Maciej Banach *Editor*

Combination Therapy In Dyslipidemia

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Preface

The idea of writing a book on the combination therapy in lipid disorders came out after the presentation of the American College of Cardiology (ACC)/American Heart Association (AHA) (2013) [1] and the British National Institute for Health and Care Excellence (NICE) (2014) lipid guidelines [2], which based their recommendations on randomized controlled trials (RCTs) only and did not suggest any combination therapy for dyslipidemic patients. The large discussion has started since that time among lipidologists and other physicians involved in the lipid disorder therapy, not only due to the fact that the experts of these guidelines did not decide to include any genetic, perspective, or epidemiological cohort studies and meta-analyses but also on the quality and selection criteria of included RCTs and whether one should follow these recommendations, and especially whether there is indeed no effective combination therapy for lipid disorder patients available [3,4]. The correct answer on this question is important due to the fact that we can observe more and more patients with severe dyslipidemias, mostly without achieved therapy goals [5], as well as subjects with statin intolerance (even up to 15–20 %), for which combination therapy might be often the only option [6, 7].

The book presents not only the most current knowledge on the different options of the combination therapy of dyslipidemia but also the future possible therapies, for which the studies at different phases have been still ongoing, the discussion around polypills, and on the role of nutraceuticals/functional food as a potentially effective option of lipid-lowering therapy. I have invited Prof. Patrick Moriarty to present the most current knowledge on the treatment of the patients with most severe lipid disorders with apheresis and lipid-lowering drug combination [8]. Prof. Nathan Wong presented the recent therapeutic achievements of wide approach to high-risk patients not only with dyslipidemia but also with hypertension [9], and as a continuation of this important subject, Prof. Jolanta Malyszko evaluated the drug combination with olmesartan and rosuvastatin [10]. Finally, Prof. Manfredi Rizzo continued the discussion started in the chapter of my authorship on the combination therapy with statins and fibrates [11], presenting the current evidences on the application of simvastatin and fenofibrate in patients with dyslipidemia [12].

Taking this opportunity, I would like to kindly thank to all the Experts that agreed to participate in this project despite numerous activities, as well as to the Springer's Editors, as only thanks to them you may have the unique book, which raise very important and debatable issue on the combination therapy in lipid disorder patients.

Lodz, Poland Maciej Banach, MD, PhD, FNLA, FAHA, FESC, FASA

References

1. Stone NJ, Robinson JG, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S1–45.
2. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. National Clinical Guideline Centre (UK); 2014.
3. Colantonio LD, Baber U, Banach M, Tanner RM, Warnock DG, Gutiérrez OM, Safford MM, Wanner C, Howard G, Muntner P. Contrasting cholesterol management guidelines for adults with CKD. J Am Soc Nephrol. 2015;26(5):1173–80.
4. Banach M, Aronow WS, Serban C, Sahabkar A, Rysz J, Voroneanu L, Covic A. Lipids, blood pressure and kidney update 2014. Pharmacol Res. 2015;95–96C:111–25.
5. Rizzo M, Barylski M, Rizvi AA, Montalto G, Mikhailidis DP, Banach M. Combined dyslipidemia: should the focus be LDL cholesterol or atherogenic dyslipidemia? Curr Pharm Des. 2013;19(21):3858–68.
6. Banach M, Serban C, Sahebkar A, Ursoniu S, Rysz J, Muntner P, Toth PP, Jones SR, Rizzo M, Glasser SP, Lip GY, Dragan S, Mikhailidis DP; Lipid and Blood Pressure Meta-analysis Collaboration Group. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. Mayo Clin Proc. 2015;90(1):24–34.
7. Banach M, Rizzo M, Toth PP, et al. Statin intolerance – an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci. 2015;11(1):1–23.
8. Moriarty P, Lipid lowering therapy and apheresis – indications and outcomes. In: M Banach, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 143–152.
9. Zhao Y, Wong ND. Combination of lipid lowering agents with antihypertensive drugs – a joint fight against the two most important risk factors? In: M Banach, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 153–164.
10. Gozdzikiewicz-Lapinska J, Malyszko J. Drug evaluation: olmesartan medoxomil + rosuvastatin for the treatment of dyslipidemia and concomitant risk factors: a chance for better compliance? In: M Banach, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 191–200.
11. Chruściel P, Mikhailidis DP, Toth PP, Rysz J, Banach M. Statins and fibrates – should it be recommended? In: M Banach, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 11–24.
12. Nikolic D, Katsiki N, Toth PP, Banach M, Al-Waili K, Al-Rasadi K, Rizzo M, Mikhailidis DP. Drug evaluation. The combination of fenofibrate and simvastatin for the treatment of dyslipidemia: when and for whom? In: M Banach, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 179–190.

Contents

Chapter 1
Use of Combination Statin and Bile Acid Sequestrant Therapy to Treat Dyslipidemia

Peter P. Toth, Dragana Nikolic, Manfredi Rizz, Jacek Rysz, and Maciej Banach

Introduction

Lipid management guidelines promulgated around the world continue to emphasize the need to reduce serum levels of low-density lipoprotein cholesterol (LDL-C) in order to reduce risk for acute cardiovascular events in both the primary and secondary prevention settings [1–3]. There is growing consensus that when it comes to LDL-C management, lower is better with no apparent lower limit that is discernible from current evidence, i.e., there is greater and greater benefit as LDL-C decreases with no apparent loss in safety [4–8]. Dyslipidemia and coronary artery disease (CAD) are widely prevalent throughout the world. Considerable effort continues to be focused on expanding the appropriate use of lipid-lowering medication in order to more optimally reduce the burden of atherogenic lipoproteins in serum.

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Much evidence suggests that despite the known relationship between LDL-C and risk for such sequelae of CAD as myocardial infarction, ischemic stroke, and cardiovascular mortality, LDL-C levels tend to be undertreated [9–11]. Some of this undertreatment stems from continued reluctance to prescribe high-dose high-potency statins, relatively high prevalence of muscle-related side effects, concerns about liver or renal toxicity, and patient resistance. The use of a statin is first-line therapy in all current lipid guidelines. However, patients frequently require adjuvant therapy with other types of lipid-lowering medication which improves goal attainment rates and can allow for the use of a lower dose of a statin in patients who do not tolerate higher doses of these agents [12, 13].

Lipid guidelines encourage the use of adjuvant therapies as appropriate in order to facilitate LDL-C and non-HDL-C goal attainment. Established LDL-C-reducing adjuvant therapies include plant stanols/sterols, ezetimibe, nicotinic acid, and the bile acid sequestrants (BASs). This chapter focuses on the BAS used as monotherapy and in combination with statins to reduce atherogenic lipoproteins as well as improve glucose homeostasis in patients with diabetes mellitus (DM).

The Role of Bile Acids in Gastrointestinal Physiology

The bile acids (cholic acid, deoxycholic acid) are produced by hepatocytes via the activity of cholesterol 7-alpha-hydrolylase, which is the rate-limiting enzyme for bile acid (BA) formation (Fig. 1.1) The BAs are conjugated with glycine to enhance solubility and pumped out of hepatocytes into the biliary tree by two ATP-binding membrane cassette transport proteins B4 and B11 (ABCB4 and ABCB11). The BAs are concentrated and stored in the gallbladder and are pumped into the duodenum in response to cholecystokinin stimulation induced by feeding and lipid ingestion. As the BAs are released into the small intestine, they serve as detergents and facilitate the solubilization of lipids, cholesterol, and fat-soluble vitamins (A, D, K). The BAs are recovered by the terminal ileum, and 95 % of the total BA mass is pumped back into the portal circulation (thus undergoing enterohepatic recirculation) by multiple transporters, including the apical sodium bile acid transporter and heterodimeric organic solute transporter Ostα/Ostβ. In order to complete the cycle of enterohepatic recirculation, the BAs are recovered by hepatocytes via the sodium taurocholate cotransporting protein and a variety of organic anion transport proteins.

The regulation of BA production and enterohepatic recirculation is complex [14]. If there is increased demand for BA, there is increased conversion of cholesterol into BA via cholesterol 7-alpha-hydroxylase. This results in a drop in intracellular cholesterol levels which activates expression of sterol regulatory element-binding proteins (SREBPs). The SREBPs are nuclear transcription factors that regulate the expression of genes involved in cholesterol and lipid metabolism.

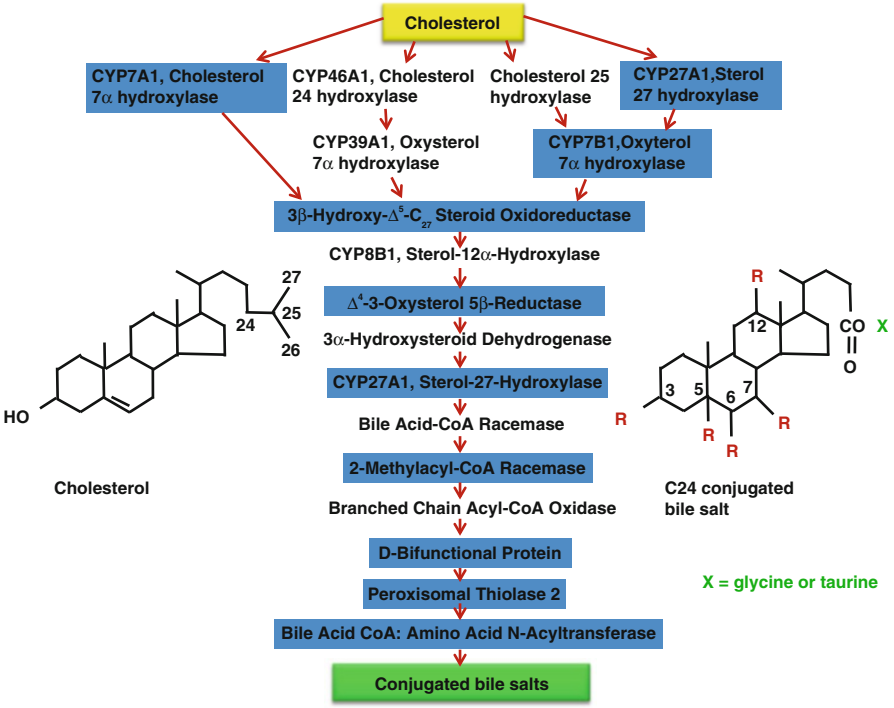

Fig. 1.1 Pathway for bile acid biosynthesis. In humans bile acids are conjugated to glycine, while in rodents they are conjugated to taurine (Reproduced with permission from Russell [50])

This results in an increase in 3-hyroxy-3-methylglutaryl-coenzyme A reductase (the rate-limiting step in cholesterol biosynthesis) activity and increased cell surface expression of the LDL receptor. The net effect of this sterol sensing is to increase intracellular cholesterol by increasing its rate of synthesis and its uptake from the systemic circulation [15].

Once taken up by the ileum, BA can agonize a variety of nuclear transcription factors that provide a negative feedback loop on hepatic BA biosynthesis. As an initial step, BA binds to the farnesoid X receptor (FXR) within ileal enterocytes and hepatoctytes. In the ileum, as BA binds FXR, this induces increased expression of fibroblast growth factor 19 (FGF19). FGF19 is endocrinologically active and binds to fibroblast growth factor receptor 4 (FGFR4), which then inhibits expression of hepatic cholesterol 7-alpha-hydroxylase via ERK and JNK dependent pathways. The BA can also inhibit hepatic biosynthesis of BA more directly. As BA binds to FXR within the hepatocyte, this stimulates the production of small heterodimer partner (SHP), which then suppresses activity of nuclear receptor liver homolog receptor (LHR-1), a potent activator of cholesterol 7-alpha-hydroxylase [16] (Fig. 1.2). FXR also regulates BA transport in and out of the hepatocyte by controlling the expression of ABCB4, ABCB11, and Ostα/Ostβ.

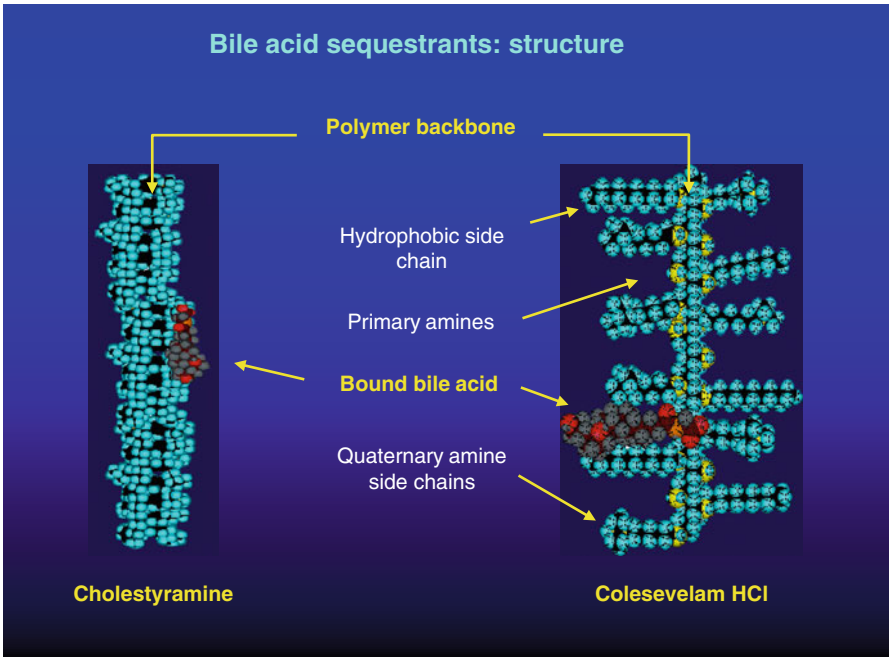

Fig. 1.2 Chemical structure of two widely used bile acid sequestration agents

Bile Acid Binding Resins

Bile acid sequestrants (BASs) are efficacious drugs for lowering serum levels of LDL:-C. Three of these agents are in widespread use: colestipol, cholestyramine, and colesevelam. They act as anion exchange resins and are not absorbed systemically. All are orally administered and serve to bind bile acids in transit through the gut. They reduce LDL-C levels by increasing the diversion of hepatic cholesterol for BA biosynthesis and by stimulating increased expression of the LDL receptor and thereby increasing LDL-C clearance [17]. All of these drugs increase fecal elimination of BA significantly [18, 19] and can provide dose-dependent reductions in LDL-C of 12–30 %. The impact of these drugs on high-density lipoprotein cholesterol (HDL-C) tends to be modest (1–3 %). They should be taken with meals when intraluminal BA levels would be highest. They provide additive reductions in LDL-C when patients are concomitantly treated with statins. These drugs are contraindicated with patients with hypertriglyceridemia as the BAS can exacerbate the elevation in triglycerides.

In one study evaluating the addition of colesevelam to statin therapy, there was a 21 mg/dL incremental reduction in LDL-C compared to placebo and increased the number of patients able to reach an LDL-C < 100 mg/dL fourfold [20]. In addition, colesevelam therapy induced an incremental 23 % reduction in high-sensitivity

C-reactive protein. Combination therapy with colesevelam and statins is safe and efficacious and can allow for the use of a lower dose of a statin and still attain a significant LDL-C reduction [12, 21–23]. The BAS can also be safely combined with ezetimibe [24] and fenofibrate [25] with additive reductions in LDL-C. Of interest is the observation that colesevelam significantly reduces LDL particle number and increases LDL particle size [26, 27].

Gastrointestinal side effects dominate the adverse event profile with all of the BASs. These include constipation, flatulence, and, occasionally, diarrhea. Rarely, bowel obstruction can occur [28]. There is no clinically significant risk for adverse events related to renal, hepatic, or hematologic function or drug-drug interactions since the drugs do not act systemically. It is generally advisable to take other medications 1 h before or 2 h after ingesting a BAS since these resins can also bind and prevent their absorption.

Clinical Trials with BAS

The Lipid Research Clinics Coronary Primary Prevention Trial evaluated the efficacy of cholestyramine for reducing first-time cardiovascular events in 3806 men with hypercholesterolemia. The trial was performed in the 1980s prior to the introduction of statins. Cholestyramine dosed at 24 g/day over a mean duration of 7.4 years. was associated with a significant 19 % reduction in risk for the primary composite end point of nonfatal myocardial infarction (MI) and mortality. Evaluated individually, nonfatal MI was reduced by 19 % and CV mortality decreased by 25 %. All-cause mortality was not decreased significantly. In addition, the incidence rates for new positive treadmill stress tests, angina pectoris, and need of coronary artery bypass grafting (CABG) surgery were decreased by 25, 20, and 21 %, respectively, in the cholestyramine group compared to the placebo treatment arm. [29] This trial demonstrated that a 20 % reduction in LDL-C correlates with a significant reduction in risk for CV events [30].

A variety of small coronary angiographic studies evaluated the capacity of BAS used in combination with other lipid-lowering medications to impact rates of CAD progression. In the National Heart, Lung and Blood Institute Type II Coronary Intervention Study, patients with dyslipidemia and CAD were treated with a low-fat, low-cholesterol diet and randomly assigned to treatment with either 6 g cholestyramine four times daily or placebo. This double-blind study evaluated the effects of cholestyramine on the progression of CAD as assessed by quantitative coronary angiography (QCA) in 116 patients treated for 5 years [31]. After adjustment for risk factor covariates between groups, 33 % of placebo-treated and 12 % of cholestyramine-treated patients manifested lesion progression among target lesions > 50 % occlusive ($p < .05$). The Cholesterol-Lowering Atherosclerosis Study (CLAS) was another randomized, placebo-controlled QCA trial that evaluated the impact of combined colestipol (30 g daily) and nicotinic acid (4.2 g daily) treatment in 162 men aged 40–59 years with a history of CABG revascularization [32]. During

2 years of treatment, there was a 43 % reduction in LDL-C and a 37 % increase in high-density lipoprotein cholesterol (HDL-C). Treated patients experienced a reduction in the mean number of lesions with progression as well as development of new coronary atheromatous plaque or occlusive disease in saphenous vein bypass grafts (all $P < .03$). This trial also demonstrated perceptible improvement in overall coronary status, which occurred in 16.2 % of colestipol-niacin-treated vs 2.4 % placebo-treated ($P = .002$) patients. In a subgroup analysis of the CLAS trial, 103 patients who remained on therapy demonstrated even more impressive results with 4 years of therapy [33]. Drug treatment was associated with continued improvement in nonprogression (52 % drug- vs 15 % placebo-treated) as well as regression (18 % drug- vs 6 % placebo-treated) of atherosclerotic plaque in coronary artery lesions. Significantly fewer drug-treated subjects developed new atherosclerotic plaques in coronary arteries (14 % drug- vs 40 % placebo-treated) and saphenous vein bypass grafts (16 % drug- vs 38 % placebo-treated).

Other studies also explored the impact of combination therapy on atherosclerotic disease burden using combinations of lipid-lowering therapies that included BAS. In the Familial Atherosclerosis Treatment Study, patients underwent dietary counseling and were randomly assigned to one of three treatments: lovastatin (20 mg twice daily) and colestipol (10 g three times daily); niacin (1 g four times daily) and colestipol (10 g three times daily); or conventional therapy (diet, exercise) with placebo [34]. Mean changes in LDL-C and HDL-C were relatively small in the conventional treatment group (−7 and +5 %, respectively). In the treatment arms, these changes were much more significant with lovastatin/colestipol (−46 and +15 %) or niacin/colestipol (−32 and +43 %). In the placebo group, 46 % of patients experienced plaque lesion progression, and 11 % experienced regression. In the active treatment arms, plaque progression occurred in 21 % of those treated with lovastatin and colestipol and 25 % of those treated with niacin and colestipol. Significantly more patients experienced plaque regression in the lovastatin/colestipol (32 %) and niacin/colestipol (39 %) treatment groups compared to placebo (both $P < 0.005$). Multivariate regression LDL-C reduction and HDL-C elevation both correlated with regression of established coronary plaques. The University of California, San Francisco, Specialized Center of Research Study (UCSF-SCOR) evaluated the impact of therapy with a combination of colestipol, niacin, and lovastatin on CAD progression in 72 patients with heterozygous familial hypercholesterolemia over 2 years of follow-up [35]. The primary outcome measure was within-patient mean change in percent area stenosis. The mean change in percent area stenosis for the control and treatment arms was +0.80 (net progression) and −1.53 (net regression), respectively ($P = .039$). The change in percent area stenosis correlated with attained levels of LDL-C. In the St. Thomas Arteriosclerosis Regression Study (STARS), the use of 16 g of cholestyramine plus dietary measures was more efficacious than placebo or diet alone for promoting coronary plaque regression in men with established CAD [36]. Clearly, BAS used either alone or in combination with other lipid-lowering medications impacts CAD in a beneficial manner in terms of both disease progression and risk for CV events.

Impact of BAS on Gluose Metabolism

In addition to their lipid-lowering effects, the BASs also have the capacity to beneficially impact glucose metabolism [37–39]. In general, the use of a BAS can reduce hemoglobin A1C levels by approximately 0.5 % and also beneficially impact fasting and postprandial serum glucose levels in a dose-dependent manner. The BASs have been shown to provide incremental reductions in hemoglobin A1C levels when used in combination with metformin [40], insulin [41], or sulfonylurea drugs [42]. In patients with both dyslipidemia and type 2 DM, BAS therapy can provide efficacy for reducing atherogenic lipoprotein burden in serum and improving glycemic control.

There appear to be multiple mechanisms by which the BAS may help to improve glycemic control. The first is mediated by FXR and results in less hepatic gluconeogenesis (via inhibition of phosphoenolpyruvate carboxykinase) [43] and increased glycogen synthesis [44, 45]. The second involves TGR-5, a G-protein-coupled bile acid receptor [46, 47]. As bile acids increase in the luminal compartment of the ileum, they can bind TGR-5, which in turn activates the production of glucagon-like peptide-1 (GLP-1) by enteric L cells [48]. As GLP-1 levels rise, insulin production is stimulated by pancreatic islet cells, and serum glucose levels improve. There is also evidence that activation of FGF19 suppresses hepatic gluconeogenesis [49]. Yet other mechanisms may also play a role.

Conclusions

1. Lipid treatment guidelines promulgated throughout the world emphasize that reducing LDL-C is the primary goal in patients at risk for sustaining acute cardiovascular events.
2. Risk-stratified LDL-C goal attainment rates are suboptimal. Many patients with dyslipidemia are undertreated.
3. It is important to treat with appropriate doses and potencies of statins to reduce atherogenic lipoprotein burden in serum. If patients cannot attain LDL-C goals because they are treated with the highest dose of a statin or tolerate only low doses of these drugs, then it may be necessary to use adjuvant therapy with a BAS. In statin-intolerant patients, a BAS may be combined with ezetimibe as needed.
4. The BASs have been shown to induce meaningful reductions in LDL-C and reduce risk for cardiovascular events.
5. The BASs used either as monotherapy or in combination with other lipid-lowering drugs (statins, niacin) have been shown to retard rates of atherosclerotic plaque progression and even induce plaque regression.
6. The BASs potentiate improvements in glucose homeostasis by increasing intestinal L cell production and secretion of GLP-1 and reducing hepatic gluconeogenesis.

7. The BASs act within the gastrointestinal lumen to bind bile acids and promote their elimination in fecal waste.
8. The production of bile acids is regulated by a number of signaling pathways that control nuclear transcription factors responsible for the switching on an off of hepatic bile acid biosynthesis and cell surface recovery translocases along the hepatocyte cell surface.
9. The BASs do not act systemically and have a favorable safety profile. The elimination of BASs is independent of hepatic and renal function.

References

1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45.
2. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32:1769–818.
3. Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations. Can J Cardiol. 2009;25:567–79.
4. Wiviott SD, Cannon CP, Morrow DA, Ray KK, Pfeffer M, Braunwald E. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy a Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) substudy. J Am Coll Cardiol. 2005;46(8):1411–6.
5. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350:1495–504.
6. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol. 2006;48:438–45.
7. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267–78.
8. Emberson JR, Kearney PM, Blackwell L, et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One. 2012;7, e29849.
9. Shammas N, Lemke J, Deckert J, Toth P, McKinney D, Dippel E. Gender differences in adhering to national guidelines in a community lipid clinic. Prev Cardiol. 2006;9:215–8.
10. Peter PT, Victoria Z, Jane MS, Dave L. Lipid therapy utilization rates in a managed-care mixed dyslipidemia population. J Clin Lipidol. 2008;2:365–74.
11. Davidson MH, Maki KC, Pearson TA, et al. Results of the National Cholesterol Education (NCEP) Program Evaluation ProjecT Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. Am J Cardiol. 2005;96:556–63.
12. Armani A, Toth PP. Colesevelam hydrochloride in the management of dyslipidemia. Expert Rev Cardiovasc Ther. 2006;4:283–91.

13. Morrone D, Weintraub WS, Toth PP, et al. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. Atherosclerosis. 2012;223:251–61.
14. Mazuy C, Helleboid A, Staels B, Lefebvre P. Nuclear bile acid signaling through the farnesoid X receptor. Cell Mol Life Sci. 2015;72:1631–50.
15. Out C, Groen AK, Brufau G. Bile acid sequestrants: more than simple resins. Curr Opin Lipidol. 2012;23:43–55.
16. Goodwin B, Jones SA, Price RR, et al. A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. Mol Cell. 2000;6:517–26.
17. Shepherd J, Packard CJ, Bicker S, Lawrie TD, Morgan HG. Cholestyramine promotes receptor-mediated low-density-lipoprotein catabolism. N Engl J Med. 1980;302:1219–22.
18. Donovan JM, Von Bergmann K, Setchell KD, et al. Effects of colesevelam HC1 on sterol and bile acid excretion in patients with type IIa hypercholesterolemia. Dig Dis Sci. 2005;50:1232–8.
19. Grundy SM, Ahrens Jr EH, Salen G. Interruption of the enterohepatic circulation of bile acids in man: comparative effects of cholestyramine and ileal exclusion on cholesterol metabolism. J Lab Clin Med. 1971;78:94–121.
20. Bays HE, Davidson M, Jones MR, Abby SL. Effects of colesevelam hydrochloride on low-density lipoprotein cholesterol and high-sensitivity C-reactive protein when added to statins in patients with hypercholesterolemia. Am J Cardiol. 2006;97:1198–205.
21. Davidson MH, Toth P, Weiss S, et al. Low-dose combination therapy with colesevelam hydrochloride and lovastatin effectively decreases low-density lipoprotein cholesterol in patients with primary hypercholesterolemia. Clin Cardiol. 2001;24:467–74.
22. Hunninghake D, Insull Jr W, Toth P, Davidson D, Donovan JM, Burke SK. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL cholesterol additively. Atherosclerosis. 2001;158:407–16.
23. Knapp HH, Schrott H, Ma P, et al. Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. Am J Med. 2001;110:352–60.
24. Bays H, Rhyne J, Abby S, Lai YL, Jones M. Lipid-lowering effects of colesevelam HCl in combination with ezetimibe. Curr Med Res Opin. 2006;22:2191–200.
25. McKenney J, Jones M, Abby S. Safety and efficacy of colesevelam hydrochloride in combination with fenofibrate for the treatment of mixed hyperlipidemia. Curr Med Res Opin. 2005;21:1403–12.
26. Rosenson RS, Abby SL, Jones MR. Colesevelam HCl effects on atherogenic lipoprotein subclasses in subjects with type 2 diabetes. Atherosclerosis. 2009;204:342–4.
27. Rosenson RS. Colesevelam HCl reduces LDL particle number and increases LDL size in hypercholesterolemia. Atherosclerosis. 2006;185(2):327–30.
28. Merten DF, Grossman H. Intestinal obstruction associated with cholestyramine therapy. AJR Am J Roentgenol. 1980;134:827–8.
29. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA. 1984;251:351–64.
30. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA. 1984;251:365–74.
31. Brensike JF, Levy RI, Kelsey SF, et al. Effects of therapy with cholestyramine on progression of coronary arteriosclerosis: results of the NHLBI Type II Coronary Intervention Study. Circulation. 1984;69:313–24.
32. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA. 1987;257:3233–40.
33. Cashin-Hemphill L, Mack WJ, Pogoda JM, Sanmarco ME, Azen SP, Blankenhorn DH. Beneficial effects of colestipol-niacin on coronary atherosclerosis. A 4-year follow-up. JAMA. 1990;264:3013–7.

34. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. 1990;323:1289–98.
35. Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ. Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. JAMA. 1990;264:3007–12.
36. Watts GF, Lewis B, Brunt JN, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS). Lancet. 1992;339:563–9.
37. Garg A, Grundy SM. Cholestyramine therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. A short-term, double-blind, crossover trial. Ann Intern Med. 1994;121:416–22.
38. Yamakawa T, Takano T, Utsunomiya H, Kadonosono K, Okamura A. Effect of colestimide therapy for glycemic control in type 2 diabetes mellitus with hypercholesterolemia. Endocr J. 2007;54:53–8.
39. Zieve FJ, Kalin MF, Schwartz SL, Jones MR, Bailey WL. Results of the glucose-lowering effect of WelChol study (GLOWS): a randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesevelam hydrochloride on glycemic control in subjects with type 2 diabetes. Clin Ther. 2007;29:74–83.
40. Bays HE, Goldberg RB, Truitt KE, Jones MR. Colesevelam hydrochloride therapy in patients with type 2 diabetes mellitus treated with metformin: glucose and lipid effects. Arch Intern Med. 2008;168:1975–83.
41. Goldberg RB, Fonseca VA, Truitt KE, Jones MR. Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. Arch Intern Med. 2008;168:1531–40.
42. Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR. Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. Diabetes Care. 2008;31:1479–84.
43. De Fabiani E, Mitro N, Gilardi F, Caruso D, Galli G, Crestani M. Coordinated control of cholesterol catabolism to bile acids and of gluconeogenesis via a novel mechanism of transcription regulation linked to the fasted-to-fed cycle. J Biol Chem. 2003;278:39124–32.
44. Stayrook KR, Bramlett KS, Savkur RS, et al. Regulation of carbohydrate metabolism by the farnesoid X receptor. Endocrinology. 2005;146:984–91.
45. Yamagata K, Daitoku H, Shimamoto Y, et al. Bile acids regulate gluconeogenic gene expression via small heterodimer partner-mediated repression of hepatocyte nuclear factor 4 and Foxo1. J Biol Chem. 2004;279:23158–65.
46. Maruyama T, Miyamoto Y, Nakamura T, et al. Identification of membrane-type receptor for bile acids (M-BAR). Biochem Biophys Res Commun. 2002;298:714–9.
47. Kawamata Y, Fujii R, Hosoya M, et al. A G protein-coupled receptor responsive to bile acids. J Biol Chem. 2003;278:9435–40.
48. Prawitt J, Staels B. Bile acid sequestrants: glucose-lowering mechanisms. Metab Syndr Relat Disord. 2010;8 Suppl 1:S3–8.
49. Potthoff MJ, Boney-Montoya J, Choi M, et al. FGF15/19 regulates hepatic glucose metabolism by inhibiting the CREB-PGC-1alpha pathway. Cell Metab. 2011;13:729–38.
50. Russell DW. Fifty years of advances in bile acid synthesis and metabolism. J Lipid Res. 2009;50:S120–5.

Chapter 2
Statins and Fibrates: Should They Be Recommended?

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While waiting for the new effective agents for patients with lipid disorders, both low-density lipoprotein cholesterol (LDL-C) lowering as well as residual risk reducing, fibrates seem to be a very important alternative, especially for patients with atherogenic dyslipidaemia, which might be often observed in patients with diabetes and metabolic syndrome.

This chapter presents the current state of knowledge on fibrates, the potential benefits of the combination therapy with statins, and explains the doubts raised after US and European lipid guidelines in 2013 and 2014.

Fibrates' Mechanism of Action

Understanding the mechanism of action of fibrates itself took 30 years. The basic mechanism was identified only in the 1990s, when a new superfamily of nuclear receptors was discovered, different from the previously known steroid receptors,

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whose ligands may include a large group of compounds such as fatty acids and fibrates [1]. The receptors mediate the proliferative response of peroxisomes, and thus their name – peroxisome proliferator-activated receptors (PPARs) [2–5]. Today, three groups of the receptors – PPARα (NR1C1), PPARβ/δ (NR1C2) and PPARγ (NR1C3) – have been identified [3]. PPARα are located primarily in mitochondria-rich cells – in the liver, kidneys and heart as well as in the mucous membrane of intestines – while the two other types are expressed throughout the entire body [3–5]. Fibrates act as ligands primarily for PPARα (only bezafibrate activates α, β/δ and γ receptors to the same degree) [6–8]. An activated receptor recognises and binds to strictly defined DNA sites, thus causing activation or inhibition of a relevant gene – in the case of fibrates, it has been proven that binding to PPARα induces the expression of genes which are involved in intracellular processes of metabolism of fatty acids and genes controlling protein synthesis (enzymes and apolipoproteins [Apos]), connected with the metabolism of lipids and lipoproteins [9, 10].

The beneficial effect of fibrates on lipid levels is exerted via several mechanisms: (1) they enhance lipolysis by increasing the activity of lipoprotein lipase [11] and reduce hepatic production of Apo C-III, a component of very large density lipoprotein (VLDL), which inhibits the enzyme [12]; (2) they increase hepatic beta-oxidation of fatty acids, which are precursors of triglycerides (TGs) – reduction in the concentration of substrates for the production of TGs results in reduced production of TG-rich VLDL particles in the liver [13, 14]; (3) they increase the elimination of LDL particles – during therapy with fibrates, LDL lipoproteins having increased affinity for LDL receptor are formed, which significantly facilities and hastens their catabolism [15]. This leads to changes in LDL-C subfractions – mainly small dense lipoproteins are reduced, while the subfraction of larger LDL particles increases [15–17]; (4) they reduce the production of TG-rich lipoproteins by reducing the exchange of TGs and cholesterol esters between high-density lipoprotein (HDL) particles and VLDL particles [18]; (5) they increase the production of HDL-C – fibrates have the ability to increase the production of Apos A-I and A-II in the liver, which results in increased plasma levels of HDL-C and more efficient transfer of cholesterol from peripheral tissues [19, 20] and is associated with decreased concentration of Lp-AI (HDL subfraction containing Apo A-I without Apo A-II) and increased concentration of Lp-AI:AII [21, 22]. Recently, it has been postulated that favourable modification of the HDL subfraction towards larger particles might be possible, although the results are not unequivocal [23, 24].

In the light of the mechanisms described above, the clinical effects of fibrates are as the following: they reduce plasma levels of TG by 30–50 % and increase HDL-C levels by 2–20 %; however, their effect on LDL cholesterol levels is relatively weak – from even no effect (less than 5 %) to a 10–20 % reduction [7, 25, 26].

The Most Important Studies with Fibrates

The most important studies of fibrates include the Helsinki Heart Study (HHS) [27] and the Veterans Affairs high-density lipoprotein cholesterol intervention trial (VA-HIT) [28] – both with gemfibrozil – the Bezafibrate Infarction Prevention

(BIP) [29] and the Lower Extremity Arterial Disease Event Reduction (LEADER) [30] – both with bezafibrate – and two large studies with fenofibrate: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) [31] and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial [32].

Taking into account the fact that in many European countries only fenofibrate is available, the authors of this chapter have focused on the studies/trials dedicated to this fibrate. However, it is worth emphasising that in the light of high prevalence of dyslipidaemias and lack of efficacy of residual risk reduction, accessibility of such potent fibrates like gemfibrozil and bezafibrate would be much expected.

The FIELD was a multi-centre, double-blind, and randomised study that was aimed at determining whether therapy with fibrate, compared with placebo, reduces the risk of cardiovascular (CV) incidents in patients with type 2 diabetes (DMt2). The primary end point was either coronary heart disease (CHD) death or non-fatal myocardial infarction (MI) or both events combined [31]. Participants had to meet at least one of the following lipid criteria: serum total cholesterol (TC) levels 3.0–6.5 mmol/L (115–250 mg/dL) and/or TC-to-HDL-C ratio ≥4 or TG level 1–5 mmol/L (90–445 mg/dL). Individuals were not eligible if they: had indications for the use of other hypolipidemic agents (although the use of such agents during the study was allowed), had a CV event in the last 3 months or suffered from chronic kidney disease (CKD; creatinine >130 μmol/L) or chronic liver disease or symptomatic gallbladder disease [31].

