIGH [108] studies carried out on a larger sample size of high-risk patients, did not demonstrate any significant effect of different formulations of niacin (± statins) in the prevention of major CV event with an increased risk of hemorrhagic stroke. The lack of preventive outcomes was, however, associated with a high rate of untoward adverse effects.

The two almost unavoidable side effects with nicotinic acid are flushing and the increase in serum uric acid concentration [109] that appear with a different time-course during treatment with niacin. Indeed, while the flushing occurs after the first dose of the drug, the increase in uric acid levels is a consequence of a long-term administration. The nicotinic acid treatment is also associated with severe gastrointestinal side effects and can worsen the glycaemic control [108].

Since the results of the two large studies concerning nicotinic acid [107,108] have shown no beneficial CV effect and an increased rate of serious adverse events, no medication containing nicotinic acid is currently approved in Europe. More in general, niacin is no longer indicated as an add-on therapy to reduce cardiovascular disease risk in statin-treated subjects.

3. ω-3 Polyunsaturated fatty acids

ω-3 Polyunsaturated fatty acids (ω-3 PUFA) [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] are used at pharmacological doses (2–4 g/day) to lower TGs. The underlying mechanism is poorly understood, although it may be in part related to their ability to interact with lipoprotein-lipase and PPARs and to a decreased secretion of apoB, with a particular reduction in VLDL [110].

Observational studies in Western and Asian populations have reported that regular consumption of fish is associated with lower risks of death from CHD. This was only partially confirmed by several large trials that have reported conflicting results [110]. Two recent meta-analyses suggested that ω-3 PUFA do not modify the rate of fatal or non-fatal coronary artery disease or any major vascular events [110,111]. However, the metanalyses should be interpreted with caution because of the heterogeneity of the study involved and the treatment approach. First of all, they compare studies using different doses and formulations (with different pharmacokinetics) of fish oil, EPA alone, or the combination of EPA+DHA. Second, neither dietary intake of ω-3 PUFA nor the blood levels of ω-3 PUFA after therapy are taken into account, even though this represent the better predictor of positive outcome [112].

Finally, the recent publication of the results of the Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention (REDUCE-IT) Trial has shown a beneficial effect of purified EPA in 8179 patients with high CV risk and TG levels between 135 and 499 mg/dL despite appropriate statin therapy [16]. Adding 2 g of EPA twice daily to statin treatment reduces by 25% the relative risk of MACE during a follow-up of 4.9 years. The positive effect could be mainly related to the correct target of patients involved in the trial (moderately hypertriglyceridemic patients with optimal LDL-C levels), the adequate PUFA selection (icosapent ethyl) at the adequate dosage.

The most common ω-3 PUFA adverse events are gastrointestinal events, such as belching, dyspepsia and taste disturbances, occurring in up to 3–4% of patients. Trials with omega-3-acids have demonstrated prolongation of bleeding time, although the effect has neither exceeded safety limits nor produced clinically significant bleeding episodes [113].

4. Conclusions

Dyslipidemia is widely prevalent in adult population and often requires pharmacological treatment. The main lipid-lowering drugs with a proven effect on lipid control and prevention of CV disease are statins, alone or associated with ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, fenofibrate, polyunsaturated fatty acids. Improvement in the use of these drugs is mandatory by increasing patient persistence and the rate of attainment of desired LDL-Cholesterol and triglycerides levels.

5. Expert opinion

Hypercholesterolemia is the only reversible CV risk factor with a direct and linear relationship between its reduction and the clinical efficacy without apparent J-curve effect. This applies also to serum TG even if to a lesser extent of confidence. An overwhelming amount of data supports the use of the LDL-C lowering drugs (statins, ezetimibe and PCSK9 inhibitors) in order to reduce the CV risk. Their efficacy is largely proportional to their ability to reduce the LDL-C plasma level, in agreement with the LDL-C targets based on the individual CV risk and the results of randomized clinical trials. On the other side, a growing body of epidemiological and genetic evidence supports the role of hypertriglyceridemia as an additional risk factor for CV disease. The overall impact of serum TG is probably weaker than LDL-C in the general population, but they could exert a primary role in some sub-populations of high-risk patients (e.g. diabetes and metabolic syndrome). A recent very large study published in JACC has clearly demonstrated an absolute increase in the risk of MACE in patients with high TGs levels not eligible for statin treatment according to risk cards or guidelines [114]. Most of the trials carried out with TG lowering drugs have given limited results in term of CV risk reduction, probably because of the heterogeneity of the patients and the lack of high-TG as inclusion criteria. Anyway, the recent data from the REVEAL-IT trial have demonstrated the importance of treatment in patients with high TG levels and have raised new interest in TG lowering treatment for CV risk reduction.

However, despite the huge number of favorable results, a large proportion of subjects with lipid abnormalities still have elevated plasma lipid levels. This could have several possible explanations: the lack of perception of health risk related to dyslipidemia (by patients and physicians), the alarm for statin-related side effects (by patients and physicians), and the therapeutic inertia (by physicians) [115,116]. The cost of drugs is currently negligible in most part of the world, since the price of statins and ezetimibe has been dramatically reduced after patent expiry with the availability of generic drugs. Currently, the issue of price applies only to the expensive PCSK9 inhibitors, whose indication is however limited to high-risk subjects, where the cost–benefit ratio is more favorable [117]. The main current challenges in the modern approach to lipid disorders are: the improvement of the patient persistence on therapy, the increase in the percentage of patients reaching the ambitious LDL-C target and the control of all the other lipid fraction (in particular s-TG) influencing the probability of a major CV event beyond LDL-C [12]. The solution of the problem could be the progressive titration of drug dosages, the increased care for possible pharmacological interaction, and the extensive use of fixed-dose, single-pill combination, tailoring the drug choice on the patient profile.

The available lipid-lowering drugs are potentially able to control both LDL-C and TG levels in most patients and in daily clinical practice. The association of lifestyle improvement, high doses of high potency statins and ezetimibe is able to improve LDL-C level in more than two-third of the patients [118], thus largely restricting the number of patients to be treated with more innovative and expensive drugs. Furthermore, the prescription of fenofibrate or highly dosed PUFAs (alone or in association with statins) could dramatically improve TG plasma levels. As it regards the use of PUFAs, it has yet not fully clarified which kind of pharmaceutical formulation, eicosapentaenoic acid/docosahexaenoic acid ratio, and dosage are the most cost-effective. However, the REDUCE-IT trial [16] has suggested that a relatively high dose is needed to obtain an effective cardiovascular disease prevention. Of course, optimization of lipid profile should not exclude the management of any secondary causes of dyslipidemia (i.e.: hypothyroidism, insulin-resistance), improvement in lifestyle and use of metabolically neutral concomitant medications. Finally, we have not included in this review some possible therapeutic options as Mipomersen and Lomitapide that are very expensive drugs with very specific indication for the treatment of HoFH resistant to other standard available treatment.

In conclusion, the treatment of lipid disorders is based on a remarkable number of effective therapeutic options that have demonstrated their capacity of reducing the rate of major cardiovascular diseases and mortality. A relatively large number of trials are currently evaluating the clinical effect of new lipid-lowering drugs that may integrate the current treatments. Nevertheless, the need for new therapeutic solutions appears subsidiary to an adequate prescription of the available options and their combination that can make the use of future drugs limited to a narrow range of non-responders patients.

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