The study finally involved 9,795 patients, mean time from the diagnosis of DMt2 was 5 years, the subjects were aged 50–75 years and the vast majority (7,664) of participants had no signs or symptoms of CVD at enrolment. After initial 16-week observation (4 weeks of diet, 6 weeks of placebo and 6 weeks of fenofibrate), the patients were randomised either to micronised fenofibrate 200 mg/day ($n=4,895$) or placebo ($n=4,900$). Median follow-up was 5 years [31]. The results were unconvincing – in the fenofibrate group, the rates of CHD deaths and non-fatal MI were reduced by 11 % (95 % confidence interval [CI]: −24 to 5; $p=0.16$), but the reduction was not significant, which was related to a significant drop in the non-fatal MI rate by 24 % (95 %CI: 6–37) and non-significant increase in the CHD death rate by 19 % (95 %CI: −10 to 56) [31]. The lack of significant reduction in the primary end point (apart from non-fatal MI) was widely discussed. It was especially pointed out that the lack of benefits from fenofibrate therapy might have been caused by more frequent use of statins in the placebo group (17 vs 8 %; adjusted analysis which allowed to withdraw all patients with statin therapy showed significant changes of primary end point in fenofibrate group) [31, 33]. It was due to the fact that the Heart Protection Study (HPS) was meanwhile published, and according to the recommendations based on its results, the FIELD investigators were forced to use statins in patients with diabetes [33]. Another possible explanation of these negative results was an unfavourable fibrate selection of subjects with relatively high baseline HDL-C levels (mean 42 mg/dL) in whom only slight increase in HDL-C was seen at the end of the study (by 1.2 %). It is known that the lower the baseline HDL-C, the greater the effect of fenofibrate, which was also seen in the FIELD study – in the subgroup of patients with the lowest baseline HDL levels (<40 mg/dL), a statistically significant reduction in CV events was seen in those receiving fenofibrate ($p=0.02$). However, it is worth

remembering that the slight increase in HDL levels in diabetic patients may have been caused by decreased affinity of fibrates for PPARα, which is seen in this group of patients [34]. On the other hand, it needs to be also taken into account that in the patients of diabetes we might expect the impaired HDL functionality, therefore this explanation seems to be also questionable [35].

Were there any benefits of fenofibrate therapy in the FIELD study? Of the secondary end points, a statistically significant 10 % reduction in all CV events was seen – CV deaths, MIs, strokes and coronary and carotid revascularisation (95 %CI: 1–19; absolute risk reduction by 1.4 %) [31, 33]. The inhibition of the progression of micro-angiopathic complications was also seen – fenofibrate reduced the risk of peripheral amputations ($p=0.011$), the progression of albuminuria ($p=0.002$) and diabetic retinopathy [33, 36]. In patients diagnosed with diabetic retinopathy prior to enrolment, retinopathy progression by at least two grades occurred considerably less frequently during therapy with fenofibrate (3 subjects [3.1 %] in the fenofibrate group vs 14 subjects [14.6 %] in the placebo group; $p=0.004$) [36]. Also, the need for laser therapy occurred less frequently (164 subjects [3.4 %] vs 238 subjects [4.9 %]; $p=0.0002$), which was reflected in a significant reduction in the composite end point of progression of retinopathy by two grades, progression of macular oedema and increase in the need for laser therapy [36].

Despite negative results of FIELD trial (mainly due to methodological limitations), ineffectiveness of statin monotherapy with persistent low levels of HDL-C and especially high levels of TG should prompt physicians to consider treatment with fenofibrate [33]. It is also of interest in the FIELD study, in a small subgroup of patients undergoing combination therapy, there was a significant reduction in coronary events' risk by 49 % ($p<0.001$) and all CV events by 26 % ($p<0.001$) [33, 36].

Because of the negative results obtained in the FIELD trial and new guidelines how to treat patients with DMt2 (=statins as a first line), there was a need for another trial investigating the effect of fenofibrate as an *add-on* to statin therapy in diabetic patients. In 2010, the results of another multi-centre, prospective, double-blind study with fenofibrate were announced – ACCORD LIPID, the lipid arm of the ACCORD study [32]. The fundamental question to consider was whether or not combination therapy with statin (simvastatin) and fibrate reduced CV risk compared with statin monotherapy in patients with DMt2. The study finally involved 5,518 subjects – patients with clinical CVD aged 40–79 years and, in the case of subclinical CVD or at least two risk factors for the disease, older patients aged 55–79 years [32]. Prior to the study, LDL-C levels were 60–180 mg/dL (1.55–4.65 mmol/L), HDL-C <55 mg/dL (1.42 mmol/L) in females and in blacks and <50 mg/dL (1.29 mmol/L) in all other subjects, TG levels were <750 mg/dL (8.5 mmol/L) without hypolipidemic therapy or <400 mg/dL (4.5 mmol/L) during therapy [32]. Subjects were randomised to two groups – 2,753 patients were treated with simvastatin (20 mg for primary prevention or 40 mg for secondary prevention), and 2,765 patients were treated with statin in combination with fenofibrate (160 mg if estimated glomerular filtration rate (eGFR) >50 mL/min/1.73 m^2

or one third of the dose if renal function was moderately impaired: eGFR 30–50 mL/min/1.73 m^2). The primary end point was the occurrence of death from CV causes, non-fatal MI and non-fatal stroke. Secondary end points were the combination of primary end point and revascularisation or hospitalisation for congestive heart failure; combination of fatal cardiac event, MI or unstable angina pectoris; MI; fatal or non-fatal stroke; non-fatal stroke; death from any cause; death from CV causes and hospitalisation or death due to heart failure [32]. In the study, end points related to microvascular disorders were also assessed: progression of retinopathy by at least three grades on the Early Treatment Diabetic Retinopathy Study (EDTRS) scale, the need for photocoagulation or vitrectomy and progression of renal function impairment [32, 33].

After nearly 5 years, significant beneficial changes in lipid profile were seen in both groups: reduction in LDL-C levels (from 100 to 81.1 mg/dL in the fenofibrate group and from 101.1 to 80 mg/dL in the placebo group), reduction in TG levels (from 189 to 147 mg/day and from 186.2 to 170, respectively) and increase in HDL-C levels (from 38 to 41.2 mg/dL in the fenofibrate group and from 38.2 to 40.5 mg/dL in the placebo group) [32]. However, no reduction in the primary end point was observed in the group of subjects undergoing combination therapy compared with statin monotherapy – a 10.1 % risk reduction in both groups ($p = 0.32$) or in secondary end points. One of the reasons of these negative results, which were highly discussed after the study completion, was the fact that patients included to the study were very effectively treated with statins and in fact there were no indications to fenofibrate therapy taking into account their baseline lipid profile [32, 33]. However, in the subgroup of subjects with the lowest levels of HDL-C and, at the same time, the highest levels of TG (≤34 and ≥204 mg/dL, respectively), even 31 % reduction in the primary end point was seen in those undergoing combination therapy (12.37 vs 17.32 % of subjects with a vascular episode; $p = 0.057$). What is important, the benefits from this approach were seen also in subjects who achieved low LDL-C levels (<70 mg/dL) [32]. In addition, as was anticipated, slowing of the progression of micro-angiopathy was confirmed, reduction in albuminuria was observed and the progression of retinopathy was slower – in 6.5 % of subjects treated with fenofibrate vs 10.2 % of subjects receiving placebo (odds ratio [OR] 0.60; 95 %CI 0.42–0.87; $p = 0.006$); however, subjects without retinopathy at the moment of the enrolment as well as subjects with severe initial lesions did not benefit from additional therapy with fenofibrate [37, 38].

The results of the FIELD and ACCORD studies were deemed disappointing, and many lipidologists announced the start of the twilight of fibrate therapy. Yet, a question should be asked if such a statement was warranted, since both of those large studies were limited by their design, and on the other hand, they have shown that there is a specific subgroup of diabetic patients in whom CV risk may be reduced by combination therapy with a statin and fibrate – patients with low levels of HDL cholesterol and high levels of TG (atherogenic dyslipidaemia); and in clinical practice, predominantly patients with abdominal obesity or metabolic syndrome; moreover, in all diabetic patients' therapy with fenofibrate, the progression of

microvascular complications can be slowed down. No doubt, patients would not rashly give up the benefits, which might be obtained from such treatment, and before rejecting it, every physician should seriously consider if such a decision is not too hasty [33].

The Safety of Fenofibrate Therapy

Treatment with fenofibrate appears to be safe, and undesirable effects are rare. Systemic symptoms which may be noticed by patients receiving fenofibrate, although it has not been definitely established whether or not they are caused by the drug itself, might include weight loss, fatigue/weakness and flu-like symptoms (about 5 %) [39, 40]. Gastrointestinal undesirable effects are quite common – they include dyspepsia (5 %), nausea/vomiting (4 %), flatulence, abdominal pain, constipation or diarrhoea (3 %) and belching (1 %) [39–43]. In addition, fenofibrate may contribute to increased cholesterol excretion into the bile and the development of cholelithiasis [42]. Also, an increased incidence of acute pancreatitis may be one of the undesirable effects of the drug – in the FIELD study, it was developed by 0.8 % of subjects in the fenofibrate group and 0.5 % subjects in the placebo group; however, it is not clear if this was caused by the drug or by hypertriglyceridaemia, which often coexists in this group of patients [31]. Dermal symptoms are similarly rare – they usually include rash (6 %) or pruritus (3 %). Considerably less common effects are photosensitivity, lupus-like syndrome, ichthyosis, telangiectasia and alopecia [42–45].

Muscle-related complications of fenofibrate therapy are rare. They result from the fact that the risk related to therapy with gemfibrozil in combination with a statin is often applied to fenofibrate [46]. However, the metabolism of fenofibrate is completely different from that of gemfibrozil, and it does not cause a significant increase in plasma concentration of statins or the risk of rhabdomyolysis (which is 15 times lower than with gemfibrozil) [46–49]. For example, in the ACCORD study [32], a significant increase in the concentration of creatine kinase (CK) over the normal level (ten times) was observed only in ten (0.4 %) subjects receiving fenofibrate and in nine (0.3 %) subjects receiving placebo. In the FIELD study [31], the most serious complication – rhabdomyolysis – developed only in three subjects receiving fenofibrate and in one subject receiving placebo. To further minimise the risk of myopathy during combination therapy, it is recommended that fenofibrate be taken in the morning and a statin in the evening, so that peak blood concentrations do not overlap [47–49]. Another type of therapy is an alternate-day therapy – new studies on the use of fenofibrate in combination therapy for hyperlipidaemia indicate that the effectiveness of therapy with atorvastatin and fenofibrate taken either on the same day or on alternate days is comparable [47–49]. It is worth emphasising that the meta-analysis showed that combination therapy with statin and fibrate is comparatively safe as therapy with statin only [49].

An adverse effect of fibrates on kidneys is usually seen in CKD patients. There is some risk related to accumulation of the fenofibrate main metabolite – fenofibric

acid and the development of myositis and rhabdomyolysis leading to acute renal failure [50, 51]. In patients without CKD, fenofibrate may lead to a slight increase in blood levels of creatinine – e.g. in the ACCORD study, in the first year of fenofibrate therapy, persistent insignificant elevation of creatinine levels was seen (increase from 0.93 to 1.1 mg/dL), but interestingly a similar increase was seen in the placebo group (from 0.93 to 1.04 mg/dL) [32]. In addition, therapy with fibrate was not associated with an increased need for dialysis (75 subjects in the fenofibrate group and 77 subjects in the placebo group). Taking into consideration all the data, it is recommended that fenofibrate be not used in patients with severe impairment of renal function (eGFR <30 mL/min/1.73 m^2); when using fenofibrate in other patients, blood levels of creatinine should be monitored and renal function should be assessed – according to the European guidelines, preferably once a year [51]; according to the American guidelines, prior to therapy initiation, within 3 months of therapy initiation and then periodically every 6 months, bearing in mind that in patients with moderate impairment of renal function (eGFR 30–59 mL/min/1.73 m^2), the daily dose of fenofibrate should not exceed 54 mg [52].

During therapy with fenofibrate, a significant increase in aminotransferase level, exceeding three times the upper limit of normal (ULN), is possible (in about 6 % of patients). Liver damage may occur as soon as after several weeks or after many years of therapy with fenofibrate and is dose dependent [39–44].

It is also worth noting that the FIELD study [31] therapy with fenofibrate was associated with slightly increased rates of deep vein thrombosis (1.4 % in the fenofibrate group vs 1.0 % in the placebo group) and pulmonary embolism (1.1 vs 0.7 %), likely to have been caused by elevated levels of homocysteine, which in itself had no effect on CV events and whose levels may always be reduced by adding n-3 fatty acids. Other undesirable effects are very rare. They may occur as with any other drugs and may be idiosyncratic [39–44].

Indications for Fibrate Therapy According to the Recent Guidelines

The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines (2011) on the management of dyslipidaemias [51], on the basis of the studies referred to, clearly define situations in which fibrates, including fenofibrate, should be used or should be considered for use.

According to the ESC/EAS guidelines [51] the desired TG level should not be higher than 1.7 mmol/L (150 mg/dL), and higher levels, despite the lack of entirely convincing evidence, are considered a risk factor for CV complications. However, pharmacotherapy should be used only in patients with the TG level >2.3 mmol/L (200 mg/dL), in whom TG reduction could not be achieved through non-pharmacological treatment – exercise, weight reduction and diet. Although statins are the treatment of choice for moderate hypertriglyceridemia, in the ESC/EAS guidelines, fibrates – due to the documented effect of reducing CV risk – are

presented as playing a vital role in the treatment of this dyslipidaemia. Fibrates should be used as first-line treatment in the high-risk group (class IB), while in other patients the addition of fibrates to a statin should always be considered if statin monotherapy does not bring about satisfactory reduction in TG levels [51]. Hypertriglyceridaemia is one of the causes of acute pancreatitis – it is estimated that about 10 % of all cases are caused by elevated blood TG levels [33, 51]. The risk occurs with TG >5 mmol/L (440 mg/dL) and increases with the increase in TG levels. Hypertriglyceridemia-related acute pancreatitis is a clear indication for therapy with fibrates, as an adjunct to the right diet and omega fatty acids [51].

A little bit different approach concerning the diagnosis and management of hypertriglyceridaemia was present in EAS Consensus Panel paper (2014) [53]. The authors redefined the definition of hypertriglyceridaemia and recommended the following definition: (1) normal TG levels: triglyceride concentration less than 2.0 mmol/L (175 mg/dL), (2) mild-to-moderate: TG concentration between 2.0 and 10.0 mmol/L (175–885 mg/dL) and (3) severe: TG concentration more than 10.0 mmol/L (885 mg/dL) [53]. According to this consensus paper, treatment of hypertriglyceridaemia has two distinct objectives: immediate prevention of pancreatitis in patients with severe hypertriglyceridaemia (TG concentration >10 mmol/L) and reduction of global CVD risk (TG concentration between 2 and 10 mmol/L) [53]. The Panel recommends non-pharmacological therapy for individuals with TG concentrations of more than 2 mmol/L (175 mg/dL), and the decision to initiate pharmacological therapy depends on the amount of TG elevation. Individuals with TG concentrations >10 mmol/L warrant immediate and aggressive TG reduction to minimise the risk of acute pancreatitis, with use of a strict fat-reduced diet and avoidance of simple carbohydrates; use of fibrates, nicotinic acid or omega-3 fatty acids could also be considered. The experts also emphasised that because of the uncertain clinical benefits, practice guidelines are not universal or consistent regarding the management of individuals with TG concentrations of 2–10 mmol/L [53].

The authors of the ESC/EAS 2011 guidelines point to an unfavourable lipid profile seen in many human immunodeficiency virus (HIV)-infected patients – low HDL-C level and elevated TG and LDL-C levels and unfavourable response to highly active antiretroviral therapy (HAART), which consists primarily in increasing atherogenic small, dense LDL and TG particles. The role of statins in this group of patients is emphasised, as well as the role of fibrates, with hypertriglyceridaemia being the dominant disorder [51, 54].

Therapy with fibrates (in combination with a statin) appears to be also the best solution for the treatment of a very rare autosomal recessive familial dysbetalipoproteinaemia, in which mutation in apolipoprotein E (a ligand for LDL receptor on hepatocytes) results in reduced elimination of remnants and elevated levels of TC and TG [55]. Clinical manifestation of the disease includes a very high risk of atherosclerotic complications and accompanying dermal symptoms manifested as xanthomas [55].

A completely different approach to the use of fibrates has been adopted by British [56] and American experts [52]. It was connected to the fact that first the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines in

November 2013 and next the National Institute for Health and Care Excellence (NICE) guidelines in July 2014 based their recommendations only on randomised controlled trials (RCTs). The large discussion has begun since that time, not only due to the fact that these experts decided to include only RCTs, and no genetic, perspective, epidemiological cohort studies, and meta-analyses, but also on the quality and selection criteria of included RCTs. It is especially important concerning the recommendations on the combination therapy in dyslipidaemic patients, including the ones concerning fibrates, because they were based mainly on FIELD and ACCORD trials, which were very limited (what was mentioned above), and no direct conclusions could be drawn based on these outcomes [52, 56].

The mentioned NICE guidelines do not recommend the use of fibrates either for the primary or the secondary prevention of CVD at all, even in patients with diabetes (type 1 or type 2) [56], and the ACC/AHA guidelines of 2013 allow the use of fibrates (excluding gemfibrozil) in combination with a low- or moderate-dose statin to reduce CV risk or to reduce TG levels >500 mg/dL but only if the expected benefits may outweigh possible undesirable effects of such treatment (class IIB) [52].

Taking into account the above controversies, it seems that one should follow the ESC/EAS recommendations (2011), which suggests fibrates to be always considered in patients with high and very high CV risk and in diabetic patients with high TG and very low HDL-C [51].

Conclusions

In everyday practice, the physician considering the use of fenofibrate should follow the guidelines for the management of patients with dyslipidaemias and type 2 diabetes, which clearly define the groups of patients for whom fenofibrate is indicated. However, it is hard to agree with the British and American recommendations, which were based on randomised clinical trials only. In the case of fenofibrate, both FIELD and ACCORD studies had a number of limitations and therefore may not be considered conclusive (what is more, in its recommendations from May 2011, the US Food and Drug Administration points to the need for further investigations) [57]. The more so that there have been convincing prospective and genetic studies which proved the efficacy of this class of drugs [58–60]. Finally, promising new reports of the use of fenofibrate (with or without statin therapy) for conditions which had not been considered before (e.g. retinopathy and other diabetic complications, as well as for the prevention of diabetes mellitus and its complications) generate interest in possible new useful roles,which this relatively old drug might play in present-day pharmacotherapy [31–36, 38].

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References

1. Dreyer C, Krey G, Keller H, Givel F, Helftenbein G, Wahli W. Control of the peroxisomal beta-oxidation pathway by a novel family of nuclear hormone receptors. Cell. 1992;68: 879–87.
2. Issemann I, Green S. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. Nature. 1990;347:645–50.
3. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: from orphan receptors to drug discovery. J Med Chem. 2000;43:527–50.
4. Robinson-Rechavi M, Carpentier AS, Duffraisse M, Laudet V. How many nuclear hormone receptors are there in the human genome? Trends Genet. 2001;17:554–6.
5. Nuclear Receptors Nomenclature Comittee. A unifid nomenclature system for the nuclear receptor superfamily. Cell. 1999;97:161–3.
6. Kliewer S, Sundseth S, Jones S, Brown P, Wisely G, Koble C, Devchand P, Wahli W, Willson T, Lenhard J, Lehmann J. Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. Proc Natl Acad Sci U S A. 1997;94:4318–23.
7. Forman B, Chen J, Evans R. Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta. Proc Natl Acad Sci U S A. 1997;94:4312–7.
8. Devchand P, Keller H, Peters J, Vazquez M, Gonzalez F, Wahli W. The PPARa-leukotriene B4 pathway to inflammation control. Nature. 1996;384:39–43.
9. Schoonjans K, Staels B, Auwerx J. Role of the peroxisome proliferator activated receptor (PPAR) in mediating effects of fibrates and fatty acids on gene expression. J Lipid Res. 1996;37:907–25. 26. Schoonjans K, Staels B, Auwerx J. The peroxisome proliferator activated receptors (PPARs) and their effects on lipid metabolism and adipocyte differentiation. Biochim Biophys Acta. 1996;1302:93–109.
10. Gulick T, Cresci S, Caira T, Moore D, Kelly D. The peroxisome proliferator-activated receptor regulates mitochondrial fatty acid oxidative enzyme gene expression. Proc Natl Acad Sci U S A. 1994;91:11012–6.
11. Heller F, Harvengt C. Effects of clofibrate, bezafibrate, fenofibrate, and probucol on plasma lipolytic enzymes in normolipidaemic subjects. Eur J Clin Pharmacol. 1983;23:57–63.
12. Malmendier C, Lontie J-F, Delcroix C, Dubois D, Magot T, De Roy L. Apolipoproteins C-II and C-III metabolism in hypertriglyceridemic patients: effect of a drastic triglyceride reduction by combined diet restriction and fenofibrate administration. Atherosclerosis. 1989;77: 139–49.
13. Martin G, Schoonjans K, Lefebvre A, Staels B, Auwerx J. Coordinate regulation of the expression of the fatty acid transporter protein (FATP) and acyl CoA synthetase (ACS) genes by PPARa and PPARg activators. J Biol Chem. 1997;272:28210–7.
14. Schoonjans K, Watanabe M, Suzuki H, Mahfoudi A, Krey G, Wahli W, Grimaldi P, Staels B, Yamamoto T, Auwerx J. Induction of the acylcoenzyme A synthetase gene by fibrates and fatty acids is mediated by a peroxisome proliferator response element in the C promoter. J Biol Chem. 1995;270:19269–76.
15. Caslake M, Packard C, Gaw E, Murray E, Griffin B, Vallance B, Shepherd J. Fenofibrate and LDL metabolic heterogeneity in hypercholesterolemia. Arterioscler Thromb. 1993;13:702–11.
16. Bruckert E, Dejager S, Chapman M. Ciprofibrate therapy normalises the atherogenic low-density lipoprotein subspecies profile in combined hyperlipidemia (published erratum appears in Atherosclerosis. 1993 102:129). Atherosclerosis. 1993;100:91–102.
17. de Graaf J, Hendriks J, Demacker P, Stalenhoef A. Identification of multiple dense LDL subfractions with enhanced susceptibility to in vitro oxidation among hypertriglyceridemic subjects: normalization after clofibrate treatment. Arterioscler Thromb. 1993;13:712–9.
18. Mann C, Yen F, Grant A, Bihain B. Mechanism of plasma cholesteryl ester transfer in hypertriglyceridemia. J Clin Invest. 1991;88:2059–66.

19. Vu-Dac N, Schoonjans K, Kosykh V, Dallongeville J, Fruchart J, Staels B, Auwerx J. Fibrates increase human apolipoprotein A-II expression through activation of the peroxisome proliferator-activated receptor. J Clin Invest. 1995;96:741–50.
20. Berthou L, Duverger N, Emmanuel F, Langouët S, Auwerx J, Guillouzo A, Fruchart J-C, Rubin E, Denèfle P, Staels B, Branellec D. Opposite regulation of human versus mouse apolipoprotein A-I by fibrates in human apo A-I transgenic mice. J Clin Invest. 1996;97:2408–16.
21. Bard J-M, Parra HJ, Camare R, Luc G, Ziegler O, Dachet C, Bruckert E, Douste-Blazy P, Drouin P, Jacotot B, De Gennes JL, Keller U, Fruchart J-C. A multicenter comparison of the effects of simvastatin and fenofibrate therapy in severe primary hypercholesterolemia, with particular emphasis on lipoproteins defined by their apolipoprotein composition. Metabolism. 1992;41:498–503.
22. Lussier-Cacan S, Bard J-M, Boulet L, Nestruck A, Grothé A-M, Fruchart J-C, Davignon J. Lipoprotein composition changes induced by fenofibrate in dysbetalipoproteinemia type III. Atherosclerosis. 1989;78:167–82.
23. Franceschini G, Favari E, Calabresi L, Simonelli S, Bondioli A, Adorni MP, Zimetti F, Gomaraschi M, Coutant K, Rossomanno S, Niesor EJ, Bernini F, Benghozi R. Differential effects of fenofibrate and extended-release niacin on high-density lipoprotein particle size distribution and cholesterol efflux capacity in dyslipidemic patients. J Clin Lipidol. 2013;7(5):414–22.
24. Kei A, Liberopoulos E, Tellis C, Elisaf M, Tselepis A. Lipid-modulating treatments for mixed dyslipidemia increase HDL-associated phospholipase A2 activity with differential effects on HDL subfractions. Lipids. 2013;48(10):957–65.
25. Han SH, Quon MJ, Koh KKZ. Beneficial vascular and metabolic effects of peroxisome proliferator-activated receptor-alfa activators. Hypertension. 2005;46:1086–92.
26. Israelin-Konaraki Z, Reaven PD. Peroxisome proliferator-activated receptor-alfa and atherosclerosis: from basic mechanisms to clinical implications. Cardiol Rev. 2005;13:240–6. 4.
27. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987;317(20):1237–45.
28. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999;341(6):410–8.
29. Israeli Society for Prevention of Heart Attacks, Tel-Hashomer, Israel. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. Bezafibrate Infarction Prevention (BIP) study. Circulation. 2000;102(1):21–7.
30. Meade T, Zuhrie R, Cook C, Cooper J. Bezafibrate in men with lower extremity arterial disease: randomised controlled trial. BMJ. 2002;325(7373):1139.
31. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M, The FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366:1849–61.
32. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–74.
33. Katsiki N, Nikolic D, Montalto G, Banach M, Mikhailidis DP, Rizzo M. The role of fibrate treatment in dyslipidemia: an overview. Curr Pharm Des. 2013;19(17):3124–31.
34. Fruchart JC, Sacks F, Hermans MP, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. Am J Cardiol. 2008;102(supl. 10):1K–34.
35. Otocka-Kmiecik A, Mikhailidis DP, Nicholls SJ, Davidson M, Rysz J, Banach M. Dysfunctional HDL: a novel important diagnostic and therapeutic target in cardiovascular disease? Prog Lipid Res. 2012;51(4):314–24.

36. Keech AC, Mitchell P, FIELD Study Investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet. 2007;370(9600):1687–97.
37. ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363:233–44.
38. Chew EY, Davis MD, Danis RP, Lovato JF, Perdue LH, Greven C, Genuth S, Goff DC, Leiter LA, Ismail-Beigi F, Ambrosius WT, Action to Control Cardiovascular Risk in Diabetes Eye Study Research Group. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. Ophthalmology. 2014;121(12):2443–51.
39. Adkins JC, Faulds D. Micronised fenofibrate: a review of its pharmacodynamic properties and clinical efficacy in the management of dyslipidaemia. Drugs. 1997;54:615–33.
40. Kirchgassler KU, Schmitz H, Bach G. Effectiveness and tolerability of 12-week treatment with micronised fenofibrate 200mg in a drug-monitoring programme involving 9884 patients with dyslipidaemia. Clin Drug Investig. 1998;15:197–204.
41. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. Am J Med. 1987;83:26–36.
42. Roberts WC. Safety of fenofibrate–US and worldwide experience. Cardiology. 1989;76: 169–79.
43. Guay DR. Micronized fenofibrate: a new fibric acid hypolipidemic agent. Ann Pharmacother. 1999;33:1083–103.
44. Farnier M, Bonnefous F, Debbas N, Irvine A. Comparative efficacy and safety of micronized fenofibrate and simvastatin in patients with primary type IIa or IIb hyperlipidemia. Arch Intern Med. 1994;154:441–9.
45. Leroy D, Dompmartin A, Lorier E, Leport Y, Audebert C. Photosensitivity induced by fenofibrate. Photodermatol Photoimmunol Photomed. 1990;7:136–7.
46. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. Am J Cardiol. 2005;95:120–2.
47. Franssen R, Vergeer M, Stroes ES, Kastelein JJ. Combination statin–fibrate therapy: safety aspects. Diabetes Obes Metab. 2009;11:89–94.
48. Harivenkatesh N, David DC, Haribalaji N, Sudhakar MK. Efficacy and safety of alternate day therapy with atorvastatin and fenofibrate combination in mixed dyslipidemia: a randomized controlled trial. J Cardiovasc Pharmacol Ther. 2014;19(3):296–303.
49. Geng Q, Ren J, Chen H, Lee C, Liang W. Adverse events following statin-fenofibrate therapy versus statin alone: a meta-analysis of randomized controlled trials. Clin Exp Pharmacol Physiol. 2013;40(3):219–26.
50. Rysz J, Aronow WS, Stolarek RS, Hannam S, Mikhailidis DP, Banach M. Nephroprotective and clinical potential of statins in dialyzed patients. Expert Opin Ther Targets. 2009;13(5):541–50.
51. Reiner Z, Catapano AL, DeBacker G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32:1769–818.
52. Stone NJ, Robinson JG, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S1–45.
53. Hegele RA, Ginsberg HN, Chapman MJ, et al. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol. 2014; 2(8):655–66.
54. Bekolo CE, Nguena MB, Ewane L, Bekoule PS, Kollo B. The lipid profile of HIV-infected patients receiving antiretroviral therapy in a rural Cameroonian population. BMC Public Health. 2014;14:236.

55. Koopal C, Retterstøl K, Sjouke B, Hovingh GK, Ros E, de Graaf J, Dullaart RP, Bertolini S, Visseren FL. Vascular risk factors, vascular disease, lipids and lipid targets in patients with familial dysbetalipoproteinemia: a European cross-sectional study. Atherosclerosis. 2015; 240(1):90–7.
56. Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease. National Clinical Guideline Centre (UK). 2014. http://www.ncbi.nlm.nih.gov/pubmed/25340243.
57. 19 May 2011, Advisory Committee meeting for choline fenofibrate/fenofibric acid (Trilipix®) and the ACCORD-Lipid trial. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM255550.pdf.
58. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. Am J Cardiol. 2002;90(8A):22i–9.
59. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E, PROVE IT-TIMI 22 Investigators. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol. 2008; 51(7):724–30.
60. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation. 2007;115(4):450–8. Epub 2006 Dec 26.

Chapter 3
Statins and Ezetimibe

Ulrich Laufs

Ezetimibe: Mechanism of Action

In 1929, Schoenheimer reported that mammals not only synthesize cholesterol de novo but also absorb dietary cholesterol from the intestine while excluding dietary plant sterols [1]. Both dietary cholesterol consumption and intestinal cholesterol absorption contribute to plasma cholesterol concentrations. Ezetimibe lowers plasma cholesterol by decreasing cholesterol absorption in the small intestine.

Ezetimibe (1-(4-Fluorophenyl)-3(*R*)-[3-(4-fluorophenyl)-3(*S*)-hydroxypropyl]-4(*S*)-(4-hydroxyphenyl)-2-azetidinone, formerly known as SCH 58235) is a compound of the 2-azetidinone class (Fig. 3.1). The primary mechanism of action is the inhibition of the uptake of dietary and biliary cholesterol into the enterocytes of the brush border of the small intestine (Fig. 3.2).

The primary mechamism of ezetimibe is blocking the function of the protein encoded by the Niemann-Pick C1Like 1(NPC1 L1) gene that plays a critical role in the absorption of intestinal cholesterol. NPC1L1 expression is enriched in the brush border membrane of enterocytes of the small intestine [2]. Additional effects are not fully understood and may include inhibition of NPC1L1 in hepatocytes, blocking of aminopeptidase N, or interruption of the calveolon-1/annexin-1 complex that is involved in trafficking cholesterol [3].

After oral administration, ezetimibe is absorbed and conjugated to a pharmacologically active phenolic glucuronide (Table 3.1). Within 4–12 h of the oral administration of a 10-mg dose to fasting adults, the attained mean ezetimibe peak plasma concentration (C_{max}) is 3.4–5.5 ng/ml. Mean C_{max} (45–71 ng/ml) of ezetimibe-glucuronide is attained within 1–2 h. The concomitant administration of food (high-fat

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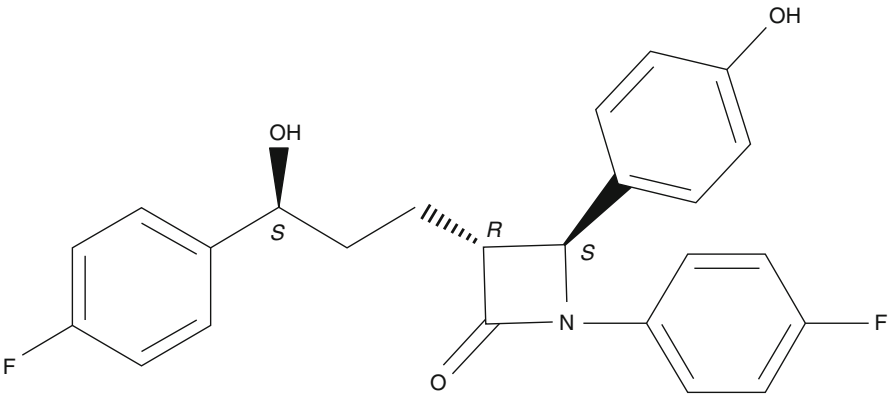

Fig. 3.1 Molecular formula of Ezetimibe ($C_{24}H_{21}F_2NO_3$)

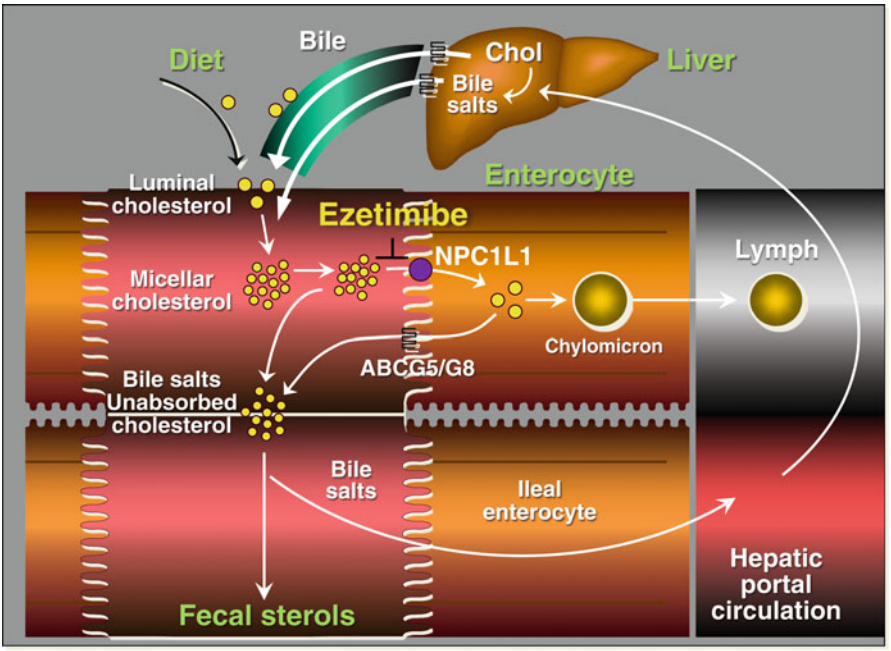

Fig. 3.2 Mechanism of Ezetimibe. Both dietary cholesterol consumption and intestinal cholesterol absorption contribute to plasma cholesterol concentrations. Ezetimibe lowers cholesterol absorption and plasma cholesterol by blocking Niemann-Pick C1-like protein 1 (*NPC1L1*) in the small intestine

Table 3.1 Properties of ezetimibe

Bioavailability	35–65 %
Molecular weight	409.4
Protein binding	>90 %
Half-life	19–30 h
Excretion	Renal 11 %, faecal 78 %

vs. nonfat meals) has no effect on the extent of absorption of ezetimibe. However, coadministration with a high-fat meal increases the C_{max} of ezetimibe by 38 %. The absolute bioavailability cannot be determined, since ezetimibe is insoluble in aqueous media suitable for injection. Ezetimibe and its active metabolite are highly bound to human plasma proteins (90 %) (Zetia label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021445s033lbl.pdf). Ezetimibe is primarily metabolized in the liver and the small intestine via glucuronide conjugation with subsequent renal and biliary excretion. Both ezetimibe and ezetimibe-glucuronide are eliminated from plasma with a half-life of approximately 22 h. Ezetimibe lacks significant effects on cytochrome P-450 isoenzymes, which explains its limited number of drug interactions (Zetia label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021445s033lbl.pdf).

Inhibition of intestinal cholesterol absorption reduces LDL- and total cholesterol concentrations but promotes a compensatory increase of hepatic cholesterol synthesis. Ezetimibe also reduces plasma concentrations of the noncholesterol sterols sitosterol and campesterol [4]. Sitosterolemia is a very rare inherited disorder that results in increased absorption and decreased excretion of plant sterols (sitosterol, campesterol) and severe premature atherosclerosis. Ezetimibe is able to decrease the elevated plasma concentrations of sitosterol [5].

Ezetimibe undergoes glucuronidation in the intestinal wall and the liver. The elimination half-life for ezetimibe and ezetimibeglucuronide is approximately 22 h, which allows for once-daily dosing [6]. Pharmacokinetics of ezetimibe do not depend on sex, age, and renal or hepatic function [7]. The LDL-C lowering effect of ezetimibe correlates with dose and plasma concentration. A pooled analysis of 399 patients receiving either placebo or ezetimibe 0.25, 1, 5, or 10 mg once daily showed a median percentage reduction of LDL-C of 0 %, 12.7 %, 14.7 %, 15.8 %, and 19.4 %, respectively [7]. Ezetimibe 10 mg a day reduces cholesterol absorption by 54 % compared with placebo. This leads to a decrease of LDL-C of 20.4 % and a compensatory increase of 89 % in cholesterol synthesis [4, 6]. Therefore, the combination of statins and ezetimibe exerts a synergistic effect on LDL-C lowering.

Genetic Association of Mutations of NPC1L1 with LDL-C and CV Risk

The principle of Mendelian randomization tests how genetically determined changes of a biomarker, e.g., a laboratory parameter, correlates with clinical events. With respect to HDL-cholesterol concentrations, individuals with genetically determined changes of this lipoprotein have an unchanged myocardial infarction risk compared to the general population. Therefore, the genetic data suggest that HDL-C is a cardiovascular risk marker but not a true causal risk factor [8]. With respect to gene-induced changes of the serum LDL-cholesterol concentration, a linear association for the risk of myocardial infarction has been shown [8, 9]. A large meta-analysis in over 300,000 individuals demonstrated that lifelong exposure to LDL-C serum concentrations is linearly associated with a lower cardiovascular risk. Lifelong

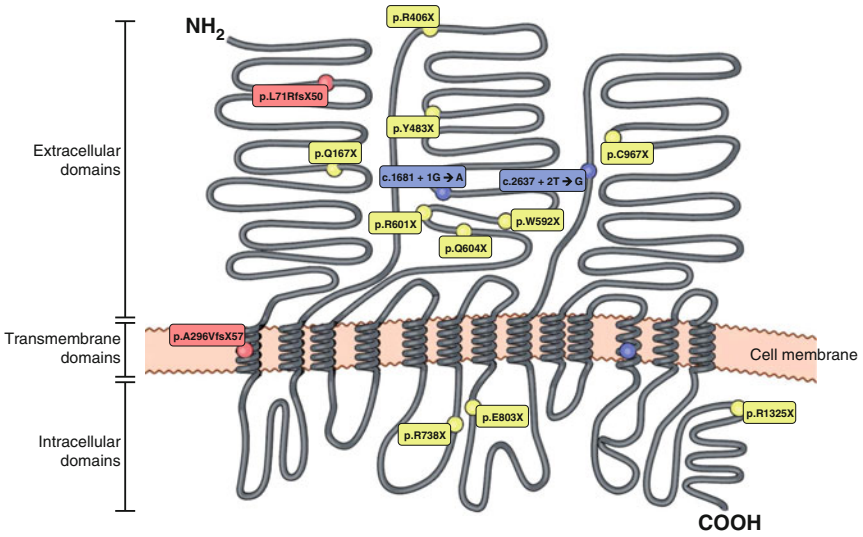

Fig. 3.3 Inactivating Mutations of NPC1L1Inactivating Mutations of NPC1L1 (Niemann-Pick C1-like protein 1) as identified by the Myocardial Infarction Genetics Consortium, adapted from [8]. The 15 circles represent the identified mutations. *Red*: insertion/deletion mutations; *blue*: splice site mutations; *yellow*: single nucleotide variants. NH2 denotes the N-terminus and COOH the C-terminus of the NPC1L1 protein, which contains 13 transmembrane domains and 3 extracellular domains

reduction of LDL-C by 1 mmol/L (39 mg/dl) by genetic determination translates to a 55 % reduction of CV risk [10]. New data presented by Brian Ference at the AHA Scientific Sessions 2014 showed that this relationship also holds true for mutations of NPC1L1 (the molecular target of ezetimibe) and for genetic variations of PCSK9 (the molecular targets of the novel PCSK9 inhibitors) [11].

Recently, several inactivating mutations of NPC1L1 were identified (Fig. 3.3) [12]. One of 650 individuals is a heterozygous carrier of an inactivating NPC1L1 mutation which is associated with an average LDL-C reduction by 12 mg/dl and accompanied by a 53 % coronary artery disease risk reduction. This NPC1L1-associated risk reduction appears to be greater than what was observed in other genetic studies [10]. NPC1L1 not only mediates the intestinal transport of cholesterol but also of plant sterols. Experimental evidence has suggested that plant sterols cause endothelial dysfunction and accelerate atherogenesis in mice [13]. One could speculate whether inhibition of sterol uptake by NPC1L1 may contribute to the preventive effect.

Examples of Clinical Studies with Ezetimibe and Statins

In a double-blind study, Ballantyne et al. randomized 628 patients with baseline LDL-C 145–250 mg/dL to receive one of the following for 12 weeks: ezetimibe (10 mg/d); atorvastatin (10, 20, 40, or 80 mg/d); ezetimibe (10 mg) plus atorvastatin (10, 20, 40, or 80 mg/d); or placebo [14] (Fig. 3.4). Coadministration of ezetimibe provided an

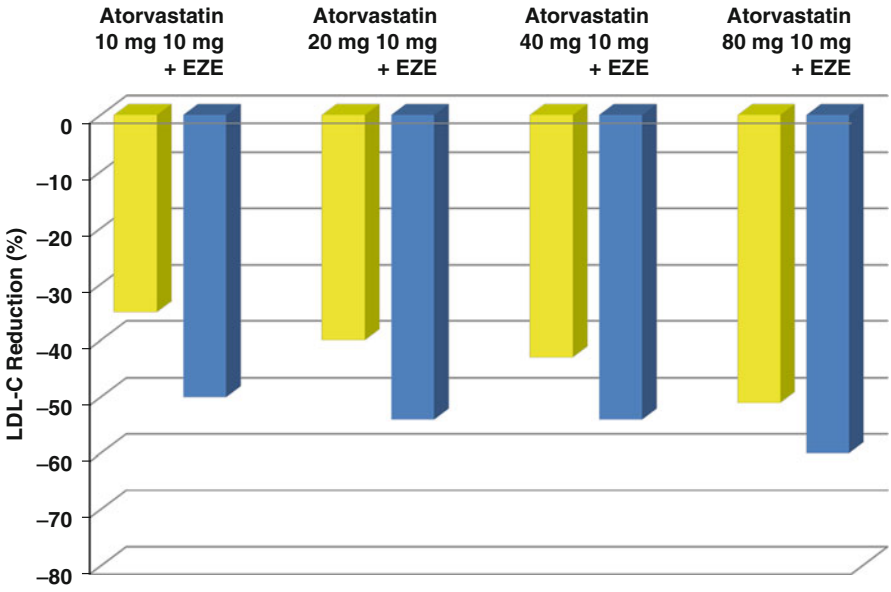

Fig. 3.4 Effects of Ezetimibe 10 mg (EZE) plus Statin versus Statinmonotherapy on LDL-C lowering (Modified from Lipka et al. [30], Melani et al. [31], Davidson et al. [32], Ballantyne et al. [33])

additional 12 % LDL-C reduction, 3 % HDL-C increase, 8 % triglyceride reduction, and 10 % hs-CRP reduction versus atorvastatin alone. Ezetimibe plus atorvastatin provided LDL-C reductions of 50–60 %, triglyceride reductions of 30–40 %, and HDL-C increases of 5–9 %, depending on atorvastatin dose. LDL-C reductions with ezetimibe plus 10 mg atorvastatin (50 %) and 80 mg atorvastatin alone (51 %) were similar [14].

Leiter et al. studied the change of LDL-C after the addition of ezetimibe 10 mg to atorvastatin 40 mg compared with uptitration to atorvastatin 80 mg in hypercholesterolemic patients [15]. In this double-blind, parallel-group study, atorvastatin 40 mg plus ezetimibe reduced LDL-C by 27 % versus atorvastatin 80 mg by 11 % ($p < 0.001$). Both treatments were generally well tolerated [15].

The INFORCE study assessed the lipid-altering efficacy and safety profile of switching to Eze/Simva 10/40 mg vs. doubling the dose of statin in $n = 424$ high-risk patients recently hospitalized for a recent coronary event [16]. LDL-C values were 1.74 mmol/l in the Eze/Simva group and 2.22 mmol/l in the statin group resulting in a significant between-group difference of 0.49 mmol/l.

The IN-CROSS study [17] evaluated the efficacy of switching from a previous statin monotherapy to ezetimibe/simvastatin vs. rosuvastatin in $n = 618$ patients with hypercholesterolemia and high cardiovascular risk. Ezetimibe/simvastatin 10/20 mg produced greater reductions in LDL-C (−27.7 % vs.−16.9 %) and total cholesterol and apolipoprotein B compared with rosuvastatin 10 mg, while both treatments were equally effective at increasing HDL-C.

The TEMPO study was a 6-week, randomized, parallel-group study on 196 patients treated with atorvastatin 20 mg that received atorvastatin 20 mg plus ezetimibe 10 mg oratorvastatin 40 mg for 6 weeks [18]. Adding ezetimibe 10 mg to

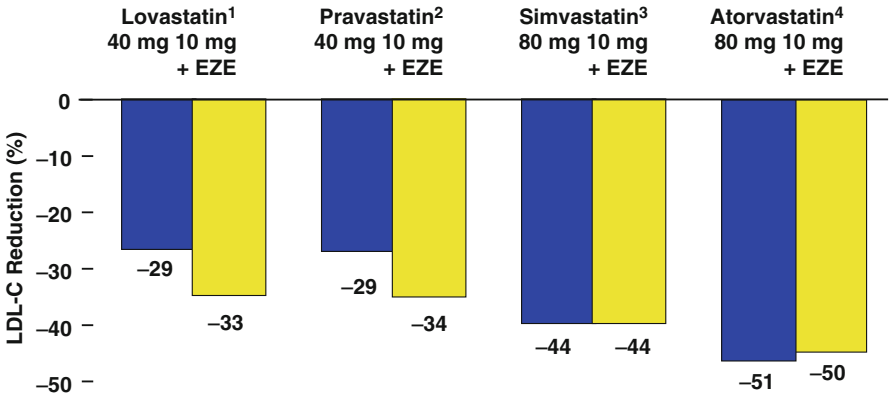

Fig. 3.5 Ezetimibe 10 mg (*EZE*) plus Atorvastatin versus Atorvastatin-Monotherapy on LDL-C lowering (Modified from Ballantyne et al. [34])

atorvastatin 20 mg produced greater reductions in LDL cholesterol than increasing atorvastatin to 40 mg (−31 % vs −11 %, $p<0.001$). The two treatment groups had comparable results for high-density lipoprotein cholesterol, triglycerides, apolipoprotein A-I, and high-sensitivity C-reactive protein. The incidences of clinical and laboratory adverse experiences were similar between groups [18].

The ezetimibe add-on to statin for effectiveness (EASE) trial showed in 3030 randomized patients that ezetimibe added to statin therapy significantly reduced the LDL-C level by an additional 23 % in the total population; the treatment difference ranged from −19.9 to −24.0 % ($p<0.001$) in all NCEP ATP III risk category subgroups [19] (Fig. 3.5).

In the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, ultrasonographic imaging in patients with familial hypercholesterolemia (FH) and combined therapy with ezetimibe and simvastatin did not result in a significant difference in intima–media thickness (IMT) compared with simvastatin alone [20], a result that was explained by Kastelein et al. by the normal IMT in the specific FH population studied. The Stop Atherosclerosis in Native Diabetics Study (SANDS) in patients with type 2 diabetes suggested that reducing LDL-C to aggressive targets results in similar regression of CIMT in patients who attained equivalent LDL-C reductions from a statin alone or statin plus ezetimibe [21].

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial was designed to study the effects of long-term, intensive cholesterol lowering with daily use of simvastatin and ezetimibe in $n=1873$ patients with asymptomatic, mild-to-moderate aortic-valve stenosis and no other indication for lipid-lowering treatment [22]. During a median follow-up of 52.2 months, the primary outcome occurred in 333 patients in the simvastatin–ezetimibe group and in 355 patients in the placebo group (hazard ratio in the simvastatin–ezetimibe group $p=0.59$). Aortic-valve replacement did not differ between groups. Fewer patients experience ischemic cardiovascular events in the simvastatin–ezetimibe group (148 patients) than in the placebo group (187 patients) ($p=0.02$).

The SHARP (Study of Heart and Renal Protection) trial aimed to assess the safety and efficacy of reducing LDL cholesterol in more than 9000 patients with

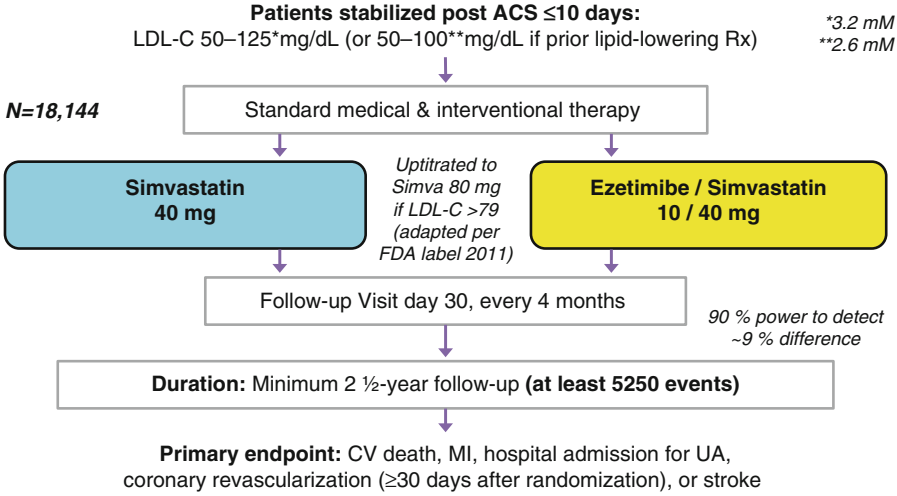

Fig. 3.6 IMPROVE-IT Study Design Design of the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) (Adapted from Cannon [24]). In the trial, 18,144 patients after acute coronary syndrome were randomized to simvastatin 40 mg or the combination of simvastatin 40 and 10 mg ezetimibe. If LDL-C was above 79 mg/dl in the simvastatin arm, the dose was up-titrated to 80 mg. *Abbreviations*: *ACS* acute coronary syndrome, *LDL-C* low-density lipoprotein cholesterol, *Rx* medication, *FDA* food and drug administration, *CV* cardiovascular, *MI* myocardial infarction, *UA* unstable angina

chronic kidney disease. Allocation to simvastatin plus ezetimibe yielded an average LDL cholesterol difference of 0.85 mmol/L during a median follow-up of 4.9 years and produced a 17 % proportional reduction in major atherosclerotic events (526 [11·3 %] simvastatin plus ezetimibe *vs* 619 [13.4 %] placebo; $p = 0.0021$). The results showed that reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily reduced the incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease [23].

Outcome Study with Ezetimibe: IMPROVE-IT

At the American Heart Association (AHA) Scientific Sessions 2014, the data of the IMPROVE-IT trial were presented [24]. The aim of the study was to answer two questions: (1) Is lower LDL-C better even at very low LDL-C? (2) Does adding another LDL-lowering drug (ezetimibe) to a statin reduce outcomes? IMPROVE-IT randomized 18,144 patients after acute coronary syndrome (ACS) randomized to simvastatin 40 mg or the combination of simvastatin 40 and 10 mg ezetimibe (Fig. 3.6) [25, 26]. If LDL-C was above 79 mg/dl in the simvastatin arm, the dose was uptitrated to 80 mg (27 % of patients) [24]. The first patient was randomized in 2005, and the data bank was closed almost 10 years later in October 2014. Thus, IMPROVE-IT represents one of the largest and longest randomized clinical training spanning almost 100,000 patient-years (mean follow-up 6 years). The two treatment

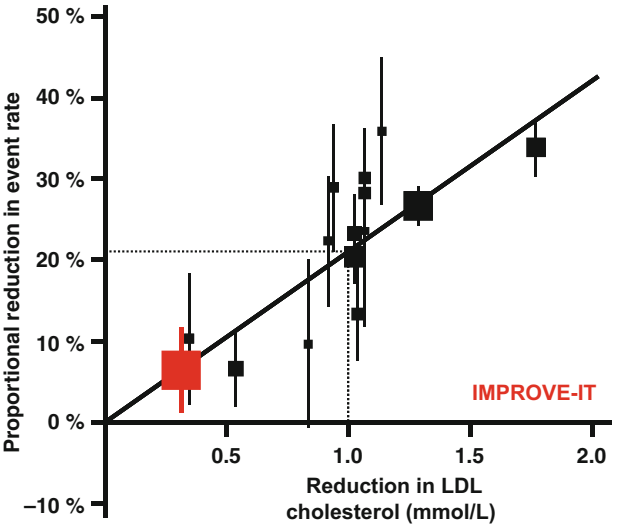

Fig. 3.7 IMPROVE-IT vs. CTT analysis. The Cholesterol Treatment Trialists (CTT) Cooperation found a 25 % relative reduction of cardiovascular risk per 1 mmol/L (39 mg/dl) LDL-C lowering in men and women in a prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins [10]. The outcome data of the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) plotted onto the CTT analysis regression line underline that LDL-lowering by ezetimibe plus statin reduced events in a similar fashion compared to a statin alone (Adapted from Cannon [24])

groups were balanced with respect to patient characteristics such as age, gender, risk factors, type of ACS, prior lipid therapy, and LDL at enrolment (95 mg/dl). With respect to treatment effects, LDL-cholesterol in the simvastatin control group averaged to 70 mg/dl mg/dl (1.8 mmol/L). In the ezetimibe group, LDL-C was 16 mg/dl lower with a mean of 54 mg/dl (1.4 mmol/L).

The primary end point of the study was the combination of cardiovascular death, myocardial infarction, and hospitalization for unstable angina, coronary revascularization, and stroke. The combined end point occurred in 34.7 % (2742 events) in the simvastatin group and was reduced to 32.7 % (2572 events) in the ezetimibe/simvastatin combination group (6.4 % treatment effect, $p = 0.016$). The intention-to-treat analysis resulted in a needed-to-treat number of 50 for the 7 year study period. Taking into account only patients on continuous treatment with the study drug (on-treatment analysis), the treatment effect increased to 7.6 % with an accordingly lower NNT of 38.

An important result of the IMPROVE-IT trial is the safety analysis, which is meaningful due to the size and duration of the study. No differences were observed with respect to rhabdomyolysis, myopathies, hepatopathy, gallbladder disease, or malignancies between the simvastatin and the simvastatin-plus-ezetimibe groups.

Chris Cannon, the presenter of the IMPROVE-IT data, plotted the results on the CTT regression line (Fig. 3.7) [24]. This figure shows that LDL lowering by ezetimibe plus statin reduced events in a similar fashion compared to a statin alone, supporting that lowering of LDL-C levels is the primary mechanism of prevention.

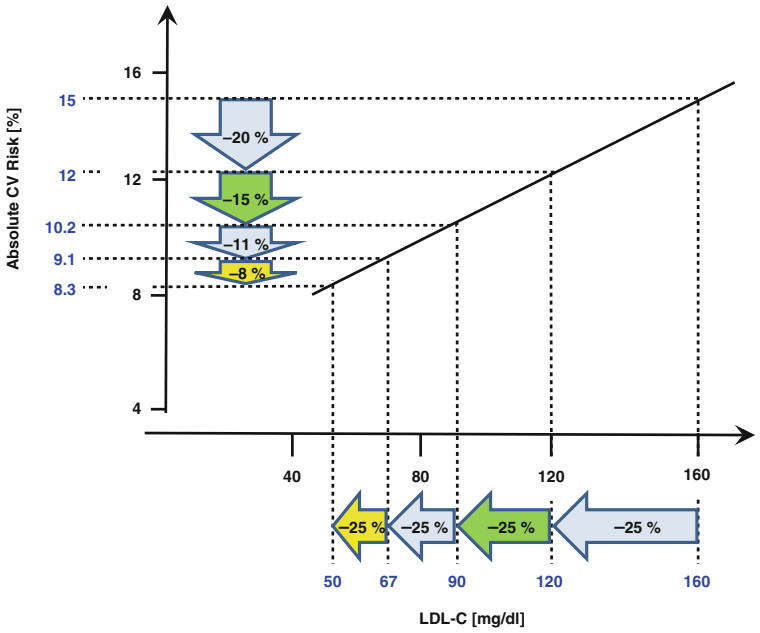

Fig. 3.8 Increasing absolute risk reduction for the same relative LDL-C lowering with higher baseline LDL-C. Absolute cardiovascular (CV) risk reduction increases with higher baseline LDL cholesterol concentrations. LDL reduction by 25 % in patients with a baseline LDL-C of 67 mg/dl results in a relative CV risk reduction of 8 % and an absolute CV risk reduction of 0.8 % (*yellow arrows*), whereas in patients with a baseline LDL-C of 120 mg/dl, risk reduction is doubled to 15 % (relative) and 1.8 % (*absolute*) (*green arrows*) (Modified from Laufs et al. [35])

IMPROVE-IT is the first trial demonstrating that a nonstatin intervention to lower LDL-cholesterol improves cardiovascular event-free survival. Secondly, the study shows that lowering LDL-C below 70 mg/dl, here 53 mg/dl, leads to a further event reduction, implicating that "the lower the better" holds true in a population that is already well treated with a statin. As a third important finding, the trial showed an excellent safety and tolerability profile of both drugs. Based on these findings, the IMPROVE-IT trial results will likely influence future guidelines on CV prevention.

An important aspect for clinical practice is the observed absolute risk reduction (ARR). Because of the importance of LDL-C for cardiovascular risk, absolute event reduction depends on the baseline LDL. Therefore, it is important to translate the IMPROVE-IT results from a baseline LDL-C of around 70 mg/dl to patients with higher baseline LDL-C. As exemplified in Fig. 3.8, an LDL reduction by 25 % in patients with a baseline LDL-C of 67 mg/dl results in an ARR of 0.8 % (RRR 8 %), whereas in patients with a baseline LDL-C of 120 mg/dl, risk reduction is doubled to 1.8 % (RRR 15 %). Based on the IMPROVE-IT findings, LDL-C lowering using ezetimibe represents an evidence-based therapeutic option to lower both LDL-C and cardiovascular event risk in patients who do not reach LDL-C target levels by a statin in maximally tolerated dose alone, e.g., due to a high baseline LDL-C, statin intolerance, or a reduced statin response.

Summary: IMPROVE-IT Moves from LDL Hypothesis to LDL Causality

The causal role of LDL-C for the pathogenesis of endothelial dysfunction and atherogenesis has been documented by multiple studies at the cellular and molecular level. Epidemiological studies reveal the association of LDL cholesterol and cardiovascular risk. Furthermore, Mendelian randomization studies have shown that LDL-C and risk for cardiovascular events have a linear relationship. Both family analyses of individuals with genetically determined low LDL-C and patients with familial hypercholesterolemia highlight the importance of long-term exposition to low or high LDL-C concentrations. This fact underscores a need for timely diagnosis and early treatment of familial hypercholesterolemia [9]. Multiple randomized studies show the improvement of patient outcomes in different populations. The novel long-term data from WOSCOPS impressively show the potency of effects over several life decades, when treatment is started in time, i.e., when statin treatment is initiated at young or middle age [27]. In order to communicate these data, the *number needed to treat* (NNT) is not optimal, especially in younger patients. In this respect, novel terms such as "gain in event-free years" and "vascular age" may represent new strategies of communication. The IMPROVE-IT study is the first proof of the concept that a nonstatin LDL-lowering intervention further reduces cardiovascular risk to a similar extent as statins [24]. The data of this large trial can be regarded as the final scientific proof needed to confirm the role of LDL-cholesterol as a causal risk factor for atherosclerosis and myocardial infarction. Therefore, as indicated in Fig. 3.9, the term "LDL hypothesis" should be replaced by the term "LDL causality."

However, even with ezetimibe on top of statin therapy, unmet clinical need remains. Individuals with inadequate treatment response, patients with symptoms associated with statin treatment such as muscle pain, and patients at goal still experiencing major CV events exemplify the need for additional LDL-C lowering therapies [28, 29].

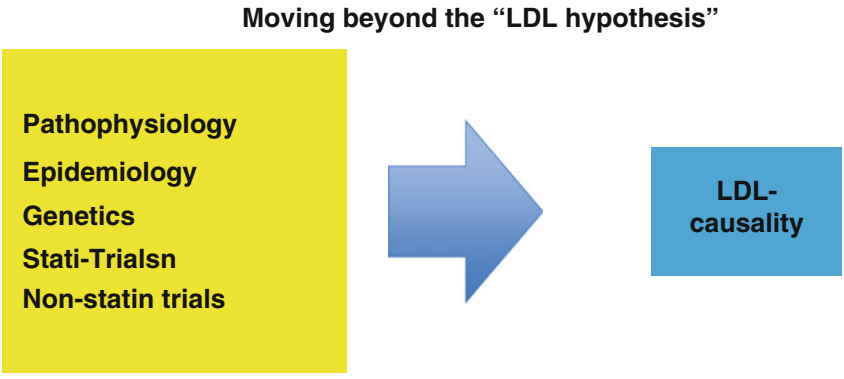

Fig. 3.9 Moving beyond the "LDL hypothesis" toward "LDL causality"

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References

1. Schoenheimer R. Über die Bedeutung der Pflanzensterine für den tierischen Organismus. Z Phys Chem. 1929;180:1.
2. Altmann SW, Davis Jr HR, Zhu LJ, Yao X, Hoos LM, Tetzloff G, et al. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science. 2004;303(5661):1201–4.
3. Phan BA, Dayspring TD, Toth PP. Ezetimibe therapy: mechanism of action and clinical update. Vasc Health Risk Manag. 2012;8:415–27.
4. Sudhop T, Lutjohann D, Kodal A, Igel M, Tribble DL, Shah S, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation. 2002;106(15):1943–8.
5. Salen G, von Bergmann K, Kwiterovitch P, et al. Ezetimibe is an effective treatment for homozygous sitosterolemia. Circulation. 2002;106(suppl II):II–185. Abstract.
6. Sudhop T, von Bergmann K. Cholesterol absorption inhibitors for the treatment of hypercholesterolaemia. Drugs. 2002;62(16):2333–47.
7. Bruckert E, Giral P, Tellier P. Perspectives in cholesterol-lowering therapy: the role of ezetimibe, a new selective inhibitor of intestinal cholesterol absorption. Circulation. 2003;107(25): 3124–8.
8. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet. 2012;380(9841):572–80.
9. Klose G, Laufs U, März W, Windler E. Familial hypercholesterolemia: developments in diagnosis and treatment. Dtsch Arztebl Int. 2014;111(31–32):523–9.
10. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol. 2012;60(25):2631–9.
11. Ference BA. Effect of naturally random allocation to lower LDL-C mediated by polymorphisms in NPC1L1, HMGCR or both on the risk of coronary heart disease: a 2x2 Factorial Mendelian Randomization Study. American Heart Association Scientific Sessions, Chicago; 16 Nov 2015 2014.
12. Stitziel NO, Won HH, Morrison AC, Peloso GM, Do R, et al. Myocardial Infarction Genetics Consortium I Inactivating mutations in NPC1L1 and protection from coronary heart disease. N Engl J Med. 2014;371(22):2072–82.
13. Weingärtner O, Lütjohann D, Ji S, Weisshoff N, List F, Sudhop T, et al. Vascular effects of diet supplementation with plant sterols. J Am Coll Cardiol. 2008;51(16):1553–61.
14. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation. 2003;107(19):2409–15.
15. Leiter LA, Bays H, Conard S, Bird S, Rubino J, Hanson ME, et al. Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with uptitration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease. Am J Cardiol. 2008;102(11):1495–501.
16. Reckless JP, Henry P, Pomykaj T, Lim ST, Massaad R, Vandormael K, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/40 mg compared with doubling the statin dose in patients admitted to the hospital for a recent coronary event: the INFORCE study. Int J Clin Pract. 2008;62(4):539–54.
17. Farnier M, Averna M, Missault L, Vaverkova H, Viigimaa M, Massaad R, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared with rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy - The IN-CROSS study. Int J Clin Pract. 2009;63(4):547–59.

18. Conard SE, Bays HE, Leiter LA, Bird SR, Rubino J, Lowe RS, et al. Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) versus uptitration of atorvastatin (to 40 mg) in hypercholesterolemic patients at moderately high risk for coronary heart disease. Am J Cardiol. 2008;102(11):1489–94.
19. Hurley DL, Isley WL. Getting there: statin plus ezetimibe for low-density lipoprotein cholesterol goals. Mayo Clin Proc. 2005;80(5):587–95.
20. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008;358(14):1431–43.
21. Fleg JL, Mete M, Howard BV, Umans JG, Roman MJ, Ratner RE, et al. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. J Am Coll Cardiol. 2008;52(25):2198–205.
22. Rossebo AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med. 2008;359(13):1343–56.
23. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181–92.
24. Cannon CP. IMPROVE-IT trial: a comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes after acute coronary syndromes. American Heart Association Scientific Sessions, Chicago; 17 Nov 2014; Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015. doi:10.1056/NEJMoa1410489.
25. Blazing MA, Giugliano RP, Cannon CP, Musliner TA, Tershakovec AM, White JA, et al. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population. Am Heart J. 2014;168(2):205–12.e1.
26. Cannon CP, Giugliano RP, Blazing MA, Harrington RA, Peterson JL, Sisk CM, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J. 2008;156(5):826–32.
27. Packard CJ. Lifetime clinical and economic benefits of statin-based LDL lowering in the 20-year followup of the West of Scotland coronary prevention study. American Heart Association Scientific Sessions, Chicago; 18 Nov 2014 2014.
28. Urban D, Pöss J, Böhm M, Laufs U. Targeting the proprotein convertase subtilisin/kexin type 9 for the treatment of dyslipidemia and atherosclerosis. J Am Coll Cardiol. 2013;62(16):1401–8.
29. Schulz R, Schlüter KD, Laufs U. Molecular and cellular function of the proprotein convertase subtilisin/kexin type 9 (PCSK9). Basic Res Cardiol. 2015;110(2):463.
30. Lipka L, Kerzner B, Corbelli J. Results of ezetimibe coadministered with lovastatin in 548 patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002;39(9 suppl B):430B.
31. Melani L, Mills R, Hassman D, Lipetz R, Lipka L, LeBeaut A, et al. Ezetimibe co-administered with pravastatin in 538 patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002;39(9 suppl B):134B.
32. Davidson M, McGarry T, Bettis R, et al. Ezetimibe Study Group. Ezetimibe co-administered with simvastatin in 668 patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002;39(Suppl A):226A–227A.
33. Ballantyne C, Houri J, Notarbatolo A, et al. Ezetimibe Study Group. Ezetimibe co-administered with atorvastatin in 628 patients with primary hypercholesterolemia. J Am Coll Cardiol. 2002;39(Suppl A):227A.
34. Ballantyne CM, Lipka LJ, Sager PT, Strony J, Alizadeh J, Suresh R, Veltri EP. Long-term safety and tolerability profile of ezetimibe and atorvastatin coadministration therapy in patients with primary hypercholesterolaemia. Int J Clin Pract. 2004;58(7):653–8.
35. Laufs U, Descamps OS, Catapano AL, Packard CJ. Understanding IMPROVE-IT and the cardinal role of LDL-C lowering in CVD prevention. Eur Heart J. 2014;35(30):1996–2000.

Chapter 4
Statins and Niacin: The End of Residual Risk Therapy?

Aris P. Agouridis and Dimitri P. Mikhailidis

Introduction

Nicotinic acid (niacin) represents the first lipid-lowering drug, as it has a history of approximately 60 years in the management of dyslipidaemia, either as monotherapy or combined with other lipid-lowering agents [1]. Niacin improves several lipid parameters since it has been associated with increases in high-density lipoprotein cholesterol (HDL-C) up to 30 % and with reductions in low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglycerides, small dense LDL particles, apolipoprotein B and lipoprotein a [Lp(a)] [2–6].

In the past, niacin had been associated with reductions in total mortality and cardiovascular disease (CVD) [7–9]. This association was attributed not only to the improvement of the lipid profile but also to pleiotropic effects [10]. However, niacin use has been limited due to its side effects, particularly flushing and worsening glycaemic control in diabetic patients [11]. Niacin is no longer on the market in many countries since the negative findings of the AIM-HIGH [12] (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High TGs: Impact on Global Health Outcomes) and the HPS2-THRIVE [13] (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events) trials that will be discussed in another section below.

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Efficacy of Niacin

Niacin has been combined with statins and other lipid-lowering agents (e.g. fenofibrate, clofibrate, gemfibrozil, colestipol, colestyramine and ezetimibe) with additional effects on lipid parameters [8, 14–18].

A meta-analysis of 30 clinical trials, which included 4749 patients, showed that niacin reduced LDL-C and triglyceride levels by 12 and 20 %, respectively, and increased HDL-C levels by 16 % [19]. In addition, niacin reduced Lp(a) by 40 % [20].

Niacin exerts favourable effects on blood pressure. In 1613 patients with primary hypercholesterolaemia or mixed dyslipidaemia, extended-release niacin (ERN) use was associated with significant reductions in systolic ($p<0.05$) and diastolic ($p<0.001$) blood pressure [21]. Similar results were shown when ERN/laropiprant was added to statin treatment in 68 normotensive and hypertensive dyslipidaemic patients who were treated with a conventional statin dose and had not achieved lipid targets [22]. In addition, niacin exerts anti-inflammatory and anti-oxidant properties [23, 24]. These properties seem to be attributed to its HDL-C-raising capacity [25]. More specifically, treatment with niacin reduces inflammatory markers such as high-sensitivity C reactive protein (hsCRP) and lipoprotein-associated phospholipase A_2 (Lp-PLA2) [26–28].

Niacin may also favourably affect renal function. Several studies have suggested that niacin may decrease urinary protein excretion as well as may retard the progression of chronic kidney disease (CKD) [29, 30]. In addition, niacin may improve non-alcoholic fatty liver disease (NAFLD) [31]. NAFLD has been suggested to be an independent risk factor for CVD [32].

Niacin monotherapy has been associated with reductions in coronary artery disease (CAD) and total mortality. In the Coronary Drug Project (CPD) among 3908 patients, immediate-release niacin (IRN) significantly reduced non-fatal myocardial infarction (MI) by 27 % ($p<0.05$) and all-cause mortality by 11 % ($p=0.0004$) in men with a history of MI when compared with placebo [7].

In a meta-analysis of 11 randomized controlled trials, which included 6545 patients, niacin either alone or in combination with other lipid-lowering agents resulted in reductions in major cardiovascular events (−25 %, $p<0.0001$), stroke (−26 %, $p=0.007$) and all cardiovascular events (−27 %, $p<0.0001$) [33].

Combination of Niacin with Statins – Current Evidence

The combination of niacin with a statin leads to LDL-C and triglyceride reduction by 29–56 % and 30–47 %, respectively, and increases HDL-C levels by 26–41 % [9, 34–36].

In the HDL-Atherosclerosis Treatment Study (HATS), the combination of simvastatin plus IRN increased HDL-C by 26 % and lowered LDL-C levels by 42 % [9]. In addition, a small regression (−0.4 %) of proximal coronary plaque on coronary angiography was noted with simvastatin plus IRN, whereas a 3.9 % mean progression

was noted in the placebo group ($p<0.001$) [9]. Moreover, simvastatin plus IRN significantly reduced cardiovascular events (by 89 %) when compared with placebo ($p=0.03$) [9].

In the Arterial Biology for the Investigation of the Treatment Effects of reducing Cholesterol (ARBITER) 2, no change in carotid intima-media thickness (cIMT) was observed after 12 months of combination therapy of a statin with ERN in 167 patients with CVD with LDL-C levels well controlled with statin monotherapy, low HDL-C and elevated triglyceride levels [37]. In contrast, a significant increase in cIMT was observed in the statin monotherapy group ($p<0.001$) [37].

In the ARBITER 3 trial which included 130 patients of the ARBITER 2 trial, HDL-C was increased by 23 % in the ERN group ($p<0.001$ vs baseline) [38]. A regression in cIMT was noted in ERN groups after 12 and 24 months of treatment, but this change did not reach significance between ERN and placebo groups [38].

In the ARBITER 6-HDL and LDL Treatment Strategies (ARBITER 6-HALTS), ERN (target dose 2 g/day) or ezetimibe (10 mg/day) was administered to patients with CAD or CAD risk equivalent, who were on long-term statin therapy with LDL-C <100 mg/dL (2.6 mmol/L) and HDL-C <50 mg/dL (1.3 mmol/L) for men or 55 mg/dL (1.4 mmol/L) for women. Significant reductions in mean and maximal cIMT were observed in the ERN group when compared with the ezetimibe group ($p=0.001$ and $p=0.005$, respectively) [39]. In addition, there was a significant reduction of major cardiovascular events in the ERN group when compared with the ezetimibe group ($p=0.04$) [39]. Furthermore, hsCRP was reduced by 23 % in the ERN group ($p=0.06$). However, this trial has been criticized for early termination, small numbers of patients, the test used to assess the difference in cardiovascular events and not including those who had not completed 24 months [40].

In the AIM-HIGH trial, there was no clinical benefit from the addition of niacin to statin therapy during a 3-year follow-up period, despite significant improvements in the lipid profile [12]. More specifically, 3414 patients who were >45 years old and had established CVD with baseline HDL-C levels <40 mg/dL (1.03 mmol/L) for men and <50 mg/dL (1.29 mmol/L) for women, elevated triglyceride levels >150 and <400 mg/dL (1.69–4.52 mmol/L) and LDL-C levels <180 mg/dL (4.65 mmol/lL) were enrolled [12]. ERN ($n=1718$) or placebo ($n=1696$) were randomly administered on top of simvastatin 40–80 mg/day (plus ezetimibe 10 mg/day, if needed) so as to maintain an LDL-C level between 40 and 80 mg/dL (1.03–2.07 mmol/L) [12]. Death from CAD, non-fatal MI, ischaemic stroke, hospitalization for an acute coronary syndrome or symptom-driven coronary or cerebral revascularization occurred in 282 patients in the ERN group and in 274 patients in the placebo group (16.4 vs 16.2 %, $p=0.80$) [12] (Table 4.1). Similar results were shown in AIM-HIGH patients with CKD, where the administration of ERN to simvastatin for secondary prevention of CVD did improve the overall lipid profile but did not exert favourable effects on CVD outcomes or kidney function, since it was associated with significantly higher all-cause mortality compared with placebo ($p=0.038$) [41].

In the HPS2-THRIVE trial, among 25673 patients with atherosclerotic vascular disease, the addition of ERN/laropiprant to statin-based LDL-C-lowering therapy

Table 4.1 Clinical outcomes of the combined treatment of niacin with simvastatin

Trial	Study population	Dose of co-administered drug(s)	Duration (median)	Primary endpoint	Results
AIM-HIGH [12]	$n = 3414$ Aged > 45 years, established CVD (documented stable CAD, cerebrovascular or carotid disease, or PAD)	Simvastatin 40–80 mg ± ezetimibe 10 mg + ERN 1.5–2 g or placebo	3 years	Death from CAD, nonfatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary or cerebral revascularization	282 (16.4 %) vs 274 (16.2 %); HR (95 % CI) 1.02 (0.87–1.21), $p = 0.80$
HPS2-THRIVE [13]	$n = 25673$ Aged 50–80 years, history of MI, PAD, cerebrovascular disease or diabetes with CAD	Simvastatin 40 mg ± Ezetimibe 10 mg + ERN/LRPT 2 g/40 mg or placebo	3.9 years	Major vascular event	1696 (13.2 %) vs 1758 (13.7 %); RR (95 % CI) 0.96 (0.90–1.03), $p = 0.29$

ACS acute coronary syndrome, *CAD* coronary artery disease, *CI* confidence interval, *CVD* cardiovascular disease, *ERN* extended-release niacin, *HR* hazard ratio, *LRPT* laropiprant, *MI* myocardial infarction, *PAD* peripheral arterial disease, *RR* rate ratio

not only did not reduce the risk of major vascular events but did also increase the risk of serious adverse events [13]. Non-fatal MI, death from coronary causes, stroke or arterial revascularization occurred in 1676 patients in the ERN group and in 1758 patients in the placebo group (13.2 vs 13.7 %, $p = 0.29$) [13] (Table 4.1). This trial was stopped due to an increase in serious adverse events such as the incidence of diabetes ($p < 0.001$) as well as serious adverse events associated with the gastrointestinal system ($p < 0.001$), musculoskeletal system ($p < 0.001$), skin ($p = 0.003$), infection ($p < 0.001$) and bleeding ($p < 0.001$) [13]. New-onset diabetes occurred in 494 patients in the ERN group and in 376 patients in the placebo group (5.7 vs 4.3 %, $p < 0.001$) [13]. In addition, disturbed diabetes control occurred in 460 patients in the ERN group and in 311 patients in the placebo group, who were diabetic at baseline (11.1 vs 7.5 %, $p < 0.001$) [13].

Conclusions

Although the addition of niacin to statins seems to improve the general lipid profile, there was no benefit in terms of cardiovascular prevention in two recent large trials [12, 13]. In addition, an increase in serious adverse effects was noted in the HPS2-THRIVE trial [13]. Thus, niacin is no longer on the market in many countries. In contrast, promising results have been recently reported regarding the combination of simvastatin plus ezetimibe [42, 43]. The IMPROVE-IT (IMProved Reduction of

Outcomes: Vytorin Efficacy International Trial) trial demonstrated that adding ezetimibe to simvastatin significantly reduces cardiovascular events (cardiovascular death, MI, rehospitalization for unstable angina, coronary revascularization or stroke) when compared with simvastatin monotherapy in 18144 patients with acute coronary syndromes ($p = 0.016$) [42, 43].

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References

1. Altschul R, Hoffer A, Stephen JD. Influence of nicotinic acid on serum cholesterol in man. Arch Biochem Biophys. 1955;54:558–9.
2. Guyton JR. Extended-release niacin for modifying the lipoprotein profile. Expert Opin Pharmacother. 2004;5:1385–98.
3. White Robinson A, Sloan HL, Arnold G. The antilipidemic effects of plain and extended-release niacin. Prev Cardiol. 2000;3:131–5.
4. Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. Arterial Disease Multiple Intervention Trial. JAMA. 2000;284:1263–70.
5. Goldberg A, Alagona Jr P, Capuzzi DM, et al. Multiple-dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. Am J Cardiol. 2000;85:1100–5.
6. Vogt A, Kassner U, Hostalek U, et al. Correction of low HDL cholesterol to reduce cardiovascular risk: practical considerations relating to the therapeutic use of prolonged-release nicotinic acid (Niaspan). Int J Clin Pract. 2007;61:1914–21.
7. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol. 1986;8:1245–55.
8. Carlson LA, Rosenhamer G. Reduction of mortality in the Stockholm Ischaemic Heart Disease Secondary Prevention Study by combined treatment with clofibrate and nicotinic acid. Acta Med Scand. 1988;223:405–18.
9. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med. 2001;345:1583–92.
10. Florentin M, Liberopoulos EN, Kei A, et al. Pleiotropic effects of nicotinic acid: beyond high density lipoprotein cholesterol elevation. Curr Vasc Pharmacol. 2011;9:385–400.
11. Parhofer KG. Review of extended-release niacin/laropiprant fixed combination in the treatment of mixed dyslipidemia and primary hypercholesterolemia. Vasc Health Risk Manag. 2009;5:901–8.
12. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365:2255–67.
13. Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014;371:203–12.
14. Agouridis AP, Filippatos TD, Tsimihodimos V, et al. Combinations of ezetimibe with nonstatin drug regimens affecting lipid metabolism. Expert Rev Cardiovasc Ther. 2011;9:355–66.
15. Agouridis AP, Filippatos TD, Derdemezis CS, et al. Combination of fenofibrate with nonstatin drug regimens. Curr Pharm Des. 2010;16:3401–16.

16. Cashin-Hemphill L, Mack WJ, Pogoda JM, et al. Beneficial effects of colestipol-niacin on coronary atherosclerosis. A 4-year follow-up. JAMA. 1990;264:3013–7.
17. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. 1990;323:1289–98.
18. Whitney EJ, Krasuski RA, Personius BE, et al. A randomized trial of a strategy for increasing high-density lipoprotein cholesterol levels: effects on progression of coronary heart disease and clinical events. Ann Intern Med. 2005;142:95–104.
19. Birjmohun RS, Hutten BA, Kastelein JJ, et al. Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2005;45:185–97.
20. Carlson LA, Hamsten A, Asplund A. Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. J Intern Med. 1989;226:271–6.
21. Bays HE, Maccubbin D, Meehan AG, et al. Blood pressure-lowering effects of extended-release niacin alone and extended-release niacin/laropiprant combination: a post hoc analysis of a 24-week, placebo-controlled trial in dyslipidemic patients. Clin Ther. 2009;31:115–22.
22. Kei A, Elisaf M, Moutzouri E, et al. Add-on-Statin Extended Release Nicotinic Acid/Laropiprant but Not the Switch to High-Dose Rosuvastatin Lowers Blood Pressure: an Open-Label Randomized Study. Int J Hypertens. 2011;2011:830434.
23. Kuvin JT, Dave DM, Sliney KA, et al. Effects of extended-release niacin on lipoprotein particle size, distribution, and inflammatory markers in patients with coronary artery disease. Am J Cardiol. 2006;98:743–5.
24. Kei A, Tellis C, Liberopoulos E, et al. Effect of switch to the highest dose of rosuvastatin versus add-on-statin fenofibrate versus add-on-statin nicotinic acid/laropiprant on oxidative stress markers in patients with mixed dyslipidemia. Cardiovasc Ther. 2014;32:139–46.
25. Florentin M, Liberopoulos EN, Wierzbicki AS, et al. Multiple actions of high-density lipoprotein. Curr Opin Cardiol. 2008;23:370–8.
26. Guyton JR, Brown BG, Fazio S, et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin coadministered with extended-release niacin in patients with type IIa or type IIb hyperlipidemia. J Am Coll Cardiol. 2008;51:1564–72.
27. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. Arch Intern Med. 2002;162:1568–76.
28. Thoenes M, Oguchi A, Nagamia S, et al. The effects of extended-release niacin on carotid intimal media thickness, endothelial function and inflammatory markers in patients with the metabolic syndrome. Int J Clin Pract. 2007;61:1942–8.
29. Owada A, Suda S, Hata T. Antiproteinuric effect of niceritrol, a nicotinic acid derivative, in chronic renal disease with hyperlipidemia: a randomized trial. Am J Med. 2003;114:347–53.
30. Cho KH, Kim HJ, Kamanna VS, et al. Niacin improves renal lipid metabolism and slows progression in chronic kidney disease. Biochim Biophys Acta. 2010;1800:6–15.
31. Salama RH, Nassar AY, Nafady AA, et al. A novel therapeutic drug (copper nicotinic acid complex) for non-alcoholic fatty liver. Liver Int. 2007;27:454–64.
32. Athyros VG, Katsiki N, Karagiannis A, et al. Statins and nonalcoholic fatty liver disease: a bright future? Expert Opin Investig Drugs. 2013;22:1089–93.
33. Bruckert E, Labreuche J, Amarenco P. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. Atherosclerosis. 2010;210:353–61.
34. Stein EA, Davidson MH, Dujovne CA, et al. Efficacy and Tolerability of Low-dose Simvastatin and Niacin, Alone and in Combination, in patients with combined hyperlipidemia: a prospective trial. J Cardiovasc Pharmacol Ther. 1996;1:107–16.
35. Kashyap ML, McGovern ME, Berra K, et al. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. Am J Cardiol. 2002;89:672–8.

36. McKenney JM, Jones PH, Bays HE, et al. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). Atherosclerosis. 2007;192:432–7.
37. Taylor AJ, Sullenberger LE, Lee HJ, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation. 2004;110:3512–7.
38. Taylor AJ, Lee HJ, Sullenberger LE. The effect of 24 months of combination statin and extended-release niacin on carotid intima-media thickness: ARBITER 3. Curr Med Res Opin. 2006;22:2243–50.
39. Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. N Engl J Med. 2009;361:2113–22.
40. Paraskevas KI, Veith FJ, Mikhailidis DP. Carotid intima-media thickness and ezetimibe: the end of a misunderstanding? Curr Vasc Pharmacol. 2011;9:381–4.
41. Kalil RS, Wang JH, de Boer IH, et al. Effect of extended-release niacin on cardiovascular events and kidney function in chronic kidney disease: a post hoc analysis of the AIM-HIGH trial. Kidney Int 2015;87:1250–7.
42. Agouridis AP, Mikhailidis DP. Should we consider ezetimibe to reach even lower LDL-C targets? Curr Med Res Opin. 2015;31:459–60.
43. Filippatos TD, Elisaf MS. Are lower levels of LDL-cholesterol really better? looking at the results of IMPROVE-IT: opinions of three experts – III. Hellenic J Cardiol. 2015;56:7–9.

Chapter 5
The Role of Omega-3 Fatty Acids in Dyslipidemias

Eric J. Brandt and Michael H. Davidson

Introduction

Statins are the most widely prescribed lipid-lowering medications and have been shown to lower the relative risk for cardiovascular events by 20–50 % [1]. However, despite their lipid lowering and cardioprotective effects, substantial residual cardiovascular risk persists in some patients taking statins [2], particularly in some subgroups [3, 4], such as those with atherogenic dyslipidemia, i.e., high TG and low HDL [5–11]. In the ACCORD Lipid trial of 5518 patients with diabetes treated with simvastatin plus either fenofibrate or placebo, those receiving simvastatin monotherapy and in the upper tertile of TG (≥204 mg/dL) and the lower tertile of HDL (≤34 mg/dL) had a cardiovascular event frequency of 17.3 % vs. a frequency of 10.1 % in all other patients receiving simvastatin alone [8]. Notably, while this high TG/low HDL subgroup represented ~17 % of the study population receiving statin monotherapy, it accounted for ~25 % of the cardiovascular events. Furthermore, this subgroup had a 29 % relative risk reduction with fenofibrate + simvastatin compared to those receiving simvastatin + placebo (12.4 % vs. 17.3 % events; $p = 0.032$). In contrast, patients not included in this dyslipidemic subgroup did not significantly benefit from fenofibrate + simvastatin therapy (10.1 % vs. 10.1 % events, $p = 0.06$ for the treatment-by-subgroup interaction). Similar patterns of increased risk in subgroups of statin-treated patients with high TG and low HDL, and apparent cardiovascular benefits with therapies that lower VLDL have been observed in other cardiovascular outcomes trials, including AIM-HIGH trial [12] and JELIS [13].

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Overweight/obesity and type 2 diabetes mellitus are strongly associated with hypertriglyceridemia [14–20]. For example, in the National Health and Nutrition Examination Survey (NHANES) 1999–2004, the prevalence of TG ≥200 mg/dL was 17.5 % among those with body mass index <25 kg/m^2 compared to 42.9 % among those with body mass index ≥30 kg/m^2 [19]. There have been dramatic increases in the incidence rates for overweight/obesity and type 2 diabetes mellitus in the US in recent decades [21, 22]. It is difficult to evaluate changes in the prevalence of hypertriglyceridemia over time because of simultaneous changes in the use of lipid-altering medications (mainly statins). Based on NHANES data, the prevalence of lipid lowering medication use among US adults increased from 3.4 % in 1988 to 15.5 % in 2010 [23]. Among men and women 60 years of age and older, prevalence of lipid-lowering medication use in 2010 exceeded 40 % in men and 33 % in women [23]. Data from NHANES 1999–2008, among individuals ≥20 years of age, prevalence values for elevated TG concentrations based on cutpoints of ≥150, ≥200, and ≥500 mg/dL were 31.0, 16.2, and 1.1 %, respectively [19].

Rationale for Omega-3 Combination Therapy

Omega-3 fatty acids (OM3 FA) are characterized by a double bond connecting the third and fourth carbon atoms from the methyl terminal [24]. The human body lacks the mechanism to auto-synthesize these fatty acids from their precursor, oleic acid [25]. Therefore, they must be obtained from the diet or through supplementation. The key fatty acids in physiology include alpha-linolenic acid (ALA)(C18:3n-3), eicosapentaenoic acid (EPA)(C20:5n-3), and docosahexaenoic acid (DHA) (C22:6n-3)(See Fig. 5.1). EPA and DHA are the more biologically active OM3 FAs, which are derived from its precursor, ALA [24].

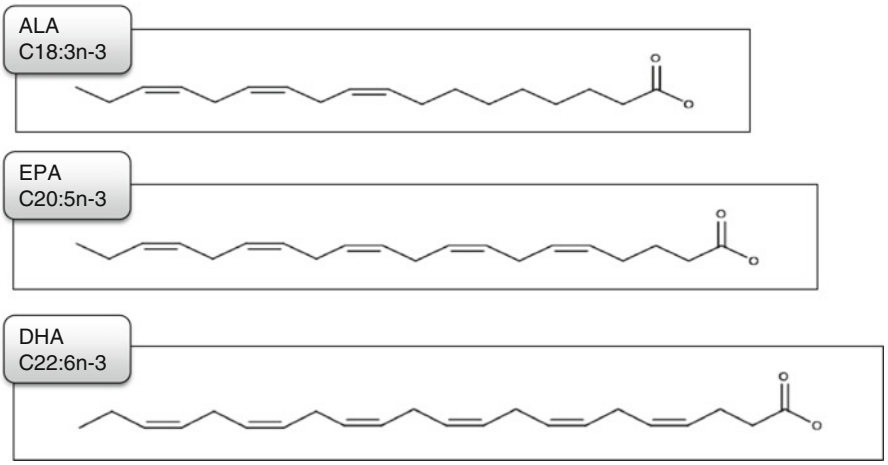

Fig. 5.1 Chemical structure of ALA, EPA, and DHA as free fatty acids. Note that all bonds present are all *cis* isomers

ALA is found in both animal and plants [25, 26], while EPA and DHA are found primarily in animal products, with highest concentrations, by far, in fish, such as salmon, sardine, and herring [24]. The role of OM3 FAs in physiology has been well studied. OM3 FAs are incorporated in cellular membranes and organelles, which contribute to cellular structure and function. They are known to be precursors to eicosanoids, which mediate vasodilatory, antiinflammatory, antithrombotic, and antiarrhythmic processes. In addition, there are known effects on gene expression from OM3 FAs [24]. Specifically in regard to lipid metabolism, OM3 FAs are thought to lower triglycerides (TG) through reduced synthesis and release of hepatic VLDL particles into circulation [27]. They also may reduce circulating TG by inhibiting hepatic lipogenesis at the genomic level, leaving less TG available to be incorporated into VLDL particles, and enhanced beta-oxidation of fatty acids [28, 29]. Both EPA and DHA decrease the TG content within VLDL while specifically DHA improves the lipolysis of VLDL and thereby conversion to LDL. Therefore, DHA appears to raise HDL-c and LDL-c more than EPA, particularly in patients with severe hypertriglyceridemia [30, 31]. The mechanisms behind these specific changes are not well understood but may relate to affects on apoC3 metabolism. Genomic studies on apoproteins have also shed light on how OM3 FAs may alter physiology. Genetic variants that carry only one Apo C3 allele were found to have a 40 % lower risk than noncarriers [32]. Apo C3 impairs binding of VLDL to cellular receptors, prolonging residence time in plasma, and resulting in formation of small dense LDL particles [33–36]. In hypertriglyceridemia, the VLDL that is secreted by the liver is enlarged with increased TG content and enhanced apo C3 content relative to apo E. Apo C3 inhibits the apo E-mediated uptake of these TG-rich lipoproteins resulting in elevated VLDL, reduced conversion of VLDL to LDL, and transfer of TG by cholesteryl ester transfer protein from VLDL to LDL and HDL resulting in small dense LDL and HDL particles [37, 38]. Apo C3 also inhibits the effect of apo C2 to stimulate lipoprotein lipase, thus slowing hydrolysis of TG from TG-rich lipoprotein particles and increasing their residence time in circulation [39]. Interventions that lower TG and TRL-C, including fibrates and OM3 FAs, also generally lower the circulating concentration of apo C3 [40–44]. Therefore, the known biochemical effects from OM3 FAs have made them an attractive option to employ into a therapeutic role at the prevention and modification of cardiovascular disease (CVD).

Early epidemiologic studies found a lower rate of cardiovascular related death among populations known to have high dietary fish content [24, 45]. However, later meta-analyses of intervention trials failed to find a benefit for mortality, cardiovascular mortality, or other adverse cardiovascular events [45]. In contrast to this, those with high measured serum concentrations of OM3 FAs are associated with a lower risk of total mortality, sudden cardiac arrest, and nonfatal and fatal myocardial infarction [45].

There is strong biochemical evidence to support the use of OM3 FAs in modification of CVD, although the details regarding employment of these properties have not yet been fully elucidated. Based on this and the epidemiologic studies, there is likely a role for utilization of OM3 FAs in certain patient populations.

Populations for Combinations Therapy

There has been significant controversy regarding the role of OM3 FAs in the prevention and management of CVD. The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focused primarily on evidence-based review rather than expert opinion, recommending high efficacy statin therapy for at-risk patients and discouraging combination therapy due to lack of evidence for benefits from randomized clinical trials [46]. An ACC/AHA panel did suggest that there is a role for combination therapy in certain high-risk patients with inadequate response to statin therapy or who have issues with statin intolerance, including those with clinical atherosclerotic CVD who are <75 years of age, those with LDL >190 mg/dL, or those with diabetes who are ages 40–75 years [46]. Other guidelines committees from other societies, including International Atherosclerosis Society (IAS), the European Atherosclerosis Society, and American Association of Clinical Endocrinologist (AACE), also recommend judicious use of combination therapy [47–49]. There are no specific recommendations for the use of prescription OM3 FAs from any of these societies. There is also discussion of the use of dietary modification as both recommendations to the general public and as part of the management of patients with severe hypertriglyceridemia (TG ≥500 mg/dL). AACE recommends OM3 FA use as adjunct therapy to niacin or fenofibrates for the treatment of hypertriglyceridemia [49].

Significant numbers of individuals on statin therapy continue to have high residual risk. Combination therapies, including OM3 FAs, appear most appropriate for patients with a high rate of events while taking optimal statin therapy. Although statins reduce the relative risk of cardiovascular events by approximately 20–50 %, depending on the LDL reduction [1], considerable risk of future events remains in some subgroups of patients, including elevated TGs, low HDL, elevated BMI, and a combination thereof [6, 8, 9, 12, 13, 50–55]. One of the strongest predictors of residual risk is hypertriglyceridemia associated with low levels of HDL [8, 9, 50, 51]. Additionally, persistent elevation in ApoB and TG are associated with recurrent cardiovascular events, despite statin therapy [10, 56].

The updated National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines recommend an optional LDL goal of <70 mg/dL in patients at very high risk, including those with established CVD in conjunction with multiple major risk factors, severe or poorly controlled risk factors, multiple metabolic syndrome components, or acute coronary syndrome [57]. Specifically, NCEP ATP III identified non-HDL as a secondary therapeutic target for individuals with TGs ≥200 mg/dL, where the goal is set 30 mg/dL higher than the LDL goal [57]. Similar recommendation, to treat to goal LDL and non-HDL were present in an Expert Panel report from the National Lipid Association (NLA) for the patient-centered management of dyslipidemia [58], and the International Atherosclerosis Society Global Recommendations for the Management of Dyslipidemia [47]. In a national survey of compliance with NCEP ATP III guidelines, 75 % of patients with

coronary heart disease (CHD) met the definition of "very high risk," yet only 18 % had an LDL <70 mg/dL, and only 4 % had an LDL level <70 mg/dL and a non-HDL level less than 100 mg/dL, when TGs were >200 mg/dL [59]. These data substantiate the use of combination therapy to reduce residual risk in statin optimized patients. Lastly, there exist additional patient populations with familial dyslipidemias and other conditions, which do not necessarily fall within guideline recommendations who may be candidates for OM3 FAs.

Lipid Serologies for the Evaluation of the Patient

Traditionally, guidelines for the management of dyslipidemias have focused on treatment to a specific LDL goal based on medical history. For certain high-risk patients, targets for other values, including non-HDL are also recommended. However, more recent evidence suggests that these traditional ways of estimating residual cardiac risk do not perform optimally. In particular, triglyceride rich lipoprotein-cholesterol (TRL-C), also called "remnant cholesterol," may be a better measure to utilize when treating to targets and estimating residual cardiovascular risk.

LDL carries ~75 % of the circulating cholesterol in particles other than HDL, making it an attractive treatment target to minimize cardiovascular risk resulting from dyslipidemias. However, there is a growing body of evidence from multiple studies to indicate that TG-rich TRL-C is at least as strongly associated with risk for CHD and other major adverse cardiovascular events as LDL, and, in some studies, even more strongly associated [60–63]. TRL-C includes cholesterol carried by all apo B-containing lipoproteins that are not in the LDL density range, including IDL, VLDL, and chylomicron particles (see Fig. 5.2), the largest portion of which is VLDL. TRL-C is ideally calculated as non-HDL minus LDL, where LDL is directly measured. This is necessary since the Friedewald calculated LDL includes IDL-C. However, the IDL fraction is small and typically allows for an accurate calculation without direct LDL, except in certain patients with conditions such as dysbetalipoproteinemia (prevalence ~0.01–0.1 %) [64], when IDL-C may predominate.

Non-HDL and LDL as Predictors of CHD

An examination of lipoprotein cholesterol as a function of increasing levels of non-fasting TG from population studies conducted in Copenhagen indicated that increased levels of plasma TG were associated with increased levels of remnant cholesterol ($R^2 = 0.96$, $p < 0.001$), and reduced levels of HDL ($R^2 = -045$, $p < 0.001$), whereas a positive association between TG and LDL was less pronounced ($R^2 = 0.12$, $p < 0.001$) [63]. Observation studies indicated that an elevated level of TG is associated with increased risk for CVD [65–68]. However, risk associated with TG elevations are contained entirely within non-HDL and HDL [68].

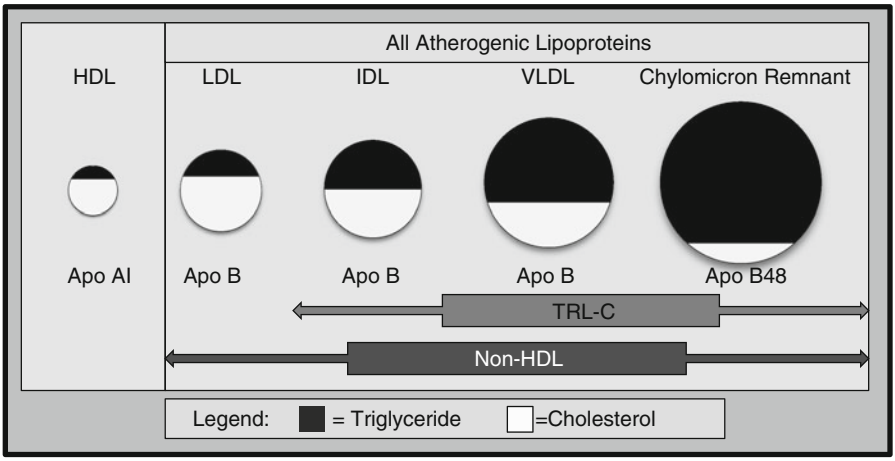

Fig. 5.2 Components of non-HDL and TRL-C

Population studies have consistently shown that non-HDL is a stronger correlate of CHD event risk than LDL in those with and without hypertriglyceridemia [47, 69–72]. An analysis of data from the Lipid Research Clinics Program Follow-up Study of 2406 men and 2056 women reported that levels of non-HDL and HDL at baseline were significant positive and inverse predictors, respectively, of cardiovascular mortality in both sexes [69]. When analyzed as continuous variables in a multivariate model including non-HDL, LDL, total-C, and HDL and adjusted for age, relative risks (RRs) and 95 % CIs for an increase of 30 mg/dL non-HDL were 1.19 (1.13, 1.26) and 1.15 (1.06, 1.25) in men and women, respectively, and RRs (95 % CIs) associated with a 10 mg/dL increase in HDL were 0.77 (0.69, 0.86) and 0.77 (0.69, 0.88) in men and women, respectively. LDL level was a somewhat weaker predictor of cardiovascular mortality: RR 1.11 (1.02, 1.22) and 1.08 (0.96, 1.22) in men and women, respectively, for each 30 mg/dL increase in LDL. The superiority of non-HDL vs. LDL for major cardiovascular event prediction was also demonstrated in a recent meta-analysis of contemporary statin trials [72]. This analysis used cut-off points of 100 mg/dL for LDL and 130 mg/dL for non-HDL demonstrated that when there was discordance between the two measures (i.e., only one was elevated), risk followed non-HDL more closely than LDL, illustrating that the elevated level of TRL-C was associated with increased CHD risk, even in the presence of low LDL (<100 mg/dL).

TRL-C, Consideration as the Preferred CHD Predictor

Recent data support the hypothesis that TRL-C is not only atherogenic, but may be even more atherogenic than LDL [61, 63, 73]. VLDL remnants are known to cross the endothelial barrier and have been identified in human arteries [74, 75]. Because

of their larger size, VLDL particles carry 5–20 times more cholesterol per particle as compared with LDL particles. Importantly, unlike native (unmodified) LDL, remnants can be taken up in an unregulated fashion by scavenger receptors expressed by resident macrophages in the subendothelial space, thus promoting foam cell formation [76, 77]. Chylomicron and VLDL remnants have been shown to rapidly penetrate the arterial wall, and contribute to atherogenesis in animal models [78, 79].

TRL-C (remnant cholesterol) as a risk factor for CHD was examined in two prospective studies and one case control study conducted in Copenhagen Denmark, including 73,514 white subjects of which 11,984 had CHD diagnosed during the follow-up periods. Associations of quintiles of lipoprotein cholesterol with risk for CHD were calculated. The hazard ratio (HR) (95 % CI) for risk for CHD for the first through fifth quintiles for TRL-C were 1.1 (0.8, 1.6), 1.2 (0.9, 1.6), 2.0 (1.5, 2.6), and 2.3 (1.7, 3.1), respectively, and for LDL were 1.0 (0.8, 1.3), 1.2 (0.9, 1.5), 1.3 (1.0, 1.6), and 1.8 (1.4, 2.2), respectively [63]. Thus, comparing the top quintile versus the bottom quintile, higher LDL was associated with an 80 % increase in CHD risk, whereas higher TRL-C was associated with a 130 % increase in CHD risk.

Analyses of several additional sets of data from prospective cohort investigations including the Women's Health Study (WHS) [80], the Health Professionals Follow-up Study (HPFS) [81], and pooled data from the Nurses Health Study (NHS) and the HPFS also provide support to the relationship between increased TRL-C and increased CVD risk (Table 5.1) [82].

Furthermore, genetic evidence demonstrates TRL-C causation of CHD over other traditionally measured factors. A small number of single-nucleotide polymorphisms were shown to be strongly associated with remnant cholesterol, remnant cholesterol/HDL, HDL, and LDL [63]. The numbers of risk alleles for remnant cholesterol (TRL-C) and LDL were more strongly associated with CHD risk than measured lipid levels. Genetic variants associated with decreased HDL alone were not associated with increased risk. Alleles associated with remnant cholesterol were more strongly linked to CHD risk (HR 2.82 [95 % CI 1.92, 4.15] per 1 mmol/L [38.7 mg/dL] increase) than those associated with LDL (HR 1.47 [95 % CI 1.32, 1.63] per 1 mmol/L [38.7 mg/dL] increase). An examination of genomic variants that alter HDL levels indicated that of the 15 variants that alter HDL, just 6 also affect risk for myocardial infarction, and all of these also alter at least one other lipid fraction [32]. These data further support that a shift is needed from the old paradigm for cardiovascular risk assessment that said that total cholesterol (TC) is equal to

Table 5.1 WHS, HPFS, and Pooled NHS and HPFS: CVD risk according to lipoprotein cholesterol level (quintile 5 compared to quintile 1 as the referent)

Study	LDL HR (95 % CI)	Non-HDL HR (95 % CI)	TG (HR (95 % CI)
WHS (n = 27,673)	1.74 (1.40, 2.16)	2.52 (1.95, 3.25)	2.58 (1.95, 3.41)
HPFS (n = 739	2.07 (1.24, 3.45)	2.75 (1.62, 4.67)	2.12 (1.21, 3.70)
Pooled NHS + HPFS (n = 1478)	1.79 (1.23, 2.64)	2.53 (1.72, 3.72)	2.17 (1.51, 3.11)

HDL (good) plus VLDL (uncertain) plus LDL (bad), to a new paradigm in which total cholesterol is equal to HDL (uncertain) plus TRL-C (bad) plus LDL (bad).

Future studies should consider utilization of TRL-C in study coordination. There are multiple lines of evidence from various study types to support the causality for TRL-C and CHD/CVD risk, including results from randomized control trials, but the evidence is limited by the designs of the studies conducted to date. The preferred CVD outcomes study design would include exclusive or predominant enrollment of subjects with elevated TRL-C (e.g., high to very high TG) and use an intervention that produces a substantial reduction in TRL-C.

Implications of the Evidence for a Causal Role of VLDL Elevation in Promoting CVD Risk

1. TRL-C is at least as strongly associated with CVD event risk per mg/dL as is LDL, which explains the superiority of non-HDL over LDL as a predictor of cardiovascular event risk.
2. Elevated non-HDL due to increased TRL-C is likely to be an important source of residual risk in a subgroup of statin-treated in patients with well-controlled LDL.
3. Because TRL-C is at least as atherogenic as LDL, non-HDL should be the preferred target of therapy.

Therapy with Omega-3 Fatty Acids

Summary of Evidence for Use

Early secondary prevention studies suggested that supplementation with daily OM3 FAs improved lipid profiles and reduced cardiac events for those with and without a history of CHD. As previously mentioned, dietary supplementation with fatty fish was found to assist in the prevention of death related to CHD in the Diet and Reinfarction Trial (DART) [83]. Initial analysis of Omacor (Lovaza), a mix of EPA and DHA, in a population of patients with hypertriglyceridemia showed significant reduction in TG by 45 %, cholesterol by 15 %, VLDL by 32 %, and an increase in HDL by 13 % and LDL by 31 % [84]. The GISSI trial was next to evaluate the efficacy of direct OM3 FA supplementation on cardiovascular events, which found that supplementation of patients $\leq$3 months post-myocardial infarction with 1 g of a combination of EPA and DHA (ratio 1:2) ethyl esters significantly reduced death and cardiovascular death [85]. These findings were further solidified when the Japan EPA Lipid Intervention Study (JELIS) demonstrated addition of EPA to statin therapy in those with or without prior myocardial infarction led to a 19 % relative reduction in major cardiac events with a 25 % decrease in LDL cholesterol [13].

Later analyses did not support the benefit from supplementation of OM3 FAs. The Alpha Omega Trial investigated dietary supplementation with ALA and combination EPA-DHA within margarines. The patients were found to have ingested 226 mg of EPA with 150 mg of DHA and/or 1.9 g of ALA, which did not show significant reductions in major cardiovascular events, although women assigned to the ALA treatment arm had a reduction in cardiovascular events that approached significance (HR 0.73; 95 % 0.51–1.03) [86]. Next, in the Outcome Reduction with an Initial Glargine Intervention (ORIGIN), supplementation with 1 g Lovaza (465 mg EPA; 375 mg DHA) in high-risk patients did not find a significant difference in cardiac events, but did find a 14.5 mg/dL decrease in TG without significant changes in other lipids [87]. Then, the Risk and Prevention Study Collaborative Group, patients with multiple cardiovascular risk factors or known atherosclerosis were assigned to 1 g of OM3 FA ethyl esters (containing EPA and DHA in ratio from 0.9:1 to 1.5:1) versus olive oil [88], which resulted in no significant findings in relation to cardiovascular mortality and morbidity. In each of these trials, patients were assigned to relatively low levels of OM3 FA supplementation, which did not lower serum TG, and although higher risk groups were selected, there was no specific selection of the high-risk patients who may have conferred a benefit. In fact, the one aforementioned group that approached near-efficacy was the group of women who had the highest OM3 FA intake at ~2 g (of ALA) per day.

Several design issues should be considered in evaluating the clinical importance of the cardiovascular outcomes trials conducted to date with OM3 FA interventions. This includes the use of low dosages of OM3 FAs that had modest effects on TG and VLDL concentrations. For example, in a large 2012 meta-analysis of OM3 FA trials to date, the median (interquartile range limits) dosage was 1.0 (0.5–1.8) g/day EPA and/or DHA, mostly as ethyl esters [89]. JELIS was the only pharmaceutical OM3 intervention trial to examine cardiovascular outcomes in which a dosage was used that is in the range required to appreciably lower TG and VLDL levels (1.8 g/day EPA ethyl esters) [13]. These studies were not conducted in patients who would be expected to have the greatest potential to benefit from TG and VLDL lowering therapy (i.e., patients with high TG or high TG and low HDL). Thus, data are needed to prospectively evaluate the potential cardiovascular benefits of using OM3 FAs as a lipid-altering intervention at a therapeutic dosage level in patients with elevated TG.

These observations led to additional analyses, which selected the highest risk groups in attempts to find potential patients who may benefit from OM3 FA supplementation. Post hoc analysis did suggest significant benefit for diabetic patients with a history of an MI and for patients who were not on statin therapy [90]. Other studies in patients already on statin therapy demonstrate improvement in lipid serologies. The aforementioned JELIS trial already elucidated some initial possible benefits of adding OM3 FAs to statin therapy. In other trials, OM3 FAs have been found to further reduce LDL 13–24 % and TG 27–30 % in patients on pravastatin 40 mg/day [91] or simvastatin 20 mg/day [92]. When added to simvastatin for patients with TG $\geq$200 and <500 mg/dL, 4 g/day of Lovaza was found to significantly decrease TG 29.5 %, VLDL 27.5 %, TC/HDL ratio 9.6 %, and raise HDL 3.4 % [93].

More recent trials of highly refined OM3 FAs (Vascepa and Epanova) have been shown to effectively treat hypertriglyceridemia and appear to have no HDL lowering effects, which may be augmented by high potency statin use [94–97]. The MARINE trial also investigated patients with TG ≥500 and <2000 mg/dL, but with or without background statin therapy, to highly purified EPA ethyl ester (AMR101 [Vascepa]) without DHA. Vascepa 4 g/day was found to significantly reduce serum TG by 27 % compared to 10 % increase with mineral oil with also reduction in non-HDL (8 % reduction with 4 g/day compared to a 8 % increase with mineral oil), apolipoprotein B, lipoprotein associated phospholipase A1, VLDL, and TC [95]. The ANCHOR trial also evaluated Vascepa, but in patients with TG ≥200 to <500 with LDL >40 and <100 mg/dL while on statin therapy. Significant placebo-adjusted reductions in TG (21.5 % with 4 g/day and 10.1 % for 2 g/day), non-HDL (13.6 % with 4 g/day and 5.5 % with 2 g/day), VLDL (26.5 % with 4 g/day and 11.3 % with 2 g/day), LDL, TC, apoB, lipoprotein-associated phospholipase A2, and high-sensitivity C-reactive protein were observed over a 12-week period [94].

A novel combination of EPA and DHA as carboxylic acid (free fatty acid), rather than ethyl esters, Epanova, has also been evaluated (Fig. 5.3). The benefit of the OM3 carboxylic acid form is an up to four-fold greater bioavailability compared to currently available OM3 ethyl ester drugs [98, 99]. This is because the free fatty acid form avoids the need for hydrolysis by dietary fat stimulated pancreatic lipases, which may have significant clinical implications since those with severe hypertriglyceridemia are recommended to follow a low-fat diet [48, 49, 98, 99]. The EVOLVE trial found that patients with TG ≥500 and <2000 mg/dL assigned to higher dose EPA and DHA as free fatty acids at a total of 2–4 g/day versus placebo in patients with TG ≥500 and <2000 mg/dL. Fasting serum TGs decrease by 25.5–30.9 % from baseline with also having reductions in non-HDL (6.9–9.6 % decline versus 2.5 % increase in placebo group), TC to HDL ratio, VLDL, TRL-C, apolipoprotein C3, lipoprotein-associated phospholipase A2, and arachidonic acid [96]. The ESPIRIT trial followed, which investigated Epanova in patients with fasting TG levels ≥200 to <500 mg/dL, with 2 or 4 g/day of Epanova versus olive oil. This trial demonstrated significant reduction in non-HDL levels of 3.9 % (2 g/day) to 6.9 % (4 g/day) versus 0.9 % (control), TG levels (14.6 % (2 g/day) to 20.6 %

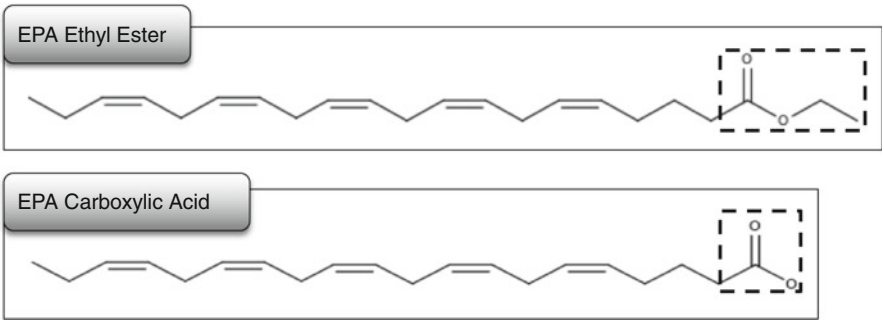

Fig. 5.3 EPA fatty acids shown as the Ethyl Ester compared to Carboxylic Acid formulations

(4 g/day) reduction versus 5.9 % (control)), increased LDL with 2 g/day dosing only (4.6 % versus 1.1 % (control)), and decreased TC, VLDL, and for higher dosages (4 g/day) also finding decreased TC/HDL ratio, apo-AI, and ApoB [97]. Based on these results, Epanova was approved by the FDA for the treatment of severe hypertriglyceridemia with either a 2 or 4-g daily dose without regards to meals.

In summary, there is emerging evidence for the use of OM3 FAs. There is a clear benefit in the reduction of TGs with the supplementation of OM3 FAs in patients with severe hypertriglyceridemia, and perhaps certain subgroups with hypertriglyceridemia where benefit of adding this therapy has yet to be completely elucidated. One criticism of many of these studies is that the dose of OM3 FAs were particularly small and perhaps the benefits were not observed due to not obtaining treatment range dosing.

Ongoing Clinical Trials

Despite the promising effects at reduction of TG and non-HDL, evidence still lacks for overt reduction of cardiovascular events with OM3 FA supplementation. However, there are ongoing trials, which seek to address whether new high-potency OM3 FAs can further reduce cardiovascular events beyond TG lowering in patients with hypertriglyceridemia on statin therapy.

The REDUCE-IT Trial is a phase-3 study of ~8000 patients with high baseline TG (≥150 mg/dL initially, then later increased to ≥200) and at least one other cardiac risk factor who are being treated with Vascepa versus control (mineral oil) as add-on to statin therapy. Outcomes being measured include composite endpoint of cardiovascular death, MI, stroke, coronary revascularization, and hospitalization for unstable angina. Estimated completion data is December 2017 [100, 101].

The STRENGTH Trial is a phase-3 study to investigate the effectiveness of adding Epanova to statin monotherapy for lowering major adverse cardiovascular events versus adding placebo, corn oil, to statin therapy. This study will include ~13,000 subjects with TG ≥200 and <500 mg/dL with low HDL (<40 mg/dL for men and <45 mg/dL for women) despite being on optimal or maximally tolerated statin dose, and at high risk for CVD. Outcome being measures is time to the first occurrence of any major adverse cardiac event (cardiovascular death, nonfatal MI, nonfatal stroke, emergent/elective coronary revascularization, or hospitalization for unstable angina). Estimated completion date is June 2019 [102].

Side Effects/Tolerance

In general, OM3 FA supplements are well tolerated with low side effects. There have been rare reports of interaction with anticoagulants, and periodic monitoring has been suggested. The ACC/AHA guidelines recommend that if OM3 FAs are

utilized that it is "reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding" [46].

Lovaza – Side effects include dyspepsia, eructation, rash, taste perversion, back pain, infection, flu syndrome, and other pain. Other less common side effects have been reported in post-marketing surveillance, but are rare [103].

Vascepa – Side effects include arthralgias and elevated fasting glucose. Evidence of increase risk of bleeding occurred in higher dose treatment (4 g/day), with 2 cases of CNS bleeding. Along with other OM3 FAs, it is recommended that patients taking Vascepa and drugs affecting coagulation be periodically monitored [104].

Epanova – Side effects gastrointestinal disorders, with higher incidences of diarrhea, nausea, eructation, abdominal pain, flatulence, and dysgeusia [97, 105]. In patients with chronic gastrointestinal diseases, there were reports of abdominal distension, constipation, vomiting, fatigue, nasopharyngitis, arthralgia, and dysgeusia [105].

Consideration Versus Fenofibrates as Add-On Therapy

There exist multiple options for add-on therapy to statins in those without optimal risk minimization. In particular, evidence suggests OM3 FA and fenofibrates as potential beneficial options. Careful consideration should be made when deciding the next add on therapy, particularly in the current era where data to support such indications are not robust. When comparing fenofibrates to OM3 FAs, one should consider side effects, their effect on non-HDL and on LDL, and potential mortality benefit.

Regarding side effects not all fibrates are well tolerated when added to statin. In particular, gemfibrozil has been found to have a particularly high risk for development of myopathy [106]. Regarding fenofibrate, although not causing increased rates of muscle-related adverse events, addition of fenofibrate to statin therapy has higher liver and kidney-related adverse events [107].

In the ACCORD trial, which tested fenofibrate + statin therapy effect on lipid serologies and cardiovascular events. Fenofibrate with statin did not demonstrate the same rate of myopathy as seen with Gemfibrozil. In this trial, patients with TG $\geq$204 mg/dL and HDL $\leq$34 mg/dL were found to have a placebo correct reduction in VLDL of 8.6 mg/dL with increase in LDL of 9 mg/dL. The cardiovascular event rate was decreased, with a HR of 0.69 ($p = 0.03$) [8]. In a similar set of patients, the ESPIRIT trial also showed placebo corrected reduction in VLDL of 7.3 mg/dL, non-HDL of 8.5 mg/dL, with minimal increase in LDL of 0.5 mg/dL. Since there is minimal effect on LDL and nearly the same effect on VLDL, OM3 FA will likely confer the same, if not better outcomes based on change in lipid profiles. What is more, OM3 FAs have a better tolerability profile.

Role in Specific Patient Populations

Statin Intolerance

OM3 FA supplementation in those who do not tolerate statins is a sensible option. Without any statin the patient with dyslipidemia is at considerable risk for cardiovascular combinations. As previously mentioned, initial trials before the statin age have shown that OM3 FA not only improve lipid profiles [84], but also decrease rate of death and cardiovascular death [85].

Familial Dyslipidemias

There are few studies to assess the efficacy of OM3s on specific familial conditions, but the few that exist suggest a potential benefit. One early study of 9 patients with familial combined hyperlipidemia, supplemented with 3.0–4.5 g/day combination EPA/DHA OM3 FAs lowered VLDL TG 42–55 %, VLDL 41–47 %, VLDL Apo-B 40–56 % (for lower and higher doses, respectively), with no overall change in LDL, although 4 patients experienced a 19 % dose dependent increase in LDL [108]. In one study, supplementation with Lovaza (4 g/day) resulted in lower of TG 21 %, VLDL 29 %, with no change in HDL or TC, and an increase in LDL by 21 % compared to placebo, suggesting a benefit from addition of OM3 FAs [109]. Other data present from additional case reports suggests that there may be additional uses for OM3 FA supplementation. In one patient with lipoprotein lipase deficiency, supplementation with 4–6 g/day OM3 FAs (EPA/DHA mix, ratio 1.4:1) was found to normalize fasting lipid profiles [110]. Similarly another case of chylomicronemia in 12 patients found that 12 weeks of OM3 FA supplementation (first with 2.16 g grams, titrated to 4.32 g for the last 8 weeks) decreased TG by 45 %, with decreases within the chylomicron fraction of TG, VLDL, and TC [111].

Conclusion

There is clear scientific understanding of how OM3 FAs integrate with physiology. These mechanisms can be exploited for the modification of disease. Current studies on how to best take advantage of this implicate that OM3 FAs alter the course of CVD both for prevention of adverse cardiovascular outcomes and treatment of derangements in lipid serologies. Current guidelines and recommendations support their regular integration into the diet and supplementation for those with severe hypertriglyceridemia as adjunct therapy.

Emerging data suggests that OM3 FAs may have implications in specific subpopulations. In particular, patients with elevated triglycerides may benefit from supplementation as combination therapy to statins and lifestyle changes, especially those with TGs ≥500 mg/dL, and perhaps pending results of ongoing trials, those with TGs ≥200 mg/dL and <500 mg/dL. Additional roles for OM3 FAs lie in certain subgroups with specific familial dyslipidemias and those who do not tolerate statin therapy.

In conclusion, an elevated level of TG is associated with increased CHD/CVD risk, and the risk associated with elevated TG is completely captured by non-HDL (which includes LDL-C and TG-rich lipoprotein cholesterol [typically estimated as TRL-C]) and HDL-C. Non-HDL, which reflects TG-rich lipoprotein cholesterol in addition to LDL, is at least as strong, and possibly stronger, than LDL as a predictor of CVD risk in patients with hypertriglyceridemia.

Prescription OM3 FA therapies added to optimal statin monotherapy is safe and well tolerated and reduces TRL-C/non-HDL in subjects with hypertriglyceridemia. The ongoing STRENGTH and REDUCE-IT trials are the first cardiovascular outcomes trials to appropriately target an elevated TG with an adequately powered sample and a therapy that effectively lowers the atherogenic components of non-HDL that are not sufficiently managed by statin therapy alone. The beneficial changes in non-HDL or TRL-C with OM3 FAs are comparable or superior to those observed with fibrate therapy. Based on results from fibrate trials of TG lowering and CHD/CVD reduction, the placebo-corrected reduction in TRL-C concentration achieved with 4 g/day of OM3 FAs would be expected to reduce CVD event risk by ~21 %. Moreover, previous cardiovascular outcomes trials have indicated potential cardiovascular benefits with OM3 FAs that are not mediated by reductions in non-HDL. If these trials are successful this will likely lead to the regulatory approval for the non-HDL lowering indication for high cardiovascular risk patients in combination with statin treatment.

References

1. Cholesterol Treatment Trialists Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–81. doi:10.1016/S0140-6736(10)61350-5.
2. Fruchart JC, Sacks F, Hermans MP, et al. The residual risk reduction initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. Am J Cardiol. 2008;102(4):319–35. doi:10.1016/j.amjcard.2008.10.002.
3. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267–78. doi:10.1016/S0140-6736(05)67394-1.
4. Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at Low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581–90. doi:10.1016/S0140-6736(12)60367-5.
5. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki heart study. Implications for treatment. Circulation. 1992;85:37–45. doi:10.1161/01.CIR.85.1.37.

6. Bezafibrate Infarction Prevention Study. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. Circulation. 2000;102(1):21–7. doi:10.1161/01.CIR.102.1.21.
7. The ACCORD Study Group. Relation of gemfibrozil treatment and high-density lipoprotein subpopulation profile with cardiovascular events in the veterans affairs high-density lipoprotein intervention trial. Metabolism. 2008;57(1):77–83. doi:10.1016/j.metabol.2007.08.009.
8. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563–74.
9. Scott R, O'Brien R, Fulcher G, et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetes Care. 2009;32(3):493–8. doi:10.2337/dc08-1543. Clinical.
10. Mora S, Wenger NK, Demicco DA, et al. Determinants of residual risk in secondary prevention ptients treated with high- versus Low-dose statin T therapy: the Treating to New Targets (TNT) study. Circulation. 2012;125:1979–87. doi:10.1161/CIRCULATIONAHA.111.088591.
11. Sasaki J, Yokoyama M, Matsuzaki M, et al. Relationship between coronary artery disease and non-HDL-C, and effect of highly purified EPA on the risk of coronary artery disease in hypercholesterolemic patients treated with statins: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). J Atheroscler Thromb. 2012;19:194–204. doi:10.5551/jat.8326.
12. The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365(24):2255–67.
13. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007;369:1090–8. doi:10.1016/S0140-6736(07)60527-3.
14. Mokdad A, Bowman B, Ford E, et al. The continuing epidemics of obesity and diabetes in the United States. JAMA. 2001;286(10):1195–200. doi:10.1001/jama.286.10.1195.
15. D'Agostino R, Hamman R, Karter A, et al. Cardiovascular disease risk factors predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes Care. 2004;27(9):2234–40. doi:10.2337/diacare.27.9.2234.
16. Cowie CC, Rust KF, Byrd-Hold DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. Population: national health and nutrition examination survey 1999–2002. Diabetes Care. 2006;29(6):1263–8.
17. Cowie CC, Rust KF, Byrd-Hold DD, et al. Prevalence of diabetes and high risk for population in 1988–2006. Diabetes Care. 2010;33(3). doi:10.2337/dc09-1524.
18. Ford ES, Li C, Zhao G, et al. Hypertriglyceridemia and its pharmacologic treatment among US adults. Arch Intern Med. 2009;169(6):572–8. doi:10.1001/archinternmed.2008.599.
19. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the american heart association. Circulation. 2011;123:2292–333. doi:10.1161/CIR.0b013e3182160726.
20. Menke A, Rust KF, Fradkin J, et al. Associations between trends in race/ethnicity, aging, and body mass index with diabetes prevalence in the United States. Ann Intern Med. 2014;161(5):328. doi:10.7326/M14-0286.
21. Fox CS, Pencina MJ, Meigs JB, et al. Trends in the incidence of type 2 diabetes mellitus from the 1970s to the 1990s: the Framingham heart study. Circulation. 2006;113:2914–8. doi:10.1161/CIRCULATIONAHA.106.613828.
22. Flegal KM. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 2012;307(5):491. doi:10.1001/jama.2012.39.
23. Carroll MD. Trends in lipids and lipoproteins in US adults, 1988–2010. JAMA. 2012;308(15):1545. doi:10.1001/jama.2012.13260.
24. Colussi G, Catena C, Baroselli S, et al. Omega-3 fatty acids: from biochemistry to their clinical Ese in the prevention of cardiovascular disease. Recent Pat Cardiovasc Drug Discov. 2007;2:13–21. doi:10.2174/157489007779606158.
25. Abedi E, Sahari MA. Long-chain polyunsaturated fatty acid sources and evaluation of their nutritional and functional properties. Food Sci Nutr. 2014;5(2):443–63. doi:10.1002/fsn3.121.

26. Kaur N, Chugh V, Gupta AK. Essential fatty acids as functional components of foods-a review. J Food Sci Technol. 2012;51(October):1–15. doi:10.1007/s13197-012-0677-0.
27. Bays HE, Tighe AP, Sadovsky R, et al. Prescription omega-3 fatty acids and their lipid effects: physiologic mechanisms of action and clinical implications. Expert Rev Cardiovasc Ther. 2008;6:391–409. doi:10.1586/14779072.6.3.391.
28. Harris WS, Poston WC, Haddock CK. Tissue n−3 and n−6 fatty acids and risk for coronary heart disease events. Atherosclerosis. 2007;193:1–10. doi:10.1016/j.atherosclerosis.2007.03.018.
29. Harris WS, Miller M, Tighe AP, et al. Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives. Atherosclerosis. 2008;197:12–24. doi:10.1016/j.atherosclerosis.2007.11.008.
30. Eslick G, Peter H, Smith C, et al. Benefits of fish Oil supplementation in hyperlipidemia: a systematic review and meta-analysis. Int J Cardiol. 2009;136(1):4016.
31. Jacobson T, Glickstein S, Rowe J, et al. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: a review. J Clin Lipidol. 2012;6:5–18. doi:10.1016/j.jacl.2011.10.018.
32. The TG and HDL Working Group of the Exome Sequencing Project. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. N Engl J Med. 2014;371:22–31. doi:10.1056/NEJMoa1307095.
33. Curtiss LK. ApoE in atherosclerosis. Arterioscler Thromb Vasc Biol. 2000;20:1852–3.
34. Mendivil CO, Zheng C, Furtado J, et al. Metabolism of very-low-density lipoprotein and Low-density lipoprotein containing apolipoprotein C-III and not other small apolipoproteins. Arterioscler Thromb Vasc Biol. 2010;30:239–45. doi:10.1161/ATVBAHA.109.197830.
35. Mendivil CO, Rimm EB, Furtado J, et al. Apolipoprotein E in VLDL and LDL with apolipoprotein C-III is associated with a lower rrisk of coronary heart disease. J Am Heart Assoc. 2013;2(Ldl):e000130. doi:10.1161/JAHA.113.000130.
36. Zheng C, Khoo C, Furtado J, et al. Apolipoprotein C-III and the metabolic basis for hypertriglyceridemia and the dense Low-density lipoprotein phenotype. Circulation. 2010;121:1722–34. doi:10.1161/CIRCULATIONAHA.109.875807.
37. Kawakami A, Yoshida M. Apolipoprotein CIII links dyslipidemia with atherosclerosis. J Atheroscler Thromb. 2009;16:6–11. doi:10.5551/jat.E607.
38. Zheng C. Updates on apolipoprotein CIII: fulfilling promise as a therapeutic target for hypertriglyceridemia and cardiovascular disease. Curr Opin Lipidol. 2014;25:35–9. doi:10.1097/MOL.0000000000000040.
39. Shachter NS. Apolipoproteins C-I and C-III as important modulators of lipoprotein metabolism. Curr Opin Lipidol. 2001;12:297–304. doi:10.1097/00041433-200106000-00009.
40. Lemieux I, Salomon H, Després J-P. Contribution of apo CIII reduction to the greater effect of 12-week micronized fenofibrate than atorvastatin therapy on triglyceride levels and LDL size in dyslipidemic patients. Ann Med. 2003;35(5):442–8. doi:10.1016/S1567-5688(02)80392-0.
41. Davidson MH, Maki KC, Bays H, et al. Effects of prescription omega-3-acid ethyl esters on lipoprotein particle concentrations, apolipoproteins AI and CIII, and lipoprotein-associated phospholipase A2 mass in statin-treated subjects with hypertriglyceridemia. J Clin Lipidol. 2009;3(5):332–40. doi:10.1016/j.jacl.2009.08.001.
42. Belfort R, Berria R, Cornell J, et al. Fenofibrate reduces systemic inflammation markers independent of its effects on lipid and glucose metabolism in patients with the metabolic syndrome. J Clin Endocrinol Metab. 2010;95(2):829–36. doi:10.1210/jc.2009-1487.
43. Maki KC, Bays HE, Dicklin MR, et al. Effects of prescription omega-3-acid ethyl esters, coadministered with atorvastatin, on circulating levels of lipoprotein particles, apolipoprotein CIII, and lipoprotein-associated phospholipase A2 mass in men and women with mixed dyslipidemia. J Clin Lipidol. 2011;5(6):483–92. doi:10.1016/j.jacl.2011.09.001.
44. Morton A, Furtado J, Amerine W, et al. The effect of omega-3 carboxylic acids on apolipoprotein CIII containing lipoproteins in moderate to severe hypertriglyceridemia. Circulation. 2014;130(Suppl 2): Abstract 16864.

45. Von Schacky C. Omega-3 index and cardiovascular health. Nutrients. 2014;6:799–814. doi:10.3390/nu6020799.
46. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129 (25 Suppl 2):S1–45. doi:10.1161/01.cir.0000437738.63853.7a.
47. Grundy SM, Arai H, Barter P, et al. An international atherosclerosis society position paper: global recommendations for the management of dyslipidemia – full report. J Clin Lipidol. 2014;8:29–60. doi:10.1016/j.jacl.2013.12.005.
48. Reiner Ž, Catapano AL, De Backer G, et al. ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2011;32(2011):1769–818. doi:10.1093/eurheartj/ehr158.
49. Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. Endocr Pract. 2012;18(C):1–78. http://www.ncbi.nlm.nih.gov/pubmed/22522068.
50. Saito Y, Yokoyama M, Origasa H, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2008;200:135–40. doi:10.1016/j.atherosclerosis.2008.06.003.
51. Guyton JR, Slee AE, Anderson T, et al. Relationship of lipoproteins to cardiovascular events: the AIM-HIGH Trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes). J Am Coll Cardiol. 2013;62(17):1580–4. doi:10.1016/j.jacc.2013.07.023.
52. Frick M, Elo O, Haapa K, et al. Helsinki heart study: primary-prevention trial with gemfibrozil in middle-aged Men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987;317(20):1237–45.
53. Tenkanen L, Manttari M, Kovanen P, et al. Gemfibrozil in the treatment of dyslipidemia: an 18-year mortality follow-up of the Helsinki Heart Study. Arch Intern Med. 2006;166(7):743–8.
54. Rubins H, Robins S, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999;341(6):410–8.
55. Keech A, Simes R, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366:1849–61. doi:10.1016/S0140-6736(05)67667-2.
56. Faergeman O, Holme I, Fayyad R, et al. Plasma triglycerides and cardiovascular events in the Treating to New Targets and Incremental Decrease in End-Points Through Aggressive Lipid Lowering trials of statins in patients with coronary artery disease. Am J Cardiol. 2009;104(4):459–63. doi:10.1016/j.amjcard.2009.04.008.
57. Cholesterol Treatment Trialists Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267–78. doi:10.1016/S0140-6736(05)67394-1.
58. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1 – executive summary. J Clin Lipidol. 2014;8(5):473–88. doi:10.1016/j.jacl.2014.07.007.
59. Davidson MH, Maki KC, Pearson TA, et al. Results of the National Cholesterol Education (NCEP) program evaluation project utilizing novel T-technology (NEPTUNE) II survey and implications for treatment under the recent NCEP writing group recommendations. Am J Cardiol. 2005;96:556–63. doi:10.1016/j.amjcard.2005.04.019.
60. Fedder DO, Koro CE, Italien GJL. Clinical investigation and reports New national cholesterol education program III guidelines for primary prevention lipid-lowering drug therapy. Circulation. 2002;2002:152–6.

61. Mazzone T, Meyer PM, Kondos GT, et al. Relationship of traditional and nontraditional cardiovascular risk factors to coronary artery calcium in type 2 diabetes. Diabetes. 2007;56(3):849–55. doi:10.2337/db06-0935.
62. Maki KC, Bays HE, Dicklin MR. Treatment options for the management of hypertriglyceridemia: strategies based on the best-available evidence. J Clin Lipidol. 2012;6:413–26. doi:10.1016/j.jacl.2012.04.003.
63. Varbo A, Benn M, Tybjærg-Hansen A, et al. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol. 2013;61(4):427–36. doi:10.1016/j.jacc.2012.08.1026.
64. Mahley R, Rall S. Type III hyperlipoproteinemia (dysbetalipoproteinemia): the role of apolipoprotinemia E in normal and abnormal lipoprotein metabolism. In: Scriver A, Beader W, Sly S, Valle D, editors. The metabolic and molecular basis of inherited disease. New York: McGraw Hill; 1995. p. 1953–80.
65. Assmann G, Schulte H, Funke H, et al. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. Eur Heart J. 1998;19:M8–14.
66. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10 158 incident cases among 262 525 participants in 29 western prospective studies. Circulation. 2007;115:450–8. doi:10.1161/CIRCULATIONAHA.106.637793.
67. Hokanson J, Austin M. Triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a metaanalysis of population-based prospective. J Cardiovasc Risk. 1996;3:213–19. http://cpr.sagepub.com/content/3/2/213.short.
68. Moneta GL. Major lipids, apolipoproteins, and risk of vascular disease. Yearb Vasc Surg. 2010;2010(18):42–4. doi:10.1016/S0749-4041(10)79320-9.
69. Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. Arch Intern Med. 2001;161:1413–9.
70. Liu J, Sempos CT, Donahue RP, et al. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. Am J Cardiol. 2006;98:1363–8. doi:10.1016/j.amjcard.2006.06.032.
71. Arsenault BJ, Rana JS, Stroes ESG, et al. Beyond low-density lipoprotein cholesterol. Respective contributions of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healt. J Am Coll Cardiol. 2009;55(1):35–41. doi:10.1016/j.jacc.2009.07.057.
72. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non–HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins. JAMA. 2012;307(12):1302–9.
73. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384:626–35. doi:10.1016/S0140-6736(14)61177-6.
74. Hennig B, Chung BH, Watkins BA, et al. Disruption of endothelial barrier function by lipolytic remnants of triglyceride-rich lipoproteins. Atherosclerosis. 1992;95:235–47. doi:10.1016/0021-9150(92)90027-E.
75. Botham KM, Wheeler-Jones CPD. Postprandial lipoproteins and the molecular regulation of vascular homeostasis. Prog Lipid Res. 2013;52(4):446–64. doi:10.1016/j.plipres.2013.06.001.
76. Bravo E, Napolitano M. Mechanisms involved in chylomicron remnant lipid uptake by macrophages. Biochem Soc Trans. 2007;35:459–63. doi:10.1042/BST0350459.
77. Nakajima K, Nakano T, Tokita Y, et al. Postprandial lipoprotein metabolism: VLDL vs chylomicrons. Clin Chim Acta. 2011;412(15–16):1306–18. doi:10.1016/j.cca.2011.04.018.
78. Tomkin GH, Owens D. Abnormalities in apo B-containing lipoproteins in diabetes and atherosclerosis. Diabetes Metab Res Rev. 2001;17(1):27–43. doi:10.1002/dmrr.179.
79. Vine DF, Glimm DR, Proctor SD. Intestinal lipid transport and chylomicron production: possible links to exacerbated atherogenesis in a rodent model of the metabolic syndrome. Atheroscler Suppl. 2008;9:69–76. doi:10.1016/j.atherosclerosissup.2008.05.004.
80. Mora S, Otvos JD, Rifai N, et al. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. Circulation. 2009;119:931–9. doi:10.1161/CIRCULATIONAHA.108.816181.

81. Pischon T, Girman CJ, Sacks FM, et al. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation. 2005;112:3375–83. doi:10.1161/CIRCULATIONAHA.104.532499.
82. Mendivil CO, Rimm EB, Furtado J, et al. Low-density lipoproteins containing apolipoprotein C-III and the risk of coronary heart disease. Circulation. 2011;124(19):2065–72. doi:10.1161/CIRCULATIONAHA.111.056986.
83. Burr M. Reflections on the Diet and Reinfarction Trial (DART). Eur Hear J Suppl. 2001;3:D75–8. doi:10.1016/S1520-765X(01)90124-5.
84. Harris W, Ginsberg H, Arunakul N, et al. Safety and efficacy of omacor in severe hypertriglyceridemia. J Cardiovasc Risk. 1997;4:385–91.
85. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-prevenzione trial. Lancet. 1999;354:447–55. doi:S0140673699070725 [pii].
86. Kromhout D, Giltay EJ, Geleijnse JM. N-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med. 2010;363:2015–26. doi:10.1056/NEJMoa1003603.
87. The ORIGIN, Investigators T. n–3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012;367:309–18. doi:10.1056/NEJMoa1203859.
88. The Risk and Prevention Study Collaborative Group. n–3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med. 2013;368:1800–8. doi:10.1056/NEJMoa1205409.
89. Rizos EC, Ntzani EE, Bika E, et al. Association between omega-3 fatty acid. JAMA. 2012;308:1024–33. doi:10.1001/2012.jama.11374.
90. Eussen SRBM, Geleijnse JM, Giltay EJ, et al. Effects of n-3 fatty acids on major cardiovascular events in statin users and Non-users with a history of myocardial infarction. Eur Heart J. 2012;33:1582–8. doi:10.1093/eurheartj/ehr499.
91. Contacos C, Barter PJ, Sullivan DR. Effect of pravastatin and omega-3 fatty acids on plasma lipids and lipoproteins in patients with combined hyperlipidemia. Arterioscler Thromb. 1993;13:1755–62.
92. Nordøy A, Bønaa KH, Nilsen H, et al. Effects of simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlipidaemia. J Intern Med. 1998;243:163–70.
93. Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2007;29(7):1354–67. doi:10.1016/j.clinthera.2007.07.018.
94. Ballantyne CM, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am J Cardiol. 2012;110:984–92. doi:10.1016/j.amjcard.2012.05.031.
95. Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Patients with Very High Triglyceride Levels (from the Multi-center, placebo-controlled, randomized, double-blind, 12-week study with an open-label extension [MARINE] Trial). Am J Cardiol. 2011;108(502):682–90. doi:10.1016/j.amjcard.2011.04.015.
96. Kastelein JJP, Maki KC, Susekov A, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa for lowering very high triglyceridEs (EVOLVE) trial. J Clin Lipidol. 2014;8:94–106. doi:10.1016/j.jacl.2013.10.003.
97. Maki KC, Orloff DG, Nicholls SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the cardiovascular risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (the ESPRIT trial). Clin Ther. 2013;35(9):1400–11. doi:10.1016/j.clinthera.2013.07.420.
98. Offman E, Marenco T, Ferber S, et al. Steady-state bioavailability of prescription omega-3 on a low-fat diet is significantly improved with a free fatty acid formulation compared with an ethyl ester formulation: the ECLIPSE II study. Vasc Health Risk Manag. 2013;9:563–73. doi:10.2147/VHRM.S50464.

99. Davidson MH, Johnson J, Rooney MW, et al. A novel omega-3 free fatty acid formulation has dramatically improved bioavailability during a low-fat diet compared with omega-3-acid ethyl esters: the ECLIPSE (epanova® compared to Lovaza® in a pharmacokinetic single-dose evaluation) study. J Clin Lipidol. 2012;6(6):573–84. doi:10.1016/j.jacl.2012.01.002.
100. Research and Development. 2014. http://www.amarincorp.com/products.html. Accessed 20 Feb 2015.
101. US National Institutes of Health. A study of AMR101 to evaluate its ability to reduce cardiovascular events in high risk patients with hypertriglyceridemia and on statin. The primary objective is to evaluate the effect of 4 g/Day AMR101 for preventing the occurrence of a first Major Cardi. US Natl Institutes Heal. 2015. https://www.clinicaltrial.gov/ct2/show/NCT01492361. Accessed 20 Feb 2015.
102. US National Institutes of Health. Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia (STRENGTH). US Natl Institutes Heal. 2015. https://clinicaltrials.gov/ct2/show/NCT02104817. Accessed 20 Feb 2015.
103. Lovaza. [Package Insert]. Research Triangle Park, NC: GlaxoSmithKline; 2008.
104. Vascepa. [Package Insert]. Bedminster, NJ: Amarin Pharmaceuticals Ireland Ltd; 2013.
105. Epanova. [Package Insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2014.
106. Bottorff MB. Statin safety and drug interactions: clinical implications. Am J Cardiol. 2006;97:27C–31. doi:10.1016/j.amjcard.2005.12.007.
107. Choi HD, Shin WG, Lee J-Y, et al. (2014) Safety and efficacy of fibrate–statin combination therapy compared to fibrate monotherapy in patients with dyslipidemia: a meta-analysis. Vascul Pharmacol. pii:S1537–1891. doi:10.1016/j.vph.2014.11.002.
108. Tato F, Keller C, Wolgram G. Effects of fish Oil concentrate on lipoproteins and apolipoproteins in familial combined hyperlipidemia. Clin Investig. 1993;71(4):314–8.
109. Calabresi L, Donati D, Pazzucconi F, et al. Omacor in familial combined hyperlipidemia: effects on lipids and Low density lipoprotein subclasses. Atherosclerosis. 2000;148:387–96. doi:10.1016/S0021-9150(99)00267-1.
110. Rouis M, Dugi KA, Previato L, et al. Therapeutic response to medium-chain triglycerides and ω-3 fatty acids in a patient with the familial chylomicronemia syndrome. Arterioscler Thromb Vasc Biol. 1997;17:1400–6.
111. Richter WO, Jacob BG, Ritter MM, et al. Treatment of primary chylomicronemia Due to familial Hypertriglyceridemia by omega-3 fatty acids. Metabolism. 1992;41(10):1100–5.

Chapter 6
Statins and CETP Inhibitors: Anacetrapib and Evacetrapib: The Last Hope?

Stephen J. Nicholls

Introduction

Randomized controlled trials have consistently demonstrated that lowering levels of low-density lipoprotein cholesterol (LDL-C) with statins reduces cardiovascular event rates [1]. As a result of these observations, treatment guidelines for the prevention of cardiovascular disease have increasingly emphasized the use of more intensive statin therapy to reduce cardiovascular risk in patients. Despite these benefits, there remains a considerable residual risk of clinical events [2], which suggests that there is an ongoing need for additional therapeutic strategies to further lower risk in patients.

Cholesteryl Ester Transfer Protein and Cardiovascular Disease

Laboratory studies during the 1970s characterized the transfer of esterified cholesterol from high-density lipoprotein (HDL) to very low-density lipoprotein (VLDL) and LDL particles. This movement of cholesterol between circulating lipoprotein fractions was observed to occur in exchange for triglyceride and was facilitated by a plasma-based hydrophobic glycoprotein titled cholesteryl ester transfer protein (CETP). As a result, CETP is thought to play an important role in equilibration of lipids between lipoproteins [3].

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A number of observations from animal populations and genetic studies suggest that CETP may associate with cardiovascular risk and present a potential therapeutic target for the prevention of cardiovascular disease. While rodents are commonly employed to study the factors that influence atherosclerosis, they do not endogenously express CETP. Transgenic CETP expression has proven to be confusing in rodents, with some studies reporting a proatherogenic effect, while others have demonstrated a potentially favorable effect on atherosclerotic plaque [4–7]. In contrast, rabbits express CETP in a similar manner to humans. Intervention studies in rabbit models have demonstrated that inhibiting CETP by use of antisense oligonucleotides, anti-CETP vaccines, and small-molecule CETP inhibitors each have an anti-atherosclerotic effect [8–10]. While one rabbit study demonstrated a failure of CETP inhibition to modify atherosclerosis, the levels of atherogenic lipoproteins were prohibitively high, making it highly unlikely that any anti-atherosclerotic approach would be effective.

Some [3, 11], but not all [12, 13], population studies have demonstrated a relationship between low levels and CETP mass and activity and low rates of cardiovascular events. This relationship is specifically observed when low CETP activity is accompanied by HDL-C levels greater than 60 mg/dL [14]. This is supported by observations from large cohorts that genetic polymorphisms associated with low CETP activity also associate with higher HDL-C levels and lower rates of cardiovascular events [11, 15]. In combination, the data from these studies would suggest that CETP inhibition might be an attractive approach to reducing cardiovascular risk. Critics of CETP inhibition suggest that CETP inhibition increases HDL particle size and cholesterol composition, with potentially adverse consequences on HDL functionality. In addition, given that the majority of cholesterol transferred from HDL to VLDL and LDL particles ultimately returns to the liver via the LDL receptor, it is possible that CETP plays an important role in reverse cholesterol transport. Accordingly, critics suggest that CETP inhibition may have an adverse, rather than beneficial, effect on atherosclerotic plaque. Ultimately, the impact of functional CETP inhibitors on cardiovascular risk must be tested in clinical trials.

Torcetrapib

Torcetrapib was the first CETP inhibitor to reach an advanced stage of clinical development. Early clinical studies demonstrated increases in HDL-C by 70 % and incremental lowering of LDL-C by 25 %, in addition to background statin therapy with torcetrapib [16]. While a consistent finding of blood pressure elevation, by 1–2 mmHg, was observed in early torcetrapib studies [16], there remained considerable optimism that the lipid effects would ultimately translate to cardiovascular benefit. Three clinical trials employed serial arterial wall imaging to evaluate the impact of torcetrapib on progression of vascular disease using coronary intravascular ultrasound in patients with coronary artery disease (ILLUSTRATE) [17] and carotid ultrasound to measure intima-media thickness in patients with familial hypercholesterolemia or atherogenic dyslipidemia (RADIANCE 1 and 2) [18, 19].

Despite profound and consistent effects on HDL-C and LDL-C levels, torcetrapib did not slow disease progression in any of these studies.

The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) study evaluated the impact of torcetrapib on cardiovascular events in 15,067 patients with established cardiovascular disease or type 2 diabetes who were treated with atorvastatin. While torcetrapib increased HDL-C by 72 % and decreased LDL-C by 25 %, the study was terminated prematurely due to the observation of a 58 % increase in risk of mortality and 25 % increase in the composite cardiovascular end point. In addition to an increase in cardiovascular deaths with torcetrapib, a greater number of deaths attributed to sepsis and cancer were also observed [20].

Critics of CETP inhibition argued that the findings of no benefit on atherosclerotic disease and adverse effects on cardiovascular events with torcetrapib supported the concept that this approach would have detrimental consequences on HDL functionality. A number of lines of evidence subsequently emerged that suggested that HDL functionality was intact in the setting of CETP deficiency and torcetrapib treatment [21]. Further analysis of the intravascular ultrasound and clinical event trials demonstrated that higher achieved HDL-C levels with torcetrapib associated with plaque regression [22] and lower cardiovascular event rates [23] and that HDL isolated from individuals with CETP deficiency or following treatment with torcetrapib demonstrated intact capacity to promote cholesterol efflux in cellular assays [24]. When combined with the finding that torcetrapib was associated with increases in blood pressure, activation of the renin angiotensin aldosterone system, and expression of endothelin within the aortic wall and that these changes were also observed in species that do not express CETP, the observations point to a likely off-target toxicity of torcetrapib [20, 23, 25, 26]. Accordingly, it remained possible that a CETP inhibitor, lacking such toxicity, might still be of utility in cardiovascular prevention.

A potentially favorable finding from the torcetrapib development program involved the observation that measures of glycemic control in patients with diabetes appeared to improve with torcetrapib administration [27]. This was consistent with observations that HDL appears to have favorable effects on pancreatic ß-cell function [28] and suggested that CETP inhibition might have potential cardioprotective effects via its influence not only on lipids but also due to its impact on glycemic control.

Dalcetrapib

Dalcetrapib is a modest CETP inhibitor, raising HDL-C by 25–30 % and without LDL-C lowering effects in early clinical studies [29]. Early studies in humans demonstrated that dalcetrapib administration did not have an adverse effect on plaque burden or inflammatory activity on arterial wall imaging [30] or on endothelial function [31]. The dal-OUTCOMES trial of 15,871 participants randomized to treatment with dalcetrapib or placebo soon following an acute coronary syndrome was terminated due to futility with no evidence of a reduction in cardiovascular events [32]. This was observed despite reports of a modest increase in cholesterol

efflux capacity with dalcetrapib treatment following an acute coronary syndrome [33]. Given evidence that HDL functionality may be impaired in the setting of an acute coronary syndrome [34] and that there was no relationship between changes in HDL-C and cardiovascular events in dal-OUTCOMES [32], it is possible that this is not the ideal clinical setting to evaluate the impact of CETP inhibition. Pharmacogenomic evaluation of these studies revealed that single-nucleotide polymorphisms of the ADCY9 gene on chromosome 16 identified patients in whom dalcetrapib treatment was associated with less progression of carotid intima-media thickness and lower cardiovascular event rates [35]. The totality of data, however, would suggest that modest CETP inhibition with dalcetrapib without any discernible effect on atherogenic lipoproteins has no impact on cardiovascular risk.

Anacetrapib

Anacetrapib is a potent CETP inhibitor, with evidence of profound HDL-C increases and incremental LDL-C lowering in statin-treated patients [36]. Early studies demonstrated a lack of torcetrapib-associated toxicity. The Determining the Efficacy and tolerability of CETP Inhibition with AnacEtrapib (DEFINE) study aimed to evaluate the safety and efficacy of anacetrapib in a large cohort of patients with established or high risk for developing coronary heart disease. Treatment for 18 months with anacetrapib was associated with an increase in HDL-C by 138 % and incremental LDL-C lowering by 40 %. No adverse effects on blood pressure, electrolytes, or aldosterone were observed. In addition, prespecified Bayesian analysis determined that there was a 94 % probability that anacetrapib did not have a torcetrapib-like adverse effect on cardiovascular events. In fact, further analysis demonstrated less cardiovascular events, driven predominantly by beneficial effects on coronary revascularization, in anacetrapib-treated patients [37]. Subsequent studies have determined favorable effects of anacetrapib on LDL-C in patients with familial hypercholesterolemia and that the lipoprotein effects persist, with some evidence of adipose tissue drug accumulation, the impact of which remains uncertain [38]. The Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL) study is currently being performed to evaluate the impact of anacetrapib compared with placebo on cardiovascular events in 30,000 statin-treated patients with a history of myocardial infarction, cerebrovascular atherosclerotic disease, peripheral arterial disease, or diabetes with associated coronary heart disease.

Evacetrapib

Evacetrapib is another potent CETP inhibitor with similar effects on plasma lipoproteins and lack of torcetrapib-associated adverse effects. Phase II studies demonstrated dose-dependent increases in HDL-C up to 129 % and lowering of LDL-C up

to 36 %, with evidence of similar effects when administered as monotherapy or in addition to statin therapy [39]. There is currently no evidence of evacetrapib accumulation within adipose tissue. The Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib (ACCELERATE) study is currently evaluating the impact of evacetrapib compared with placebo on cardiovascular events in 12,000 patients with a previous acute coronary syndrome, peripheral arterial disease, atherosclerotic cerebrovascular disease, or diabetes with coronary disease who are optimally treated with a statin.

Conclusion

Despite a tumultuous history of clinical development with adverse effects of torcetrapib and no clinical benefit with dalcetrapib, there remains hope that potent CETP inhibitors with favorable effects on both HDL and atherogenic lipoproteins may prove to reduce cardiovascular events in clinical trials. The results of the ongoing phase III trials will provide definitive information with regard to the efficacy and safety of this class in order to determine whether they will prove to be a useful adjunctive therapy in patients optimally treated with a statin.

References

1. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
2. Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. J Am Coll Cardiol. 2005;46:1225–8.
3. Barter PJ. CETP and atherosclerosis. Arterioscler Thromb Vasc Biol. 2000;20:2029–31.
4. El Bouhassani M, Gilibert S, Moreau M, et al. Cholesteryl ester transfer protein expression partially attenuates the adverse effects of SR-BI receptor deficiency on cholesterol metabolism and atherosclerosis. J Biol Chem. 2011;286:17227–38.
5. Westerterp M, van der Hoogt CC, de Haan W, et al. Cholesteryl ester transfer protein decreases high-density lipoprotein and severely aggravates atherosclerosis in APOE*3-Leiden mice. Arterioscler Thromb Vasc Biol. 2006;26:2552–9.
6. MacLean PS, Bower JF, Vadlamudi S, et al. Cholesteryl ester transfer protein expression prevents diet-induced atherosclerotic lesions in male db/db mice. Arterioscler Thromb Vasc Biol. 2003;23:1412–5.
7. Plump AS, Masucci-Magoulas L, Bruce C, Bisgaier CL, Breslow JL, Tall AR. Increased atherosclerosis in ApoE and LDL receptor gene knock-out mice as a result of human cholesteryl ester transfer protein transgene expression. Arterioscler Thromb Vasc Biol. 1999;19:1105–10.
8. Sugano M, Makino N, Sawada S, et al. Effect of antisense oligonucleotides against cholesteryl ester transfer protein on the development of atherosclerosis in cholesterol-fed rabbits. J Biol Chem. 1998;273:5033–6.
9. Rittershaus CW, Miller DP, Thomas LJ, et al. Vaccine-induced antibodies inhibit CETP activity in vivo and reduce aortic lesions in a rabbit model of atherosclerosis. Arterioscler Thromb Vasc Biol. 2000;20:2106–12.

10. Okamoto H, Yonemori F, Wakitani K, Minowa T, Maeda K, Shinkai H. A cholesteryl ester transfer protein inhibitor attenuates atherosclerosis in rabbits. Nature. 2000;406:203–7.
11. Barter PJ, Chapman MJ, Hennekens CH, Rader DJ, Tall AR. Cholesteryl ester transfer protein. A novel target for raising HDL and inhibiting atherosclerosis. Arterioscler Thromb Vasc Biol. 2003;23:160–7.
12. Vasan RS, Pencina MJ, Robins SJ, et al. Association of circulating cholesteryl ester transfer protein activity with incidence of cardiovascular disease in the community. Circulation. 2009;120:2414–20.
13. Ritsch A, Scharnagl H, Eller P, et al. Cholesteryl ester transfer protein and mortality in patients undergoing coronary angiography: the Ludwigshafen Risk and Cardiovascular Health study. Circulation. 2010;121:366–74.
14. Boekholdt SM, Kuivenhoven JA, Wareham NJ, et al. Plasma levels of cholesteryl ester transfer protein and the risk of future coronary artery disease in apparently healthy men and women: the prospective EPIC (European Prospective Investigation into Cancer and nutrition)-Norfolk population study. Circulation. 2004;110:1418–23.
15. Thompson A, Di Angelantonio E, Sarwar N, et al. Association of cholesteryl ester transfer protein genotypes with CETP mass and activity, lipid levels, and coronary risk. JAMA. 2008;299:2777–88.
16. Brousseau ME, Schaefer EJ, Wolfe ML, et al. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. N Engl J Med. 2004;350:1505–15.
17. Nissen SE, Tardif JC, Nicholls SJ, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. N Engl J Med. 2007;356:1304–16.
18. Bots ML, Visseren FL, Evans GW, et al. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial. Lancet. 2007;370:153–60.
19. Kastelein JJ, van Leuven SI, Burgess L, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. N Engl J Med. 2007;356:1620–30.
20. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007;357:2109–22.
21. Tall AR, Yvan-Charvet L, Wang N. The failure of torcetrapib: was it the molecule or the mechanism? Arterioscler Thromb Vasc Biol. 2007;27:257–60.
22. Nicholls SJ, Tuzcu EM, Brennan DM, Tardif JC, Nissen SE. Cholesteryl ester transfer protein inhibition, high-density lipoprotein raising, and progression of coronary atherosclerosis: insights from ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation). Circulation. 2008;118:2506–14.
23. Barter P. Lessons learned from the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial. Am J Cardiol. 2009;104:10E–5.
24. Yvan-Charvet L, Matsuura F, Wang N, et al. Inhibition of cholesteryl ester transfer protein by torcetrapib modestly increases macrophage cholesterol efflux to HDL. Arterioscler Thromb Vasc Biol. 2007;27:1132–8.
25. Vergeer M, Stroes ES. The pharmacology and off-target effects of some cholesterol ester transfer protein inhibitors. Am J Cardiol. 2009;104:32E–8.
26. Forrest MJ, Bloomfield D, Briscoe RJ, et al. Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone. Br J Pharmacol. 2008;154:1465–73.
27. Barter PJ, Rye KA, Tardif JC, et al. Effect of torcetrapib on glucose, insulin, and hemoglobin A1c in subjects in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial. Circulation. 2011;124:555–62.
28. Fryirs MA, Barter PJ, Appavoo M, et al. Effects of high-density lipoproteins on pancreatic beta-cell insulin secretion. Arterioscler Thromb Vasc Biol. 2010;30:1642–8.
29. Kuivenhoven JA, de Grooth GJ, Kawamura H, et al. Effectiveness of inhibition of cholesteryl ester transfer protein by JTT-705 in combination with pravastatin in type II dyslipidemia. Am J Cardiol. 2005;95:1085–8.

30. Fayad ZA, Mani V, Woodward M, et al. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. Lancet. 2011;378:1547–59.
31. Luscher TF, Taddei S, Kaski JC, et al. Vascular effects and safety of dalcetrapib in patients with or at risk of coronary heart disease: the dal-VESSEL randomized clinical trial. Eur Heart J. 2012;33:857–65.
32. Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med. 2012;367:2089–99.
33. Ray KK, Ditmarsch M, Kallend D, et al. The effect of cholesteryl ester transfer protein inhibition on lipids, lipoproteins, and markers of HDL function after an acute coronary syndrome: the dal-ACUTE randomized trial. Eur Heart J. 2014;35:1792–800.
34. Besler C, Heinrich K, Rohrer L, et al. Mechanisms underlying adverse effects of HDL on eNOS-activating pathways in patients with coronary artery disease. J Clin Invest. 2011;121: 2693–708.
35. Tardif JC, Rheaume E, Lemieux Perreault LP, et al. Pharmacogenomic determinants of the cardiovascular effects of dalcetrapib. Circ Cardiovasc Genet. 2015;8:372–82.
36. Bloomfield D, Carlson GL, Sapre A, et al. Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib as monotherapy and coadministered with atorvastatin in dyslipidemic patients. Am Heart J. 2009;157:352–60.
37. Cannon CP, Shah S, Dansky HM, et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med. 2010;363:2406–15.
38. Kastelein JJ, Besseling J, Shah S, et al. Anacetrapib as lipid-modifying therapy in patients with heterozygous familial hypercholesterolaemia (REALIZE): a randomised, double-blind, placebo-controlled, phase 3 study. Lancet. 2015. doi:10.1016/S0140-6736(14)62115-2.
39. Nicholls SJ, Brewer HB, Kastelein JJ, et al. Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial. JAMA. 2011;306:2099–109.

Chapter 7
Statins and Mipomersen: Mechanisms of Action and Patient Tolerability

Jing Pang, Dick C. Chan, and Gerald F. Watts

Introduction

Statins are the frontline therapy for hypercholesterolaemia and confer significant reductions in cardiovascular mortality and morbidity in both primary and secondary prevention [1]. However, patients with refractory hypercholesterolaemia, in particular those with familial hypercholesterolaemia (FH), have difficulty in achieving their therapeutic targets on statin alone [2]. Currently available lipid-lowering agents, such as bile acid sequestrants, fibrates, ezetimibe and niacin, have limited efficacy as monotherapy or in combination with a statin in lowering low-density lipoprotein (LDL) cholesterol to the target levels in such patients [3]. Several newer agents that lower LDL cholesterol concentration are in the late stages of drug development or being used as orphan drugs [3]. One of these new therapies is mipomersen, which has been approved by the US Food and Drug Administration (FDA), adjunct to lipid-lowering therapy and diet, for the treatment of homozygous FH [4]. We review the efficacy and safety issues of mipomersen and its potential as combination therapy with statins, with emphasis on the management of hypercholesterolaemia in FH.

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Hypercholesterolaemia: Dysregulation of Apolipoprotein B-100 (apoB) Metabolism

Understanding the pathophysiology of hypercholesterolaemia requires a brief review of apoB metabolism [5]. ApoB is a key structural and functional component of lipoprotein metabolism. It is involved in the assembly and secretion of very low-density lipoprotein (VLDL) from the liver. Apolipoprotein B-100 (apoB) is coded by the *APOB* gene and by a single mRNA transcript. ApoB is synthesised in the liver and functions to deliver triglycerides from the liver to the circulation. VLDL and its lipoprotein remnants, intermediate-density lipoprotein (IDL) and LDL, contain a single molecule of apoB per particle. Hence, plasma apoB concentration is an indicator of the total number of atherogenic lipoproteins including Lp(a). Elevated plasma apoB is a risk factor for atherosclerosis and is a predictor of atherosclerotic cardiovascular disease [6].

Owing to the central role of apoB in lipid metabolism, interventions that target apoB metabolism are critical. As indicated later, statins lower LDL cholesterol and apoB by enhancing the clearance of apoB-containing particles. Hence, inhibiting apoB synthesis, and the subsequent production of VLDL and LDL, provides a complimentary approach to statins for reducing elevated levels of LDL cholesterol and apoB. Antisense technology offers a form of treatment whereby a strand of DNA binds to the mRNA produced by the gene of a specific protein and thereby inhibits translation and the production of the protein. An advantage to this approach is the reduced potential of drug interactions, particularly for patients on multiple agents. Dyslipoproteinaemias due to elevated hepatic secretion of apoB may theoretically benefit from this form of therapy.

Severe Familial Hypercholesterolaemia

Patients with severe FH are at high risk of premature coronary artery disease (CAD) owing to elevated LDL cholesterol and apoB concentrations from birth [3]. FH results principally from mutations in the LDL receptor (LDLr) that impair LDL catabolism. Over 1700 mutations in the LDLr have been described worldwide; the severity of the disorder is in part associated with the residual activity of the LDLr. Patients with null mutations show poorer responses to statin treatment [7]. Statins are efficacious in lowering LDL cholesterol in FH. Despite best standard statin treatment, most homozygous and severe heterozygous FH patients do not achieve the recommended plasma concentrations of LDL cholesterol required for abolishing the risk of CAD: LDL cholesterol <2.5 mmol/L (absence of CHD or othermajor risk factors) and <1.8 mmol/L (presence of CHD or other major risk factors) [3]. Bile acid sequestrants, ezetimibe and fibrates are also relevant options as add-on therapy and/or in cases of statin intolerance. Small studies have supported combination treatment in FH [8–11], although there have been no outcome studies to date.

Beyond LDL, increased residual risk of CAD in FH relates to elevated plasma concentrations of lipoprotein(a) [Lp(a)] [12]. Lp(a) is a macromolecular complex assembled from LDL and apolipoprotein (a) (apo[a]). It is a quantitative genetic trait and is a causal and independent risk factor for cardiovascular disease in both the general population and patients with FH [13]. The atherogenicity of Lp(a) may, in part, be mediated by oxidised phospholipids, which associate with small apo(a) isoforms [14]. The apo(a) genes can predict the majority of the variation of Lp(a) levels in plasma [15], with large differences among different ethnic groups [16]. Lp(a) is refractory to lifestyle and standard lipid-lowering therapies. The only potentially effective drug for lowering Lp(a) is niacin, but severe side effects preclude its use [17]. Mipomersen has been shown to reduce plasma Lp(a) in FH patients by 20–30 % [18, 19]. Hence, reduction of Lp(a) with mipomersen presents an additional benefit that complements the LDL-cholesterol-lowering effect of this agent.

Statins

Statins can lower plasma LDL cholesterol by 20–55 % depending on statin type and dose. However, current therapeutic guidelines have lowered the optimal LDL cholesterol target to <1.8 mmol/L for high-risk coronary heart disease [20, 21], emphasising value and use of high-intensity statin therapy. Future guidelines may recommend more stringent targets, especially with clinical trial evidence demonstrating lower risk of cardiovascular events with an LDL cholesterol of <1.3 mmol/L [22]. However, a significant proportion of patients are statin intolerant [23], particularly with higher doses, with side effects including myalgia, myositis, rhabdomyolysis, hepatotoxicity, peripheral neuropathy [24] and new-onset type 2 diabetes [25, 26]. The proportion of statin-associated muscle symptoms is estimated to be between 7 and 29 % [27]. With the exception of dose reduction and re-challenge, there is little evidence to guide the management of statin-intolerant patients [27, 28]. Since statin-related adverse events are dose dependent, high-risk patients on high-intensity statins are a particularly vulnerable group.

The mechanism of action of statins on lipid metabolism fundamentally relies on the decreased conversion of HMG-CoA to mevalonic acid by competitive inhibition of HMG-CoA reductase, a rate-limiting enzyme in hepatic cholesterol synthesis. The resulting reduction in intracellular cholesterol content stimulates LDL receptor synthesis and LDL catabolism [29]. The effect of statins on Lp(a) is modest and inconsistent [13]. Long-term statin use can lower Lp(a) by approximately 20 %, although this does not appear to correlate with changes in carotid atherosclerosis in heterozygous FH subjects [30].

Because statins are not effective in lowering LDL cholesterol to recommended levels and are not generally effective on Lp(a), new therapies have been developed. This is particularly relevant for patients with severe FH, such as those with homozygous and compound heterozygous FH, where LDL receptor functions are either absent or dysfunctional. Mipomersen reduces circulating LDL levels by directly

targeting apoB synthesis, an effect that does not require functional LDL receptor activity. By contrast, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition has limited efficacy in patients with no LDL receptor function [31].

Mipomersen

Mipomersen (ISIS-301012, Kynamro™) is a second-generation antisense oligonucleotide (ASO) designed to directly inhibit the synthesis of apoB-100 by targeting its mRNA. Mipomersen is a 2'-O-methoxyethyl chimeric 20-mer oligonucleotide complementary to the coding region of human apoB-100 mRNA, modified to withstand almost all nuclease degradation [32]. Once the apoB ASO binds to the apoB mRNA, its degradation is triggered by ribonuclease H (RNAase H), and protein translation is inhibited. Subsequently, the synthesis of the apoB protein is decreased, with lowering in the level of plasma circulating apoB-containing lipoproteins such as VLDL and LDL (see Fig. 7.1). ASOs are metabolised independently of CYP450, an important advantage in relation to drug interactions [33]. Mipomersen is primarily excreted in the urine after nuclease metabolism [34].

ApoB-100 antisense was originally tested in mice models of hypercholesterolaemia. In LDLr-deficient mice, this antisense therapy lowered LDL cholesterol, consistent with its mechanism of action, and ameliorated atherosclerosis without causing hepatic steatosis [35, 36]. The first human study by Kastelein et al. (2005) showed a maximum of 35 % reduction of LDL cholesterol concentration and 50 % reduction in apoB levels after 4 weeks of multiple-dosing regime in patients with mild dyslipidaemia [37]. However, the majority (72 %) of patients experienced erythema at the injection site. Similarly, another phase I monotherapy trial demonstrated up to 61 % reductions in LDL cholesterol and apoB levels with 300 mg/week doses of mipomersen in subjects with mild-to-moderate hypercholesterolaemia, with injection site reactions experienced at least once in each subject [38]; 18 % of subjects showed consecutive transaminase elevations greater than three times the upper limit of normal. The majority who had increased hepatic transaminase were receiving the 400 mg/week regimen.

Mipomersen has now been evaluated by several phase II and III trials assessing its efficacy, safety, tolerability and utility in patients with severe hypercholesterolaemia as monotherapy (in statin-intolerant subjects) and when combined with statin therapy. These trials continue to demonstrate significant reductions in LDL cholesterol and apoB levels [18, 19, 39–44]. A summary of the trials reported to date is shown in Table 7.1.

Mipomersen for Familial Hypercholesterolaemia

Five mipomersen trials have focused on FH. Akdim et al. (2010) investigated the efficacy of mipomersen (dose range 50–300 mg/week) over a period of 6 weeks in 44 patients with heterozygous FH. Significant reductions in LDL cholesterol were

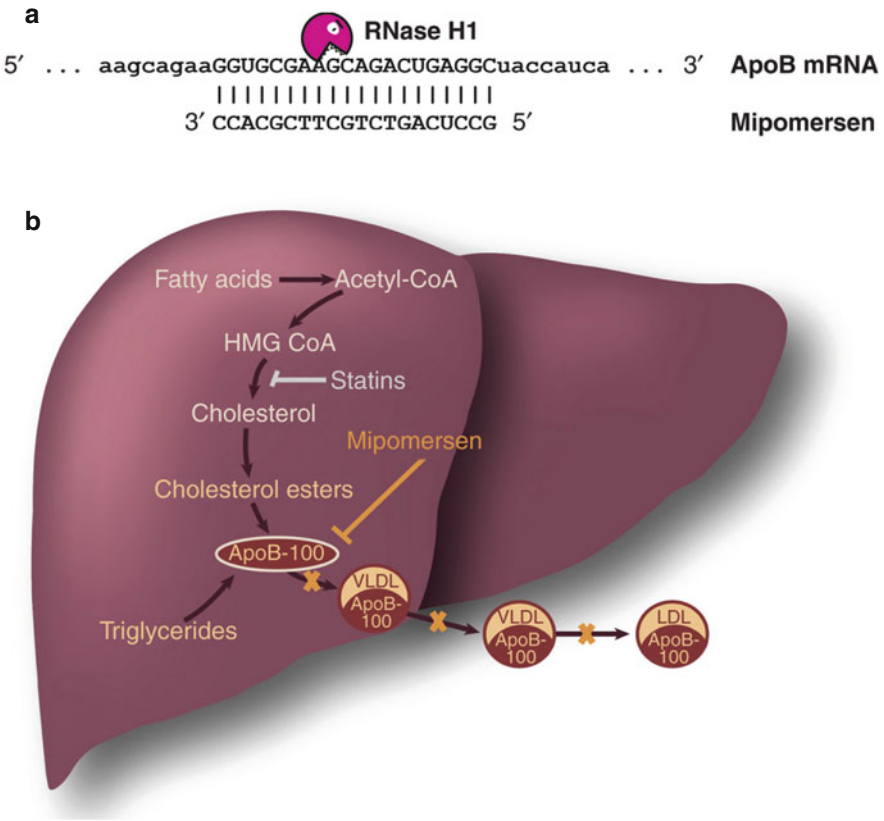

Fig. 7.1 Mechanism of action of statin and mipomersen. (**a**) Mipomersen specifically binds the apoB mRNA sequence to provide a substrate for RNase H, which hydrolyses the apoB mRNA strand and inhibits apoB synthesis. (**b**) Statins competitively inhibit HMG-CoA reductase, a rate-limiting enzyme in hepatic cholesterol synthesis, the reduced intracellular cholesterol content induces LDL receptor production and increases LDL catabolism. On the other hand, Mipomersen inhibitors apoB synthesis and reduces the production of atherogenic apoB-containing lipoproteins by the liver (Adapted from [55])

found with the 200 and 300 mg dosing regimens, with maximal reductions 21 and 33 % from baseline, respectively. Extended treatment to 13 weeks with weekly doses of 300 mg mipomersen resulted in 37 % reduction in both LDL cholesterol and apoB [40]. Similarly, Visser et al. (2010) demonstrated, in 21 heterozygous FH patients with a 13-weekly mipomesen regime at a dose of 200 mg/week, a reduction of 22 and 20 % for LDL cholesterol and apoB, respectively [41]. In a randomised trial of 124 heterozygous FH with coronary artery disease, Stein et al. (2012) showed a 28 and 26 % reduction in LDL cholesterol and apoB concentrations, respectively, after 26 weeks of weekly 200 mg mipomersen injections [19]. A trend towards an increase in intrahepatic triglyceride content was found in both studies [19, 41].

Table 7.1 Summary of clinical trials with mipomersen in humans

Author	Phase	Patient population	Co-existing medication	*n*	Duration	% reduction in LDL-C[a]	% reduction in apoB[a]	% reduction in Lp(a)[a]
Kastelein (2006) et al. [37]	I	Healthy controls	None	36	4 weeks	35	50	–
Akdim et al. (2011) [38]	I	Mild-to-moderate HC	None	50	13 weeks	45	46	42
Akdim et al. (2010) [39]	II	HC	Statins	74	13 weeks	36	36	–
Akdim et al. |(2010) [40]	II	heFH	Statins	44	6 weeks	21	23	17
Visser et al. (2010) [41]	II	heFH	Statin ± ezetimibe	21	13 weeks	22	20	20
Visser et al. (2012) [42]	II	HC, statin-intolerance	Ezetimibe, bile acid sequestrant, fibrate, niacin	33	26 weeks	47	46	27
Raal et al. (2010) [18]	III	hoFH	Statins, ezetimibe, bile acid sequestrant, niacin	51	26 weeks	25	27	31
McGowan et al. (2012) [43]	III	Severe HC	Statin ± ezetimibe	58	26 weeks	36	36	33
Stein et al. (2012) [19]	III	heFH with CAD	Stains, ezetimibe, bile acid sequestrant, fibrate, niacin	124	26 weeks	28	26	21
Thomas et al. (2013) [44]	III	HC, high-risk for CAD	Statin ± other	157	26 weeks	37	38	24
Santos et al. (2013) [45]	Open-label	heFH and hoFH	Statins, ezetimibe, bile acid sequestrant, niacin	141	Up to 104 weeks	28	31	17

[a]Refers to 200 mg/week dose of mipomersen

HC hypercholesterolaemia, *FH* familial hypercholesterolaemia, *he* heterozygous, *ho* homozygous, *CAD* coronary artery disease

In a phase III study involving 51 homozygous FH all on maximally tolerated conventional therapy, mipomersen (200 mg/week) decreased LDL cholesterol by 25 %, and apoB was similarly reduced by 27 % after 26 weeks [18]. In October 2012, the US Food and Drug Administration (FDA) approved mipomersen, adjunct to lipid-lowering therapy and diet, for the treatment of homozygous FH under a Risk Evaluation and Mitigation Strategies (REMS) program. However, Mipomersen was not approved for use in Europe by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) (see detailed reasons under the subsection on adverse reactions).

Finally, the most recent mipomersen report in FH is a 2 year interim analysis of open-label extension trial. The efficacy and safety was similar to previous randomised placebo-controlled trials. 200 mg weekly injections of mipomersen for up to 104 weeks demonstrated 28 % LDL cholesterol and 31 % apoB reductions. In a subgroup of patients who had undergone liver magnetic resonance imaging, there was also an incremental increase in liver fat in the first 6–12 months. However, regression towards baseline with continued mipomersen beyond 1 year denotes metabolic adaptation [45].

Mipomersen for Severe Hypercholesterolaemia

Four trials have studied patients with primary hypercholesterolaemia that was not specifically ascribed to FH; two were carried out on a background of statins and the others as monotherapy. The first of these trials reported that mipomersen (5 weeks, 7 doses of 100–400 mg/week) in hypercholesterolaemic subjects on stable statin therapy was associated with a 21–52 and 19–54 % reduction (across the dose ranges) in plasma LDL cholesterol and apoB concentrations, respectively [39]. In the same study, a subgroup of patients was assigned to 15 doses of 200 mg/week mipomersen over 13 weeks. A 36 % reduction in both LDL cholesterol and apoB levels was shown [39]. In another study, Visser et al. (2012) found that weekly 200 mg administration of mipomersen to high-risk statin-intolerant patients reduced plasma LDL cholesterol and apoB by 47 and 46 %, respectively, after 26 weeks [42]. Liver fat content was significantly increased, with hepatic steatosis confirmed in two subjects who had undergone liver biopsy [42].

McGowan et al. (2012) demonstrated that in severe hypercholesterolaemic patients on maximally tolerated lipid-lowering therapy, 200 mg/week of mipomersen (over 26 weeks) reduced LDL cholesterol and apoB by 36 % [43]. The most recent study by Thomas et al. (2013) randomised 157 high-risk patients with severe hypercholesterolaemia (LDL cholesterol ≥2.6 mmol/l on a maximally tolerated statin dose) to mipomersen and placebo; randomisation was stratified so that a minimum of 40 % of patients in each group would have type 2 diabetes. After 26 weeks of 200 mg weekly mipomersen, LDL cholesterol and apoB levels were lowered by 36 and 37 %, respectively [44]. Elevations in transaminases and liver fat occurred in some patients, but like other studies, these levels returned towards baseline after cessation of treatment.

Mipomersen and Lipoprotein(a)

A recent study in subjects with varying baseline levels of plasma Lp(a) (34.0–56.3 mg/day) from four phase III trials examined the effect of mipomersen on Lp(a). Mipomersen was shown to consistently and significantly lower Lp(a) levels by a median of 26.4 % across patient groups, despite varying baseline Lp(a) levels [46]. The mechanism of Lp(a) lowering by mipomersen remains to be demonstrated but is likely to involve the reduced production of Lp(a) [47]. The cardiovascular benefit of treating elevated Lp(a) is unknown. Clinical trial evidence is needed to determine whether Lp(a) lowering affects cardiovascular outcomes, although this will require a specific Lp(a)-lowering therapy, such as Lp(a) apheresis or apo(a) antisense therapy [47]. Other new agents such as PCSK9 inhibitors, lomitapide and anacetrapib (a CETP inhibitor) also have Lp(a)-lowering effects, with reductions of 31 % (in heterozygous FH) [48], 19 % (in homozygous FH) [49] and 32 % (in heterozygous FH) [50], respectively. The mechanisms of action of these agents on Lp(a) metabolism is also unclear.

Mipomersen: Adverse Reactions, Contraindications, Economics

Mipomesen is not metabolised by enzymes such as CYP450, and pharmacokinetic studies reveal no clinically relevant interactions with the clearance of statins and ezetimibe [51]. However, injection-site reactions occur in the majority of cases, and every patient experiences at least one injection-site reaction [52]. Other side effects associated with mipomersen include mild-to-moderate influenza-like symptoms and hepatic transaminase elevation (alanine transaminase and aspartate transaminase). Table 7.2 summarises these events from four phase III trials.

The main safety concern with mipomersen is increased hepatic steatosis [19, 41, 43]. The negative recommendation by the EMA was based on this. The EMA also noted that a high proportion of patients stopped taking mipomersen within 2 years, owing to side effects, and this applied even in the patients with homozygous FH. This was considered important as mipomersen was intended for long-term treatment of severe hypercholesterolaemia. The long-term consequences of liver toxicity and possible irreversible liver damage still need to be addressed. Additionally, a higher rate of cardiovascular events was observed in those on mipomersen compared with placebo. Hence, in the opinion of the EMA, the potential cardiovascular benefit did not appear to outweigh its cardiovascular risk (Table 7.3).

The current contraindications for use of mipomersen include severe hepatic impairment or active liver disease. In terms of the use by women of reproductive potential, mipomersen is a category B agent, meaning that animal reproduction studies have failed to demonstrate a risk to the fetus. However, there are no adequate studies in pregnant or lactating women. There is as yet no approved indication of use of mipomersen in paediatric patients, although there have been no differences in adverse events in paediatric compared with adult groups [18, 52].

Table 7.2 Adverse effects of mipomersen in Phase III clinical trials [18, 19, 43, 44]

	Raal et al. (2010) [18] (hoFH)		McGowan et al. (2012) [43] (severe HC)		Stein et al. (2012) [19] (heFH + CAD)		Thomas et al. (2013) [44] (high-risk HC)		All four trials	
	Mipomersen	Placebo	Mipomersen	Placebo	Mipomersen	Placebo	Mipomersen	Placebo	Mipomersen	Placebo
n	34	17	39	19	83	41	105	52	261	129
Adverse effects, *n* (%)										
All events	30 (88.2)	13 (76.5)	39 (100.0)	16 (84.2)	83 (100.0)	38 (92.7)	97 (92.4)	42 (80.8)	249 (95.4)	109 (84.5)
Injection-site reaction	26 (76.5)	4 (23.5)	35 (89.7)	6 (31.6)	77 (92.8)	17 (78.1)	82 (78.1)	16 (30.8)	220 (84.3)	43 (33.3)
Influenza-like symptoms	14 (41.2)	4 (23.5)	18 (46.2)	4 (21.1)	41 (49.4)	13 (34.3)	36 (34.3)	11 (21.2)	109 (41.8)	32 (24.8)
Laboratory abnormalities, *n* (%)										
ALT ≥ ULN and <2 × ULN	12 (35.3)	7 (41.2)	9 (23.1)	6 (31.6)	34 (41.0)	14 (34.1)	–	–	55 (21.1)	27 (20.9)
ALT ≥2 × and <3 × ULN	5 (14.7)	2 (11.8)	9 (23.1)	1 (5.3)	19 (22.9)	2 (4.9)	–	–	33 (12.6)	5 (3.9)
ALT ≥3 × and <10 × ULN	4 (11.8)	0 (0.0)	11 (28.2)	0 (0.0)	11 (13.3)	1 (2.4)	14 (13.3)	0 (0.0)	40 (15.3)	1 (0.8)
ALT ≥10 × ULN	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.0)	0 (0.0)	3 (1.1)	0 (0.0)
Withdrawals, *n* (%)										
Total withdrawals	18 (52.9)	0 (0.0)	31 (79.5)	5 (26.3)	12 (14.5)	0 (0.0)	44 (41.9)	17 (32.7)	105 (40.2)	22 (17.1)
Withdrawals related to adverse events	12 (35.3)	0 (0.0)	31 (79.5)	5 (26.3)	12 (14.5)	0 (0.0)	23 (21.9)	12 (28.8)	78 (29.9)	20 (15.5)

ALT alanine aminotransferase, *ULN* upper normal limit, *hoFH* homozygous familial hypercholesterolaemia, *HC* hypercholesterolaemia, *heFH* heterozygous familial hypercholesterolaemia, *CAD* coronary artery disease

Table 7.3 Principal contraindications, adverse reactions and drug interactions (Adapted from [56, 57])

Contraindications
Moderate or severe hepatic impairment
Acute liver disease
Adverse reactions
Injection-site reactions
Influenza-like symptoms
Nausea
Headache
Angina
Palpitations
Elevated transaminase levels
Hepatic steatosis
Drug interactions
No clinically relevant drug interactions with warfarin, simvastatin or ezetimibe
Advantages
Pregnancy category B
Disadvantages
Subcutaneous administration
Elimination half-life of 1–2 months
Boxed warning for hepatotoxicity
REMS program
Must be refrigerated
Not yet evaluated in patients receiving LDL apheresis or in paediatric patients; use in these settings is not recommended

There are other therapeutic approaches to controlling severe refractory hypercholesterolaemia including lomitapide, apheresis, PCSK9 inhibitors and CETP inhibitors. Unlike mipomersen, lomitapide has received orphan drug designation by both the FDA and EMA. Lomitapide taken orally is an inhibitor of CYP3A4, and hence able to interact with a number of drugs (including some statins); it also interacts with drugs that are metabolised by p-glycoprotein (including colchicine, dabigatran, digoxin, sitagliptin, macrolide antibiotic, antifungals and protease inhibitors). By contrast, mipomersen does not exhibit such interactions. Lomitapide is also associated with significant gastrointestinal adverse effects and increases in hepatic fat levels [53]. Mipomersen is expected to cost $176,000/year. In comparison, lomitapide is expected to be more expensive, at an estimated $250,000/year or more and additionally has a pregnancy category X (i.e. positive evidence of human fetal risk based on adverse reaction data, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits) from the FDA. Furthermore, weekly apheresis costs approximately $208,00/year (excluding costs of travel to apheresis sites) [52]. Based on current data, it is estimated that almost half of the LDL apheresis patients could avoid apheresis with the addition of mipomersen [54].

Ultimately, the long-term outcomes of mipomersen treatment are unclear. Long-term data are required to justify the cardiovascular benefit and hepatic safety profile of mipomersen.

Conclusion

Statins and mipomersen have different pharmacodynamic effects on lipid metabolism which makes the combination rational for the treatment of refractory hypercholesterolaemia. The complementary mechanisms of action, whereby statins increase LDL catabolism and mipomersen inhibits apoB synthesis, provide a good basis for combination treatment. The efficient dose-dependent reduction in plasma LDL cholesterol concentrations achieved by mipomersen therapy is highly significant. However, the risk of hepatic steatosis and injection-site reactions continues to remain a concern that bears on the clinical use of this agent. Studies of longer duration with greater numbers of participants are needed to investigate the significance of the sequelae of hepatic transaminase elevation and hepatic triglyceride accumulation. It is important to investigate whether accumulation of liver fat over time progresses to hepatic inflammation, cirrhosis and liver failure. This is important if mipomersen is extended to more common lipid disorders, such as mixed hyperlipidaemias in the setting of diabetes or insulin resistance that are per se associated with steatohepatitis. Despite the favourable effects of mipomersen on Lp(a), the cardiovascular benefit of treating elevated Lp(a) remains untested. New formulations of mipomersen that do not cause injection-site reactions are essential to increase the acceptability of this form of therapy by patients. The cost of mipomersen also needs to be lowered substantially.

Further studies of combination therapy with ezetimibe bile acid sequestrants, fibrates and including apheresis are required. Balancing the appropriateness of mipomersen therapy in respect of efficacy, acceptability and cost-effectiveness is fundamental and remains to be fully established.

References

1. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670–81.
2. Pijlman AH, Huijgen R, Verhagen SN, et al. Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: a large cross-sectional study in The Netherlands. Atherosclerosis. 2010;209(1):189–94.
3. Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Int J Cardiol. 2014;171(3):309–25.
4. Postmarket Drug Safety Information for Patients and Providers – KYNAMRO® (mipomersen sodium). http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM337472.pdf.

5. Watts G, Chan D, Barrett H. Updating the metabolism of apolipoprotein B-100 containing lipoproteins in dyslipidaemia. In: Toth PP, editor. The year in lipid disorders, vol. 2. Oxford: Clinical Publishing; 2010. p. 118–39.
6. Benn M. Apolipoprotein B levels, APOB alleles, and risk of ischemic cardiovascular disease in the general population, a review. Atherosclerosis. 2009;206(1):17–30.
7. Chaves FJ, Real JT, Garcia-Garcia AB, et al. Genetic diagnosis of familial hypercholesterolemia in a South European outbreed population: influence of low-density lipoprotein (LDL) receptor gene mutations on treatment response to simvastatin in total, LDL, and high-density lipoprotein cholesterol. J Clin Endocrinol Metab. 2001;86(10):4926–32.
8. Wierzbicki AS, Lumb PJ, Cheung J, Crook MA. Fenofibrate plus simvastatin therapy versus simvastatin plus cholestyramine therapy for familial hypercholesterolaemia. QJM. 1997; 90(10):631–4.
9. Kastelein JJP, Akdim F, Stroes ESG, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008;358(14):1431.
10. Huijgen R, Abbink EJ, Bruckert E, et al. Colesevelam added to combination therapy with a statin and ezetimibe in patients with familial hypercholesterolemia: a 12-week, multicenter, randomized, double-blind, controlled trial. Clin Ther. 2010;32(4):615–25.
11. Kawashiri MA, Nohara A, Noguchi T, et al. Efficacy and safety of coadministration of rosuvastatin, ezetimibe, and colestimide in heterozygous familial hypercholesterolemia. Am J Cardiol. 2012;109(3):364–9.
12. Alonso R, Andres E, Mata N, et al. Lipoprotein (a) levels in Familial Hipercholesterolaemia: an important predictor for cardiovascular disease independent of the type of LDL-receptor mutation. J Am Coll Cardiol. 2014;63(19):1982–9.
13. Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J. 2010;31(23):2844–53.
14. Tsimikas S, Witztum JL. The role of oxidized phospholipids in mediating lipoprotein (a) atherogenicity. Curr Opin Lipidol. 2008;19(4):369–77.
15. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein (a) gene accounts for greater than 90% of the variation in plasma lipoprotein (a) concentrations. J Clin Invest. 1992;90(1):52–60.
16. Lanktree MB, Anand SS, Yusuf S, Hegele RA, Investigators S. Comprehensive analysis of genomic variation in the LPA locus and its relationship to plasma lipoprotein(a) in South Asians, Chinese, and European Caucasians. Circ Cardiovasc Genet. 2010;3(1):39–46.
17. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. Eur Heart J. 2013;34(17):1279–91.
18. Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet. 2010;375(9719):998–1006.
19. Stein EA, Dufour R, Gagne C, et al. Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. Circulation. 2012;126(19):2283–92.
20. American Diabetes Association. Standards of medical care in diabetes – 2012. Diabetes Care. 2012;35 Suppl 1:S11–63.
21. Rydén L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD The Task Force on diabetes, prediabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013;34(39):3035–87.
22. Hsia J, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining Low-density lipoprotein cholesterol < 50 mg/dl with Rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). J Am Coll Cardiol. 2011;57(16):1666–75.

23. Fernandez G, Spatz ES, Jablecki C, Phillips PS. Statin myopathy: a common dilemma not reflected in clinical trials. Cleve Clin J Med. 2011;78(6):393–403.
24. Mancini GB, Tashakkor AY, Baker S, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Working Group Consensus update. Can J Cardiol. 2013;29(12):1553–68.
25. Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Arch Intern Med. 2012;172(2):144–52.
26. Wang KL, Liu CJ, Chao TF, et al. Statins, risk of diabetes, and implications on outcomes in the general population. J Am Coll Cardiol. 2012;60(14):1231–8.
27. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J. 2015;36:1012–22. ehv043.
28. Keen HI, Krishnarajah J, Bates TR, Watts GF. Statin myopathy: the fly in the ointment for the prevention of cardiovascular disease in the 21st century? Expert Opin Drug Saf. 2014;13(9):1227–39.
29. Brown MS, Goldstein JL. A receptor mediated pathway for cholesterol homeostasis. Science. 1986;232:34–47.
30. Van Wissen S, Smilde TJ, Trip MD, de Boo T, Kastelein JJP, Stalenhoef AFH. Long term statin treatment reduces lipoprotein (a) concentrations in heterozygous familial hypercholesterolaemia. Heart. 2003;89(8):893–6.
31. Lambert G, Chatelais M, Petrides F, et al. Normalization of low-density lipoprotein receptor expression in receptor defective homozygous familial hypercholesterolemia by inhibition of PCSK9 with alirocumab. J Am Coll Cardiol. 2014;64(21):2299–300.
32. Gebhard C, Huard G, Kritikou EA, Tardif J-C. Apolipoprotein B antisense inhibition-update on mipomersen. Curr Pharm Des. 2013;19(17):3132–42.
33. Crooke ST, Geary RS. Clinical pharmacological properties of mipomersen (Kynamro), a second generation antisense inhibitor of apolipoprotein B. Br J Clin Pharmacol. 2013;76(2):269–76.
34. Yu RZ, Kim T-W, Hong A, Watanabe TA, Gaus HJ, Geary RS. Cross-species pharmacokinetic comparison from mouse to man of a second-generation antisense oligonucleotide, ISIS 301012, targeting human apolipoprotein B-100. Drug Metab Dispos. 2007;35(3):460–8.
35. Crooke RM, Graham MJ, Lemonidis KM, Whipple CP, Koo S, Perera RJ. An apolipoprotein B antisense oligonucleotide lowers LDL cholesterol in hyperlipidemic mice without causing hepatic steatosis. J Lipid Res. 2005;46(5):872–84.
36. Mullick AE, Fu W, Graham MJ, et al. Antisense oligonucleotide reduction of apoB ameliorated atherosclerosis in LDL receptor-deficient mice. J Lipid Res. 2011;52:885–96. doi:10.1194/jlr.M011791.
37. Kastelein JJP, Wedel MK, Baker BF, et al. Potent reduction of apolipoprotein B and low-density lipoprotein cholesterol by short-term administration of an antisense inhibitor of apolipoprotein B. Circulation. 2006;114(16):1729–35.
38. Akdim F, Tribble DL, Flaim JD, et al. Efficacy of apolipoprotein B synthesis inhibition in subjects with mild-to-moderate hyperlipidaemia. Eur Heart J. 2011;32(21):2650–9.
39. Akdim F, Stroes ESG, Sijbrands EJG, et al. Efficacy and safety of mipomersen, an antisense inhibitor of apolipoprotein B, in hypercholesterolemic subjects receiving stable statin therapy. J Am Coll Cardiol. 2010;55(15):1611–8.
40. Akdim F, Visser ME, Tribble DL, et al. Effect of mipomersen, an apolipoprotein B synthesis inhibitor, on low-density lipoprotein cholesterol in patients with familial hypercholesterolemia. Am J Cardiol. 2010;105(10):1413–9.
41. Visser ME, Akdim F, Tribble DL, et al. Effect of apolipoprotein-B synthesis inhibition on liver triglyceride content in patients with familial hypercholesterolemia. J Lipid Res. 2010;51(5):1057–62.
42. Visser ME, Wagener G, Baker BF, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, lowers low-density lipoprotein cholesterol in high-risk statin-intolerant patients: a randomized, double-blind, placebo-controlled trial. Eur Heart J. 2012;33(9):1142–9.

43. McGowan MP, Tardif J-C, Ceska R, et al. Randomized, placebo-controlled trial of mipomersen in patients with severe hypercholesterolemia receiving maximally tolerated lipid-lowering therapy. PLoS One. 2012;7(11):e49006.
44. Thomas GS, Cromwell WC, Ali S, Chin W, Flaim JD, Davidson M. Mipomersen, an apolipoprotein B synthesis inhibitor, reduces atherogenic lipoproteins in patients with severe hypercholesterolemia at high cardiovascular risk: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2013;62(23):2178–84.
45. Santos RD, Duell PB, East C, et al. Long-term efficacy and safety of mipomersen in patients with familial hypercholesterolaemia: 2-year interim results of an open-label extension. Eur Heart J. 2013;39:566–75.
46. Santos RD, Raal FJ, Catapano AL, Witztum JL, Steinhagen-Thiessen E, Tsimikas S. Mipomersen, an antisense oligonucleotide to apolipoprotein B-100, reduces lipoprotein (a) in various populations with hypercholesterolemia results of 4 phase III trials. Arterioscler Thromb Vasc Biol. 2015;35(3):689–99.
47. Bos S, Yayha R, van Lennep JER. Latest developments in the treatment of lipoprotein (a). Curr Opin Lipidol. 2014;25(6):452–60.
48. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385(9965):331–40.
49. Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet. 2013;381(9860):40–6.
50. Kastelein JJP, Besseling J, Shah S, et al. Anacetrapib as lipid-modifying therapy in patients with heterozygous familial hypercholesterolaemia (REALIZE): a randomised, double-blind, placebo-controlled, phase 3 study. Lancet. 2015. http://dx.doi.org/10.1016/S0140-6736(1014)62115-62112.
51. Yu RZ, Geary RS, Flaim JD, et al. Lack of pharmacokinetic interaction of mipomersen sodium (ISIS 301012), a 2'-—O-methoxyethyl modified antisense oligonucleotide targeting apolipoprotein B-100 messenger RNA, with simvastatin and ezetimibe. Clin Pharmacokinet. 2009;48(1):39–50.
52. Bennett LL, Chalk M. Review of Mipomersen Sodium (Kynamro®) for Familial Hypercholesterolemia. J Clin Med Res Updat. 2014;1:1–10.
53. Davis KA, Miyares MA. Lomitapide: a novel agent for the treatment of homozygous familial hypercholesterolemia. Am J Health Syst Pharm. 2014;71(12):1001–8.
54. Vogt A, Parhofer KG. The potential of mipomersen, an ApoB synthesis inhibitor, to reduce necessity for LDL-apheresis in patients with heterozygous familial hypercholesterolemia and coronary artery disease. Expert Opin Pharmacother. 2013;14(6):691–7.
55. Hovingh K, Besseling J, Kastelein J. Efficacy and safety of mipomersen sodium (Kynamro). Expert Opin Drug Saf. 2013;12(4):569–79.
56. Ross JL. Homozygous familial hypercholesterolemia – role of NPs and PAs in achieving optimal outcomes using novel therapeutic interventions. Supplement to Clinician Reviews. 2015:1–9.
57. KYNAMRO (mipomersen sodium) Product Information. http://www.kynamro.com/families/product-information.aspx.

Chapter 8
Statins and Lomitapide: A Suitable Response for Homozygous Familial Hypercholesterolemia?

Angela Pirillo and Alberico Luigi Catapano

Introduction

Autosomal dominant hypercholesterolemia (ADH) is a genetic disorder characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C) from birth and the occurrence of premature cardiovascular disease and myocardial infarction [1, 2]. ADH is determined by defects in genes encoding for proteins involved in the metabolism of LDL and includes familial hypercholesterolemia (FH or ADH1), a common monogenic disorder caused by defects in the *LDLR* gene, encoding for the LDL receptor, which is involved in the binding, internalization, and processing of LDL particles in the liver (Fig. 8.1) [2]. *LDLR* mutations account for >95 % of the cases of ADH. ADH, however, includes also two other types of hypercholesterolemia: defects in the *APOB* gene, encoding for apolipoprotein B, required for the binding of LDL particle with LDLR, determine the condition known as ADH2, or familial defective apolipoprotein B100 (FDB) when localized in the LDLR-binding domain of apoB (Fig. 8.1) [3]; gain-of-function mutations in the *PCSK9* gene, encoding for proprotein convertase subtilis/kexin type 9, a convertase that binds to

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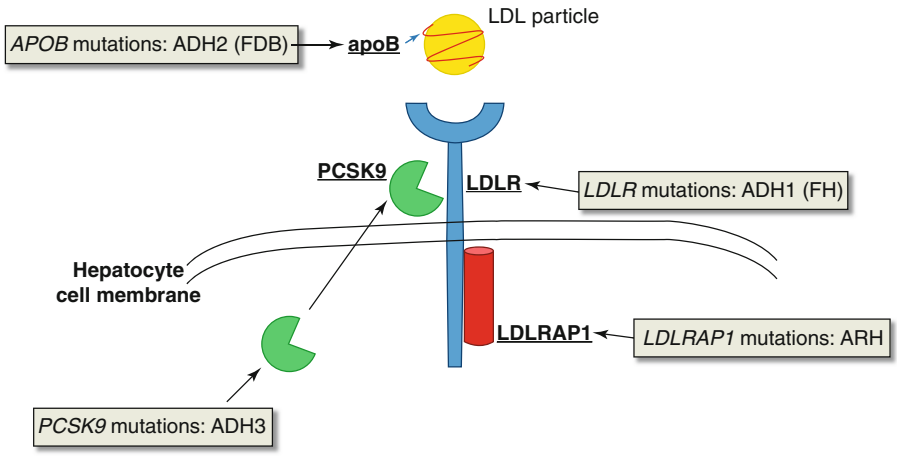

Fig. 8.1 Types of familial hypercholesterolemias

LDLR and targets it for lysosomal degradation, cause a condition referred to as ADH3 (Fig. 8.1) [2]. A recessive form of hypercholesterolemia (autosomal recessive hypercholesterolemia, ARH) is caused by the rare loss-of-function mutations in the *LDLRAP1* gene, encoding for LDLR adaptor protein 1, an adaptor protein required to facilitate the internalization of LDLR/LDL complex in the liver (Fig. 8.1) [4, 5]. ADH is associated with a high risk of premature cardiovascular disease; therapeutic interventions with statins significantly reduce this risk, particularly in subjects with heterozygous FH [6].

FH includes heterozygous FH (HeFH), the less severe form, with a prevalence of ~1:200–1:500, and homozygous FH (HoFH), a much rarer condition, with a prevalence of approximately 1:160,000–1:1,000,000 [7, 8]. HeFHs have only one mutated allele [9]; HoFH includes the true homozygotes, exhibiting the same mutation in both gene alleles (usually *LDLR*), compound heterozygotes, presenting two different mutations in the two alleles of the same gene, and the rare form of double heterozygosity, due to the presence of mutations in two different genes (generally one is *LDLR* associated with a mutation in another of the above-reported genes), and with a phenotype that is intermediate between HeFH and HoFH [8, 10]; both these conditions are inherited in an autosomal codominant manner.

These different conditions translate into different LDL-C levels: HeFHs have a reduced LDLR activity (up to 50 %), leading to about two- to threefold elevations in plasma cholesterol and development of coronary atherosclerosis at early age, usually after 30 years; HoFH patients exhibit a nonfunctional or significantly reduced LDLR pathway (2–30 % activity), with receptor-negative subjects (<2 % LDLR activity) having more severe cardiovascular conditions compared with subjects with receptor deficiency [8]. In receptor-negative HoFH, the significantly reduced LDLR expression and activity result in the subject exposure to very high cholesterol levels (>500 mg/dL) from the childhood, the presence of cutaneous xanthomas prior to 4 years of age, childhood coronary heart disease, and death from

myocardial infarction prior to 20 years of age if untreated [2, 8]. LDLR-defective HoFHs have a better prognosis, with clinical manifestations of cardiovascular disease by age 30. As for FH determined by *LDLR* gene mutations, homozygous FDB expresses a more severe disease compared with heterozygous FDB, although, compared with subjects with FH, subjects with FDB exhibit a less severe hypercholesterolemia, lower occurrence of tendinous xanthoma, and a lower incidence of coronary artery disease [3]. Plasma LDL cholesterol levels in patients with homozygous FDB are similar to the levels observed in patients with HeFH [3]. Homozygous familial hypercholesterolemia determined by *PCSK9* mutations exhibits a milder phenotype compared with FH caused by *LDLR* mutations [11].

Management of HoFH

In clinically diagnosed HoFH, the occurrence of the first major cardiovascular events is localized in the adolescence, although a significant phenotypic variability exists in subjects with HoFH in terms of cardiovascular disease and clinical outcomes, mainly due to eventual residual activity of LDLR, the therapeutic treatments, and the time of therapy initiation [12, 13]. As example, markers of atherosclerosis were significantly correlated with age at which lipid-lowering therapies started in a group of HoFH patients [12]. Thus, current guidelines recommend to lower LDL-C as early as possible, based on the evidence that the severity of atherosclerosis and cardiovascular disease correlates with the cumulative burden of high levels of LDL-C and that early lipid lowering may reduce this burden and delay the onset of cardiovascular events [8, 12, 14]. Lifestyle interventions including a low-saturated fat, low cholesterol diet, physical activity, and not smoking are strongly encouraged, but aggressive lipid-lowering treatments are essential to lower LDL-C levels drastically. Statins are the first-line therapy for lowering LDL-C levels [10, 15] and may be effective in some HoFH patients, but the presence of functional LDLR is required for such effect; thus, statins may be effective in HeFH, or in receptor-defective HoFH at the maximal dose tolerated [8, 10], and in children statins should be only those that have been proved to be relatively safe [10, 16, 17]. However, HoFH patients rarely reach the LDL-C level target, as statins in HoFH trigger an LDL-C reduction of about 20 %, which is significantly lower compared with reductions observed in other types of hypercholesterolemic patients (40–60 %) [18]. This observation points out to the need to treat HoFH patients with combined lipid-lowering therapies, using drugs with different mechanisms of action that may guarantee a higher reduction of LDL-C levels. Ezetimibe, which reduces cholesterol absorption, and LDL apheresis, which removes LDL particles from the circulation, are usually associated with statin therapy in the management of HoFH patients, resulting in an impressive LDL-C reduction [8, 19]. Other drugs may be added to the therapy, such as fibrates for HoFH subjects with high triglyceride levels [10].

Accordingly with current guidelines, recommended LDL-C goals for both HeFH and HoFH patients are <100 mg/dL (<2.5 mmol/L) for adults, <135 mg/dL

Table 8.1 Recommended LDL-C targets in HoFH subjects

Children	<135 mg/dL (<3.5 mmol/L)
Adults	<100 mg/dL (<2.5 mmol/L)
Adults with known CHD/diabetes	<70 mg/dL (<1.8 mmol/L)

Table 8.2 Percent changes from baseline of lipids and apoproteins in HoFH subjects treated with statins

	Percent change from baseline				
Statin	LDL-C	VLDL-C	TC	ApoB	TG
Simvastatin					
80 mg	−25 %***	−20.3 %	−24.1 % **	−18.1 %	−21.3 %
160 mg	−31 %***	−26.6 %**	−29.6 %**	−22.2 %*	−27 %**
Atorvastatin					
40 mg	−17 %**		−16.4 %**		−18.8 %
80 mg	−28 %**		−25.5 %**		−25 %**
Rosuvastatin					
20 mg	−18.8 %***		−17.7 % ***		−7.5 %
40 mg	−22.5 %***		−20.9 %***		−9.6 %*
80 mg	−21.4 %***		−20.0 %***	−20.0 %***	+3.3 %**

*p <0.05
**p <0.01
***p <0.0001

(<3.5 mmol/L) for children, and <70 mg/dL (<1.8 mmol/L) for adults with coronary heart disease or diabetes (Table 8.1) [10].

Statins

Several studies have established the efficacy of statin therapy in reducing either cardiovascular or all-cause mortality in homozygous familial hypercholesterolemia, even in LDLR-negative patients. High doses of simvastatin (80 or 160 mg/day) were found to significantly reduce LDL-C levels in HoFH patients (Table 8.2), even if receptor negative: at 80 mg/day there was a 25 % LDL-C reduction, and at 160 mg/day it reached 31 %, while the lower dose (40 mg/day) was less effective in reducing LDL-C levels (−13.8 %) [20]. As expected, simvastatin significantly reduced VLDL-C, total cholesterol, apoB, and TG levels (Table 8.2) [20].

As the main mechanism by which statins act is through the inhibition of endogenous cholesterol biosynthesis, with subsequent upregulation of LDLR to enhance LDL clearance, it was expected that only receptor-defective HoFH would respond to statin therapy; on the contrary, also receptor-negative subjects showed significant decreases of LDL-C levels with high-dose statin [20, 21], suggesting that alternative mechanisms of action of statins may explain this finding. Statins, by inhibiting cholesterol biosynthesis in the liver, may limit cholesterol availability for

apoB-containing lipoprotein formation, including VLDL, that are the major source of circulating LDL, and LDL itself; this mechanism is likely to play a relevant role in statin-induced LDL lowering in subjects that are receptor negative. On the contrary, in receptor-defective subjects, which may produce some functional receptors, both mechanisms may play a role. In addition, subjects exhibiting the same LDLR mutations have different LDL-C levels and respond in a heterogeneous way to the same therapy, suggesting the involvement of other mechanisms.

These findings have been confirmed by other studies: high doses of atorvastatin (40 and 80 mg/day) lowered LDL-C levels by 17 and 28 %, respectively, with similar reductions in receptor-negative subjects (14 and 28 %, respectively) [22]. Atorvastatin 40 and 80 mg significantly reduced total cholesterol and TG levels (Table 8.2) [22]. However, no additional reductions were observed by further increasing atorvastatin doses [22], suggesting a plateau effect. This is a relevant finding, yet observed in subjects with HeFH [23], suggesting a limit to the LDL-C-lowering properties of statins in FH and that drugs with a different mechanism of action should be added to statin therapy aiming at achieving LDL-C targets.

Similar results were obtained in a comparative study of atorvastatin and rosuvastatin that showed similar mean reductions with these two drugs at 80 mg/day (18 and 19 %, respectively) (Table 8.2) [24], suggesting the need of additional cholesterol-lowering treatments.

Although statins did not decrease LDL-C levels at the recommended target, these reductions of LDL-C levels might be beneficial for HoFH patients, possibly translating in a reduced risk of early onset of major cardiovascular events, especially if therapy is started early [8]. This effect was reported by a study that evaluated the impact of advances in lipid-lowering therapies (mainly statins) on cardiovascular disease morbidity and mortality in a large HoFH population: despite a mean reduction of LDL-C levels of 26 %, patients treated with lipid-lowering drugs showed a significant reduction of mortality and an increased age at which the first major adverse cardiovascular event occurred [14]. These findings suggested that, although LDL-C levels remained elevated, lipid-lowering therapy with statins is associated with a better prognosis for HoFH, with delayed cardiovascular events and prolonged survival. Nevertheless, despite the use of high-potency statins at high doses, only a small proportion of HoFH patients reach the recommended LDL-C target [10, 18]; in addition, some subjects may exhibit intolerance to statins, leading to therapy discontinuation. All these observations suggest the need of new therapeutic options to decrease LDL-C levels in these patients. Lomitapide and mipomersen were recently developed for the treatment of HoFH patients.

Microsomal Triglyceride Transfer Protein and Lomitapide

The microsomal triglyceride transfer protein (MTP) is a lipid transfer protein that plays an essential role in the assembly and secretion of apolipoprotein-B-containing lipoproteins, including very low-density lipoprotein (VLDL) and chylomicrons (Fig. 8.2) [25]. It is localized in the endoplasmic reticulum (ER) of hepatocytes and

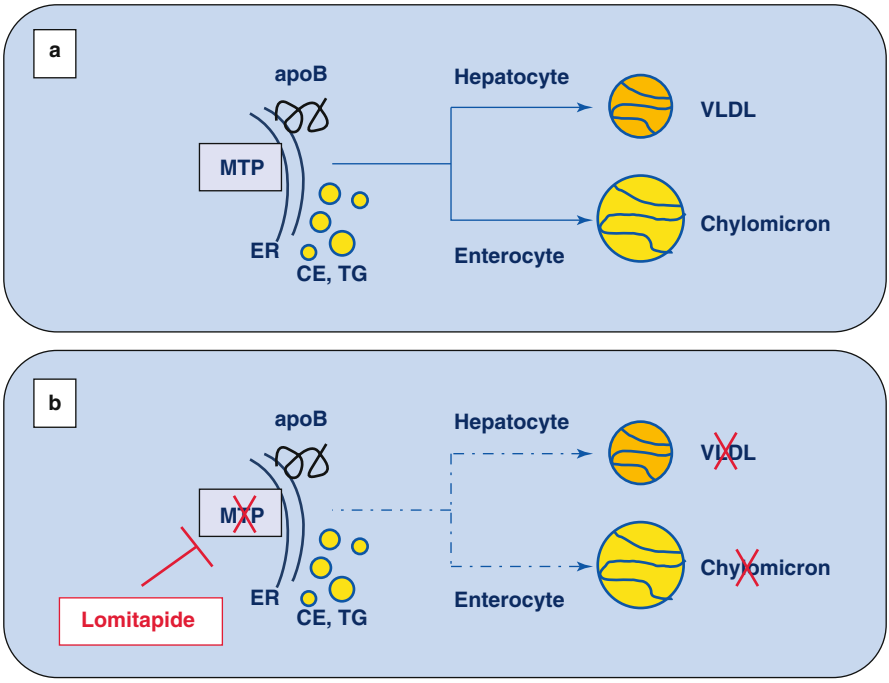

Fig. 8.2 Role of MTP in VLDL and chylomicron biosynthesis and effect of MTP inhibition by lomitapide. (**a**) MTP-mediated intracellular assembly of VLDL and chylomicrons in hepatocytes and enterocytes; (**b**) effect of lomitapide on MTP activity

enterocytes and acts by transferring neutral lipids (triglycerides and cholesteryl esters) from the ER membrane to the nascent apoB [25]. The key role of MTP has been identified in subjects carrying mutations of the gene encoding for MTP (*MTTP*), which exhibit inadequate formation of VLDL and chylomicrons and increased apoB degradation; this condition ultimately results in the significant reduction of circulating VLDL and the deriving LDL [26]. Thus, it was hypothesized that MTP inhibition could represent a possible therapeutic strategy to reduce LDL-C levels in subjects with familial hypercholesterolemia. In contrast to other lipid-lowering therapies, MTP inhibition affects the production of apoB-containing lipoproteins in both the liver and intestine, thus preventing both hepatic VLDL and intestinal chylomicron secretion and resulting in significant reduction of both cholesterol and TG plasma levels. Preclinical studies performed in animal models of HoFH supported this hypothesis, showing that MTP inhibition normalized the levels of atherogenic lipoproteins by greatly reducing the secretion rate of VLDL in WHHL rabbits [27, 28] and in *Ldlr*$^{-/-}$ mice [29].

Lomitapide is a MTP inhibitor that binds to MTP and inhibits MTP-mediated synthesis of VLDL and chylomicrons and, as a result, significantly reduces LDL-C levels (Fig. 8.2). Lomitapide was first tested in six patients with homozygous familial hypercholesterolemia [30]. The patients were 18–40 years old, and two of them

Table 8.3 Percent change from baseline of lipid/lipoprotein levels in HoFH treated with lomitapide (0.3 mg/kg and 1.0 mg/kg body weight) for 4 weeks [30]

Parameter	% Change from baseline	*P* value
LDL-C		
0.3 mg	−24.7	<0.001
1.0 mg	−50.9	<0.001
TC		
0.3 mg	−29.8	<0.001
1.0 mg	−58.4	<0.001
TG		
0.3 mg	−34.1	0.02
1.0 mg	−65.2	<0.001
apoB		
0.3 mg	−14.7	0.08
1.0 mg	−55.6	<0.001

had known clinically relevant cardiovascular disease; five patients were found to be negative for the LDLR, while one was LDLR defective [30]. The patients received lomitapide at 4 different daily doses (0.03, 0.1, 0.3 and 1.0 mg/kg body weight), each for 4 weeks. The mean LDL-C level was reduced by 24.7 % after 0.3 mg/kg for 4 weeks and by 50.9 % from the baseline level after 1.0 mg/kg for 4 weeks (Table 8.3) [30]; similarly, total cholesterol was reduced by 29.8 and 58.4 % from the baseline level, respectively (Table 8.3) [30]. Both TG and apoB were significantly reduced (TG: −34.1 and −65.2 %, and apoB: −14.7 and −55.6 %, respectively) (Table 8.3) [30]. Overall, the drug was well tolerated; the most serious adverse events were elevations in liver aminotransferase levels and hepatic fat accumulation [30]. This study showed that treating patients with HoFH with lomitapide is highly effective in reducing LDL-C levels; the accumulation of fat in the liver, however, requires further investigations for the evaluation of adverse effects during long-term treatment with lomitapide.

To answer these questions, lomitapide has been then tested in patients with HoFH in a single-arm, open-label, phase 3 study [31]. This study included a 26-week efficacy study, during which lomitapide was initiated at a starting dose of 5 mg/day for the first 2 weeks, then escalated to 10, 20, 40, and 60 mg/day at 4-week intervals (or until the maximal dose was identified for each subject on the basis of safety and tolerability) and a 52-week safety study; current lipid-lowering therapies were maintained at least during the efficacy study, then eventually modulated on the basis of lomitapide effect [31]. The design of this study, with the dose escalation of lomitapide combined with a low-fat diet, aimed to achieve a balance between efficacy and safety. Mean LDL-C (Table 8.4) was significantly reduced by 50 % compared with baseline values at the end of the efficacy phase (week 26); this led to the discontinuation of LDL apheresis in some patients and to the increase of interval time between two apheresis processes in others [31]. At the end of the study (week 78), LDL-C was still significantly reduced, but the reduction was attenuated (−38 %) compared with the values at the end of the efficacy study; this finding may be explained by the changes in the concomitant lipid-lowering therapies and in the

Table 8.4 Percent change from baseline of lipid/lipoprotein levels in HoFH treated with lomitapide at week 26 (efficacy phase) and 78 (end of study) [31]

Parameter	% Change from baseline at week 26 (*P* value)	% Change from baseline at week 78 (*P* value)
LDL-C	−50 % (<0.0001)	−38 % (0.0001)
VLDL-C	−45 % (<0.0001)	−31 % (0.0389)
Non-HDL-C	−50 % (<0.0001)	−39 % (<0.0001)
TG	−45 % (<0.0001)	−31 % (0.0368)
HDL-C	−12 % (0.0001)	−5 % (0.1396)
ApoA-I	−14 % (0.0003)	−4 % (0.1155)

reduction of lomitapide doses in patients reporting adverse effects [31]. Similarly, VLDL-C, non-HDL-C, and TG levels were significantly decreased at the end of the efficacy phase (−45 %, −50 %, and −45 % respectively), and at the end of the study such reductions resulted attenuated (−31 %, −39 % and −31 %, respectively), in line with the results obtained for LDL-C levels (Table 8.4) [31]. HDL-C and apoA-I levels were significantly reduced at week 26 (−12 and −14 %) but returned to levels similar to baseline at the end of the study (Table 8.4) [31]. Most patients reported gastrointestinal disorders during the treatment with lomitapide, classified as mild to moderate. Of 23 patients who completed the study, 10 exhibited levels of ALT, AST, or both >3 times the ULN at least once during the study, and five patients had AST or ALT >5 times the ULN; however, all these changes were transient, were resolved by reducing lomitapide doses, and were not related to changes of liver function [31]. Mean hepatic fat was increased during the efficacy phase (1.0 % at baseline, 8.6 % at week 26), but it did not further increase (8.3 % at week 78) [31]. The long-term clinical relevance of this increase of liver fat is still not clear, and further investigation must ensure that the accumulation of hepatic fat does not progress to hepatic fibrosis or cirrhosis, as treatment with lomitapide could be lifelong. Both HDL and apoA-I levels were transiently reduced during the efficacy phase but returned to levels similar to the baseline values at the end of the safety phase [31]. These findings suggest a positive benefit-risk ratio of lomitapide treatment in very-high-cardiovascular-risk patients such as those with homozygous FH, as suggested by a recent report of a patient with HoFH treated with lomitapide in addition to other lipid-lowering therapies for 5 years [32].

Most common adverse reactions during therapy with lomitapide were gastrointestinal effects that may be reduced by adhering to a low fat diet (≤20 % caloric intake from fat) and by increasing gradually the dose of lomitapide [33].

Statins and Lomitapide

Lomitapide is metabolized primarily via CYP3A4, thus it should not be administered concomitantly with moderate and strong CYP3A4 inhibitors as they may significantly increase lomitapide exposure [33]; weak CYP3A4 inhibitors (such as atorvastatin and oral contraceptives) approximately double lomitapide exposure, suggesting the use of

lower doses of lomitapide when used concomitantly with CYP3A4 inhibitors [33]. On the other hand, as lomitapide is classified as a weak inhibitor of CYP3A4, it may increase simvastatin and lovastatin exposure, thus increasing the risk of statin-associated myopathy and rhabdomyolysis [33, 34]. In fact, lomitapide at low dose (10 mg) significantly increased the exposure to the active moiety simvastatin acid (C_{max}: +35 %, $AUC_{0\text{-}t}$: +39 %), that was further increased when simvastatin was administered with lomitapide at high dose (60 mg) (C_{max}: +57 %, $AUC_{0\text{-}t}$: +68 %); also, the exposure to the inactive moiety simvastatin lactone was increased following the coadministration with lomitapide (60 mg: C_{max}: +102 %, $AUC_{0\text{-}t}$: +85 %), thus the inhibition of CYP3A4 by lomitapide leads to an increased exposure to both the acid and the lactone forms [34]. The interaction of lomitapide with lovastatin has not been directly evaluated, but based on the metabolic pathway involved in lovastatin metabolism (similar to simvastatin), an increased exposure to lovastatin when coadministered with lomitapide is expected [33]. Also, atorvastatin exposure increases during concomitant administration with high dose of lomitapide, although to a lesser extent compared with simvastatin (at 60 mg lomitapide: C_{max}: +38 % and $AUC_{0\text{-}t}$: +29 %, for the sum of all active atorvastatin moieties) [34]. Rosuvastatin does not exhibit a relevant hepatic metabolism and is mainly excreted in the feces unaltered, and only a minor part (<10 %) is metabolized through CYP2C9; thus, no interaction was expected during coadministration with lomitapide. Nevertheless, a currently nonexplainable significant increase of rosuvastatin exposure (32 %) was observed [34]. All these observations suggest that lower doses of statins should be used when coadministered with lomitapide at high doses and the need of a careful monitoring of possible adverse effects during coadministration of lomitapide and a statin.

Statins and Lomitapide: A Suitable Response for Homozygous Familial Hypercholesterolemia?

The use of lomitapide in association with statins will help in further reducing LDL-cholesterol levels and incipient CVD, yet the use of other maneuvers and drugs such as ezetimibe and LDL apheresis, if available, will promote even better reductions of the average LDL on HoFH.

Only 30 years ago, people with HoFH were with very few hopes of avoiding CVD and cardiovascular death; nowadays, we can offer a much better perspective, and the presence of lomitapide, along with other drugs, in the pharmacological armamentarium is a step forward and provides the patients with hopes for a better life.

References

1. Vogt A. The genetics of familial hypercholesterolemia and emerging therapies. Appl Clin Genet. 2015;8:27–36.
2. Sniderman AD, Tsimikas S, Fazio S. The severe hypercholesterolemia phenotype: clinical diagnosis, management, and emerging therapies. J Am Coll Cardiol. 2014;63:1935–47.

3. Whitfield AJ, Barrett PH, van Bockxmeer FM, Burnett JR. Lipid disorders and mutations in the APOB gene. Clin Chem. 2004;50:1725–32.
4. Garcia CK, Wilund K, Arca M, Zuliani G, Fellin R, Maioli M, Calandra S, Bertolini S, Cossu F, Grishin N, Barnes R, Cohen JC, Hobbs HH. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. Science. 2001;292:1394–8.
5. Fellin R, Arca M, Zuliani G, Calandra S, Bertolini S. The history of Autosomal Recessive Hypercholesterolemia (ARH). From clinical observations to gene identification. Gene. 2015;555:23–32.
6. Neil A, Cooper J, Betteridge J, Capps N, McDowell I, Durrington P, Seed M, Humphries SE. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J. 2008;29:2625–33.
7. Singh S, Bittner V. Familial hypercholesterolemia-epidemiology, diagnosis, and screening. Curr Atheroscler Rep. 2015;17:482.
8. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjaerg-Hansen A, Watts GF, Averna M, Boileau C, Boren J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J. 2014;35:2146–57.
9. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver ALBCR, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill Information Services; 2001. p. 2863–913.
10. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Boren J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjaerg-Hansen A. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34:3478–90a.
11. Mabuchi H, Nohara A, Noguchi T, Kobayashi J, Kawashiri MA, Inoue T, Mori M, Tada H, Nakanishi C, Yagi K, Yamagishi M, Ueda K, Takegoshi T, Miyamoto S, Inazu A, Koizumi J. Genotypic and phenotypic features in homozygous familial hypercholesterolemia caused by proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function mutation. Atherosclerosis. 2014;236:54–61.
12. Kolansky DM, Cuchel M, Clark BJ, Paridon S, McCrindle BW, Wiegers SE, Araujo L, Vohra Y, Defesche JC, Wilson JM, Rader DJ. Longitudinal evaluation and assessment of cardiovascular disease in patients with homozygous familial hypercholesterolemia. Am J Cardiol. 2008;102:1438–43.
13. Al-Shaikh AM, Abdullah MH, Barclay A, Cullen-Dean G, McCrindle BW. Impact of the characteristics of patients and their clinical management on outcomes in children with homozygous familial hypercholesterolemia. Cardiol Young. 2002;12:105–12.
14. Raal FJ, Pilcher GJ, Panz VR, van Deventer HE, Brice BC, Blom DJ, Marais AD. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation. 2011;124:2202–7.
15. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, Daniels SR, Gidding SS, de Ferranti SD, Ito MK, McGowan MP, Moriarty PM, Cromwell WC, Ross JL, Ziajka PE. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5:S1–8.
16. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. J Pediatr. 2003;143:74–80.

17. Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Buller HR, Sijbrands EJ, Kastelein JJ. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. JAMA. 2004;292:331–7.
18. Hovingh GK, Davidson MH, Kastelein JJ, O'Connor AM. Diagnosis and treatment of familial hypercholesterolaemia. Eur Heart J. 2013;34:962–71.
19. Bruckert E. Recommendations for the management of patients with homozygous familial hypercholesterolaemia: overview of a new European Atherosclerosis Society consensus statement. Atheroscler Suppl. 2014;15:26–32.
20. Raal FJ, Pilcher GJ, Illingworth DR, Pappu AS, Stein EA, Laskarzewski P, Mitchel YB, Melino MR. Expanded-dose simvastatin is effective in homozygous familial hypercholesterolaemia. Atherosclerosis. 1997;135:249–56.
21. Feher MD, Webb JC, Patel DD, Lant AF, Mayne PD, Knight BL, Soutar AK. Cholesterol-lowering drug therapy in a patient with receptor-negative homozygous familial hypercholesterolaemia. Atherosclerosis. 1993;103:171–80.
22. Raal FJ, Pappu AS, Illingworth DR, Pilcher GJ, Marais AD, Firth JC, Kotze MJ, Heinonen TM, Black DM. Inhibition of cholesterol synthesis by atorvastatin in homozygous familial hypercholesterolaemia. Atherosclerosis. 2000;150:421–8.
23. Hagemenas FC, Pappu AS, Illingworth DR. The effects of simvastatin on plasma lipoproteins and cholesterol homeostasis in patients with heterozygous familial hypercholesterolaemia. Eur J Clin Invest. 1990;20:150–7.
24. Marais AD, Raal FJ, Stein EA, Rader DJ, Blasetto J, Palmer M, Wilpshaar W. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Atherosclerosis. 2008;197:400–6.
25. Hooper AJ, Burnett JR, Watts GF. Contemporary aspects of the biology and therapeutic regulation of the microsomal triglyceride transfer protein. Circ Res. 2015;116:193–205.
26. Goldberg AC. Emerging low-density lipoprotein therapies: microsomal triglyceride transfer protein inhibitors. J Clin Lipidol. 2013;7:S16–20.
27. Wetterau JR, Gregg RE, Harrity TW, Arbeeny C, Cap M, Connolly F, Chu CH, George RJ, Gordon DA, Jamil H, Jolibois KG, Kunselman LK, Lan SJ, Maccagnan TJ, Ricci B, Yan M, Young D, Chen Y, Fryszman OM, Logan JV, Musial CL, Poss MA, Robl JA, Simpkins LM, Slusarchyk WA, Sulsky R, Taunk P, Magnin DR, Tino JA, Lawrence RM, Dickson Jr JK, Biller SA. An MTP inhibitor that normalizes atherogenic lipoprotein levels in WHHL rabbits. Science. 1998;282:751–4.
28. Shiomi M, Ito T. MTP inhibitor decreases plasma cholesterol levels in LDL receptor-deficient WHHL rabbits by lowering the VLDL secretion. Eur J Pharmacol. 2001;431:127–31.
29. Liao W, Hui TY, Young SG, Davis RA. Blocking microsomal triglyceride transfer protein interferes with apoB secretion without causing retention or stress in the ER. J Lipid Res. 2003;44:978–85.
30. Cuchel M, Bloedon LT, Szapary PO, Kolansky DM, Wolfe ML, Sarkis A, Millar JS, Ikewaki K, Siegelman ES, Gregg RE, Rader DJ. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med. 2007;356:148–56.
31. Cuchel M, Meagher EA, du Toit Theron H, Blom DJ, Marais AD, Hegele RA, Averna MR, Sirtori CR, Shah PK, Gaudet D, Stefanutti C, Vigna GB, Du Plessis AM, Propert KJ, Sasiela WJ, Bloedon LT, Rader DJ. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet. 2013;381:40–6.
32. Raper A, Kolansky DM, Sachais BS, Meagher EA, Baer AL, Cuchel M. Long-term clinical results of microsomal triglyceride transfer protein inhibitor use in a patient with homozygous familial hypercholesterolemia. J Clin Lipidol. 2015;9:107–12.
33. http://www.aegerion.com/Collateral/Documents/English-US/012187_JuxtapidPI_8%205x11_FIN.pdf.
34. Tuteja S, Duffy D, Dunbar RL, Movva R, Gadi R, Bloedon LT, Cuchel M. Pharmacokinetic interactions of the microsomal triglyceride transfer protein inhibitor, lomitapide, with drugs commonly used in the management of hypercholesterolemia. Pharmacotherapy. 2014;34:227–39.

Chapter 9
Statins and PCSK9 Inhibitors: Defining the Correct Patients

Michel Farnier

Introduction

Plasma low-density lipoprotein cholesterol (LDL-C) level is a major risk factor for the development of atherosclerosis and cardiovascular disease (CVD). Lowering LDL-C reduces the risk of CVD events and all-cause mortality [1], and there is a direct relation between the degree of LDL-C lowering and the degree of CVD event reduction [1, 2].

Statins are the most commonly used drugs to reduce LDL-C and cardiovascular risk. Consequently, statins are the standard of care for the treatment of hypercholesterolemia [3, 4]. However, even in randomized trials using high-dose statins, a large proportion of patients fail to achieve LDL-C target [5]. Furthermore, some patients are unable to tolerate high-dose statin therapy, because of side effects, particularly muscle adverse effects [6]. In clinical practice, a considerable number of patients at high and very high risk require LDL-C lowering larger than currently achievable with statins alone or in combination with other lipid-lowering drugs such as ezetimibe. A novel class of therapeutic agents, inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), have shown promising results, particularly with anti-PCSK9 monoclonal antibodies (mAbs). Recent comprehensive reviews have summarized the history, the function, and the modulation of PCSK9 [7–13]. The objective of this report is to provide a synoptic overview of PCSK9's role in LDL metabolism and of PCSK9 inhibitors, with a focus on the putative categories of patient candidates for this novel therapeutic approach.

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Role of PCSK9 in Lipoprotein Metabolism

PCSK9 gene is expressed in several organs, particularly the liver and also the intestine and the kidney [14]. The involvement of PCSK9 in regulating LDL-C levels became apparent in 2003 with the identification of gain-of-function mutations of PCSK9 in French families, mutations responsible for autosomal dominant hypercholesterolemia and for increased risk of CVD disease [15]. Conversely, the genetic evidence suggesting potential role for PCSK9 inhibition in decreasing LDL-C concentration came from the identification of loss-of-function (LOF) mutations and common polymorphisms associated with lower LDL-C levels. LOF mutations were associated with reductions in LDL-C [16, 17] and with reductions in the risk of coronary heart disease (CHD) [17, 18]. The improvement of CHD risk was larger than predicted with similar LDL-C reductions in statin trials [1, 2]. This fact could be explained by the effect of long-term exposure to lower LDL-C beginning early in life. This is also in agreement with the results of a Mendelian randomization analysis, in which long-term exposure to lower LDL-C was associated with a threefold greater reduction in CHD risk than that observed during statin treatment started later in life [19].

The genetic findings have generated intensive research on functions and regulations of PCSK9 [7–13]. In summary, the major function of PCSK9 is the degradation of the LDL receptor (LDLR): secreted PCSK9 binds to the LDLR in a complex with its prosegment and is subsequently internalized together with the LDLR. The binding of PCSK9 to primarily the epidermal growth factor homology domain (EGF-A) induces a modification of LDLR conformation avoiding normal recycling of LDLR to the plasma membrane and targeting the LDLR for lysosomal degradation [20] (Fig. 9.1a). LDLR protein concentrations are increased in the liver of PCSK9 knockout mice [21]. As a result, LDLR represents the main route of elimination of PCSK9 [22]. However, plasma LDL particles also act as important extracellular partners for PCSK9 with a direct interaction between PCSK9 and LDL particles [23].

Beyond the regulation of LDLR concentrations, data support an effect of PCSK9 on lipoprotein assembly and secretion, with emerging evidence of a role in the metabolism of triglyceride-rich lipoproteins and triglyceride accumulation in visceral adipose tissue [23, 24]. The function of PCSK9 in the intestine is not completely known: PCSK9 null mice are protected from postprandial hypertriglyceridemia [25]. PCSK9 can enhance chylomicron secretion and participate in the control of enterocyte cholesterol balance [26–28].

Impact of PCSK9 on Atherosclerosis

In mice fed high-fat high-cholesterol diet, gene inactivation of PCSK9 significantly reduced the accumulation of cholesteryl esters in aortas, which was markedly increased by overexpression of PCSK9 resulting in accelerated development of

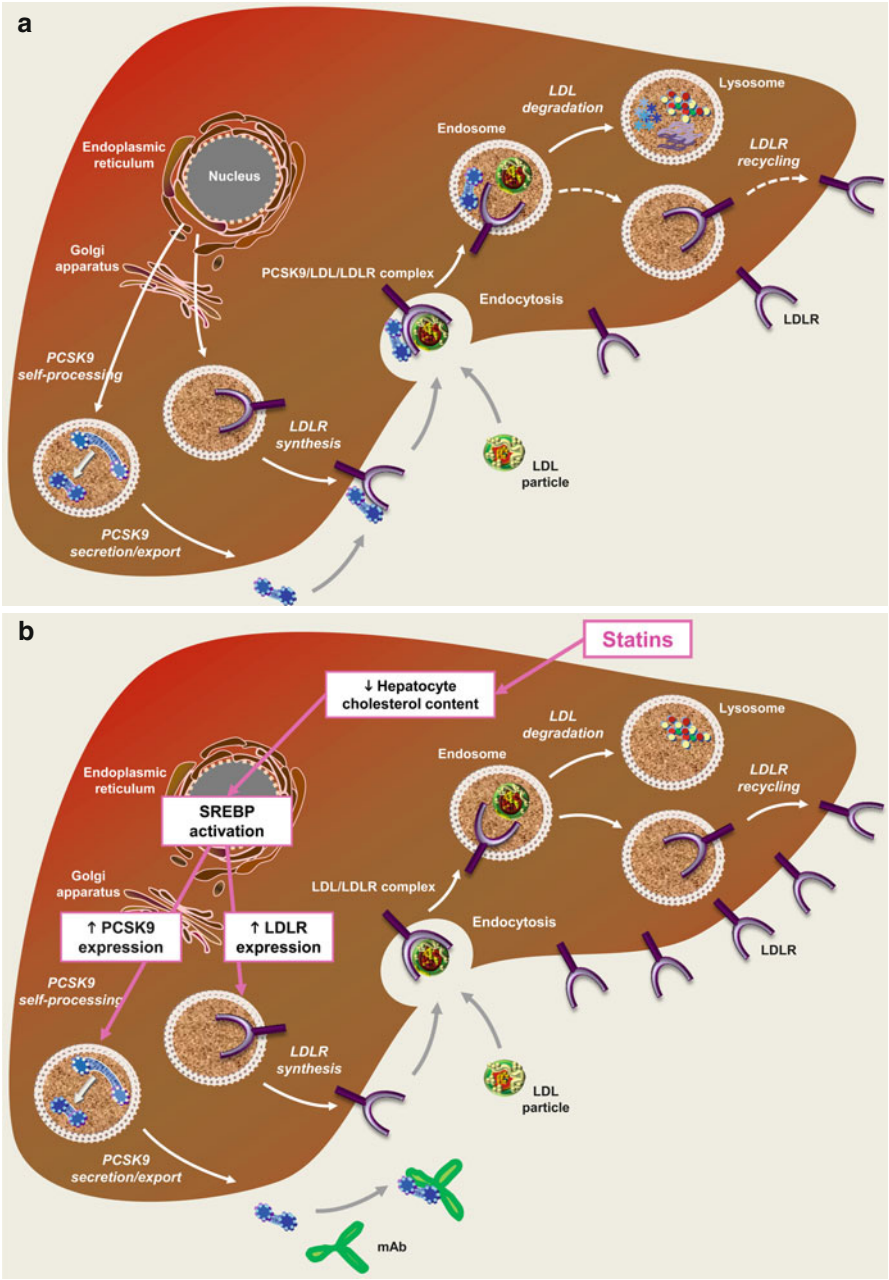

Fig. 9.1 Role of PCSK9 in the regulation of LDL-C concentrations. (**a**) PCSK9 binds to LDL Receptor (*LDLR*) and, upon internalization of the LDL/LDLR complex, directs LDLR to lysosomal degradation, decreasing the number of LDLR at the surface of hepatocyte. (**b**) Statin therapy, via SERBP2 activation, stimulates both LDLR and PCSK9 expression. Anti-PCSK9 mAb prevents binding of PCSK9 to the LDL/LDLR complex

atherosclerotic plaques [29]. Interestingly, in LDLR-deficient mice lacking or overexpressing PCSK9, no significant differences were observed in cholesteryl ester accumulation and plaque size, strongly suggesting that the process by which PCSK9 enhances atherosclerosis is primarily mediated through its action on the LDLR [29].

Cloned minipigs created by transposition of a human PCSK9 gain-of-function mutant – a model for familial hypercholesterolemia (FH) – had a significant increase in aortic atherosclerosis compared with wild-type minipigs [30]. At the opposite, inhibition of PCSK9 by a mAb, alirocumab, reduced atherosclerosis development in ApoE3Leiden. CETP mice model, and enhanced the beneficial effects of atorvastatin [31], providing an argument for statin and PCSK9 combination therapy.

The impact of PCSK9 inhibition on atherosclerotic plaques is currently evaluated by intravascular ultrasound in a large phase III trial with evolocumab, GLAGOV (GLobal Assessment of plaque reGression with a PCSK9 antibOdy as measured by intraVascular ultrasound) [32].

Rationale of Statin and PCSK9 Inhibitor Combination Therapy

PCSK9 gene expression is mainly modulated by intracellular cholesterol concentrations and consequent activation of the transcription factor sterol-responsive element-binding protein 2 (SREBP2) [21] (Fig. 9.1b), similarly to other genes involved in cholesterol homeostasis, such as LDLR. The relationship between statin treatment and PCSK9 secretion has been investigated in animals and humans. In hepatic cell lines, statins upregulated the mRNA expression of LDLR and PCSK9 [33]. Statin administration to PCSK9 knockout mice enhanced LDL clearance from plasma [21]. In humans, statins induced a dose-dependent increase in the concentration of plasma PCSK9 [34, 35]. This concomitant regulation of both PCSK9 and LDLR by cholesterol via SREBP2 helps to explain the paradoxical effect of statin therapy [36], potentially limiting the pharmacological effect of statin on LDL-C concentration. This was confirmed in patients with LOF mutations in PCSK9 gene who are more responsive to statin therapy [37]. These data support PCSK9 inhibition as a very attractive target for lowering LDL-C and enhancing the efficacy of statin treatment.

Strategies for PCSK9 Inhibition

Several therapeutic approaches to the inhibition of PCSK9 have been proposed [38], including inhibition of PCSK9 synthesis by gene-silencing agents, such as antisense oligonucleotides (ASOs) or small interfering RNA (siRNA); inhibition of PCSK9 binding to LDLR by mAbs, small peptides, or adnectins; and inhibition of PCSK9 autocatalytic processing by small molecule inhibitors. These strategies targeting either extracellular or intracellular PCSK9 have been extensively described in recent reviews [39–43].

Preclinical studies on inhibition of PCSK9 synthesis by ASOs were promising, but the development of two ASOs by BMS/ISIS (BMS-84421) and Santaris Pharma (SPC5001) was stopped in Phase I [43]. siRNA is another approach [44, 45]. In rats, siRNA targeting PCSK9 reduced LDL-C level by around 30 %, and in nonhuman primates, single-dose administration of 5 mg of the drug decreased LDL-C by 56–70 % [44]. In a phase I trial of ALN-PCS, an siRNA developed by Alnylam Pharmaceuticals, a dose-dependent reduction in LDL-C was observed, with a 40 % reduction with the highest dose, associated with a 70 % reduction in plasma PCSK9 concentrations [46]. Inhibition of PCSK9 binding to LDLR by small peptide inhibitors such as SX-PCK9 (Serometrix, East Syracuse, NY, USA) or adnectins such as BMS-962476 (BMS/Adnexus, Waltham, MA, USA) are in preclinical development or phase I [39–41]. On the basis of the discovery of a LOF mutation in the autocatalytic cleavage site of PCSK9 [47], inhibition of PCSK9 autocatalytic processing is the approach chosen by Cadila Healthcare and Shifa Biomedical [39] with molecules in preclinical development phase. Finally, mAbs [48] are the most studied and advanced approach in terms of clinical development with published phase I, II, and III human trials. An alternative approach for PCSK9 inhibition could be a peptide-based anti-PCSK9 active vaccination approach providing the opportunity for long-term LDL-C management [49].

Efficacy of PCSK9 Inhibition with mAbs

Several mAbs targeting PCSK9 have been tested in preclinical studies to assess their disruption of the PCSK9-LDLR interaction or inhibition of PCSK9 internalization [39, 43]. Human data are mainly available for three mAbs: Alirocumab (SAR236553/REGN727) and evolocumab (AMG 145), two fully human mAbs developed by Sanofi/Regeneron and Amgen, respectively, and bococizumab (RN316/PF04950615), a humanized mAb developed by Pfizer/Rinat. The data obtained in phase II have been already extensively described [11, 42, 43]: globally, in combination with a statin – and also in monotherapy – mAbs induced dramatic significant decreases in all the atherogenic lipoproteins.

Three large phase III programs have been developed with alirocumab, evolocumab, and bococizumab. The lipid-lowering phase III trials [50–73] with these three mABs are summarized in Tables 9.1, 9.2, and 9.3. Current data indicate that mAbs are very effective at lowering concentrations of atherogenic lipoproteins, with significant decreases in LDL-C, apoB, non-HDL-C, and also Lp(a) concentrations. So far, in the phase III programs, efficacy has been demonstrated

- In patients with heterozygous FH [50–52, 62] and with homozygous FH [67, 74]
- In high-risk patients not controlled by maximally tolerated statin and other lipid-lowering therapies [53–55]
- In combination with statins in patients with high LDL cholesterol [58, 59, 63, 66]
- In patients as monotherapy [56, 64]
- In patients who could not tolerate statins due to muscle-related side effects [57, 65]

Table 9.1 Lipid-lowering phase III trials with Alirocumab (ODYSSEY Programme)

Study acronym (NCT number)	Study population (number of subjects)	Duration; dosage; comparator	LDL-C reduction[a] (% change vs placebo[1] or from BL[2])	Reference/status
ODYSSEY FH I (NCT 01623115)	Heterozygous FH not controlled on maximally tolerated statin ± other LLT ($n = 486$)	78-weeks DB; 75/150 mg Q2W; placebo	−57.9[1]	Presented at the ESC congress 2014 [50]
ODYSSEY FH II (NCT 01709500)	Heterozygous FH not controlled on maximally tolerated statin ± other LLT ($n = 249$)	78-weeks DB; 75/150 mg Q2W; placebo	−51.4[1]	Presented at the ESC congress 2014 [51]
ODYSSEY HIGH FH (NCT 01617655)	Heterozygous FH on maximally tolerated statin ± other LLT and LDL-C >160 mg/dL ($n = 105$)	78-weeks DB; 150 mg Q2W; placebo	−39.1[1]	Presented at the AHA congress 2014 [52]
ODYSSEY LONG TERM (NCT 01507831)	Heterozygous FH or high CV risk patients on maximally tolerated statin ± other LLT and LDL-C ≥70 mg/dL ($n = 2341$)	78-weeks DB; 150 mg Q2W; placebo	−61.9[1]	Robinson et al. [53]
ODYSSEY COMBO I (NCT 01644175)	High CV risk patients not controlled on maximally tolerated statin ± other LLT ($n = 316$)	52-weeks DB; 75/150 mg Q2W; placebo	−45.9[1]	Presented at the AHA congress 2014 [54]
ODYSSEY COMBO II (NCT 01644188)	High CV risk patients not controlled on maximally tolerated statin ($n = 720$)	104-weeks DB; 75/150 mg Q2W; ezetimibe	−50.6[2]	Cannon et al. [55]
ODYSSEY MONO (NCT 01644174)	Hypercholesterolemic patients with moderate CV risk, not receiving any LLT ($n = 103$)	24-weeks DB; 75/150 mg Q2W; ezetimibe	−47.2[2]	Roth et al. [56]
ODYSSEY ALTERNATIVE (NCT 01709513)	Statin intolerant patients (with statin rechallenge arm) ($n = 314$)	24-weeks DB; 75/150 mg Q2W; ezetimibe	−45.0[2]	Presented at the AHA congress 2014 [57]

ODYSSEY OPTIONS I (NCT 01730040)	Patients not controlled on ATV 20 or 40 mg (n = 355)	24-weeks DB; 75/150 mg Q2W; addition of ezetimibe or doubling ATV dose or switching from ATV 40 mg to RSV 40 mg	−44.1[2] (entry ATV 20 mg) −54.0[2] (entry ATV 40 mg)	Presented at the AHA congress 2014 [58]
ODYSSEY OPTIONS II (NCT 01730053)	Patients not controlled on RSV 10 or 20 mg (n = 305)	24-weeks DB; 75/150 mg Q2W; addition of ezetimibe or doubling RSV dose	−50.6[2] (entry RSV 10 mg) −36.3[2] (entry RSV 20 mg)	Presented at the AHA congress 2014 [59]
ODYSSEY CHOICE I (NCT 01926782)	Patients (1) not controlled on maximally tolerated statin, (2) with moderate CV risk not receiving statin, or (3) with statin intolerance (n = 803)	48-weeks DB; 300 mg Q4W (or 150 mg Q2W after week 12); placebo	−52.4[1] (no statin group) −58.7[1] (statin group)	Presented at the ACC congress 2015 [60]
ODYSSEY CHOICE II (NCT 02023879)	Patients not receiving statin, but ezetimibe, fenofibrate or diet alone, with (1) statin intolerance or (2) moderate CV risk (n = 233)	24-weeks DB; 150 mg Q4W (or 150 mg Q2W after week 12); placebo	−56.4[1]	Presented at the ACC congress 2015 [61]

[a]Results at week 24 (primary efficacy endpoint)

ATV atorvastatin, *BL* baseline, *CV* cardiovascular, *DB* double-blind, *FH* familial hypercholesterolemia, *LLT* lipid lowering therapy, *Q2W* once every 2 weeks, *Q4W* once every 4 weeks, *RSV* rosuvastatin

Table 9.2 Lipid-lowering phase III trials with Evolocumab (PROFICIO Programme)

Study acronym (NCT number)	Study population (number of subjects)	Duration; dosage; comparator	LDL-C reduction[a] (% change vs placebo[1] or from BL[2])	Reference/status
RUTHERFORD-2 (NCT 01763918)	Heterozygous FH not controlled (LDL-C ≥100 mg/dL) on statin ± other LLT[b] ($n = 331$)	12-weeks DB; 140 mg Q2W or 420 mg Q4W; placebo	−59.2[1] (Q2W) −61.3[1] (Q4W)	Raal et al. [62]
DESCARTES (NCT 01516879)	Hypercholesterolemic patients on LLT with diet alone or diet plus ATV 10 mg, ATV 80 mg or ATV 80 mg plus EZE 10 mg, and LDL-C ≥75 mg/dL ($n = 905$)	52-weeks DB; 420 mg Q4W; placebo	−55.7[1] (diet alone) −61.6[1] (entry ATV 10 mg) −56.8[1] (entry ATV 80 mg) −48.5[1] (entry ATV 80 mg + EZE 10 mg)	Blom et al. [63]
MENDEL −2 (NCT 01763827)	Patients with LDL-C ≥100 and <190 mg/dL and Framingham risk score ≤10% ($n = 614$)	12-weeks DB; 140 mg Q2W or 420 mg Q4W; placebo or ezetimibe	−56.5[1] (Q2W) −57.4[1] (Q4W)	Koren et al. [64]
GAUSS-2 (NCT 01763905)	Statin intolerant patients ($n = 307$)	12-weeks DB; 140 mg Q2W or 420 mg Q4W; ezetimibe	−56.1[2] (Q2W) −52.6[2] (Q4W)	Stroes et al. [65]
LAPLACE-2 (NCT 01763866)	Hypercholesterolemic patients on statin therapy (moderate- or high-intensity) ($n = 1899$)	12-weeks DB; 140 mg Q2W or 420 mg Q4W; placebo or ezetimibe	−76.3[1] (Q2W) −70.5[1] (Q4W) (entry ATV 80 mg) −68.3[1] (Q2W) −55.0[1] (Q4W) (entry RSV 40 mg) −71.4[1] (Q2W) −59.2[1] (Q4W) (entry ATV 10 mg) −70.6[1] (Q2W) −60.4[1] (Q4W) (entry SIM 40 mg) −68.2[1] (Q2W) −64.5[1] (Q4W) (entry RSV 5 mg)	Robinson et al. [66]

TESLA (Part B) (NCT 01588496)	Homozygous FH on LLT and not receiving LDL-apheresis (n = 50)	12-weeks DB; 420 mg Q4W; placebo	−30.9[l]	Raal et al. [67]
TAUSSIG (NCT 01624142)	Homozygous and heterozygous FH (n = 310)	Open-label trial; 140 mg Q2W or 420 mg Q4W	NA	Ongoing [68]

[a]Results at week 12 (primary efficacy endpoint), excepted for DESCARTES (week 52)
[b]exclusion of fibrates
ATV atorvastatin, *BL* baseline, *DB* double-blind, *EZE* ezetimibe, *FH* familial hypercholesterolemia, *LLT* lipid lowering therapy, *NA* not available, *Q2W* once every 2 weeks, *Q4W* once every 4 weeks, *RSV* rosuvastatin, *SIM* simvastatin

Table 9.3 Lipid-lowering phase III trials with Bococizumab (SPIRE Programme)

Study acronym (NCT number)	Study population (number of subjects)	Duration; dosage; comparator	Reference/status
SPIRE-FH (NCT 01968980)	Heterozygous FH receiving highly effective statins ($n = 300$)[a]	52-weeks DB; 150 mg Q2W; placebo	Ongoing [69]
SPIRE-HR (NCT 01968954)	Hypercholesterolemic patients receiving highly effective statins ($n = 600$)[a]	52-weeks DB; 150 mg Q2W; placebo	Ongoing [70]
SPIRE-LDL (NCT 01968967)	Hypercholesterolemic patients receiving highly effective statins ($n = 1932$)[a]	52-weeks DB; 150 mg Q2W; placebo	Ongoing [71]
SPIRE-LL (NCT 02100514)	Hyperlipidemic patients receiving background statin therapy ($n = 690$)[a]	52-weeks DB; 150 mg Q2W; placebo	Ongoing [72]
SPIRE-SI (NCT 02135029)	Statin intolerance ($n = 150$)[a]	24-weeks DB; 150 mg Q2W; placebo or atorvastatin	Ongoing [73]

[a]estimated number
DB double-blind, *FH* familial hypercholesterolemia

These mAbs are administered as subcutaneous (SC) injections, with various doses and strategies: in the ODYSSEY program, alirocumab SC injections are mainly realized every 2 weeks (Q2W). Two doses, 75 and 150 mg, have been tested in the majority of phase III trials, with the possibility to uptitrate alirocumab from 75 to 150 mg Q2W depending on LDL-C goal achievement. The frequency of injections every 4 weeks (Q4W) and the dose of 300 mg Q4W have been recently evaluated in CHOICE trials [60, 61]. In the PROFICIO program, two doses of evolocumab have been tested, 140 mg Q2W and 420 mg Q4W [62–68]. Finally, the SPIRE program is conducted with bococizumab 150 mg Q2W.

Globally, in combination with a statin, mAbs decrease LDL-C levels by 39–61 % in heterozygous FH and by 46–76 % in other hypercholesterolemic patients.

In the TESLA trial, the mean decrease in LDL-C is – as expected – less in patients with homozygous FH [67], with a greater response on evolocumab (–40.8 % in LDL-C) in patients defective in one or both alleles, providing a new complementary therapeutic strategy to treat these very high patients.

Moreover, treatment with mAbs induces a significant decrease in Lp(a) levels. A pooled analysis from 1359 patients in 4 phase II trials showed a dose-dependent reduction of Lp(a) levels with evolocumab (–29.5 and –24.5 % with 140 mg Q2W and 420 mg Q4W respectively) [75]. Complementary studies are needed to characterize the mechanism underlying this effect and to determine the clinical relevance of the Lp(a) reducing effect. However, especially considering that current therapies effective in reducing Lp(a) are limited to mipomersen (an anti-apoB antisense oligonucleotide) or lomitapide (an MTP inhibitor) [76], PCSK9 inhibitors might be an effective option to improve the CVD risk of patients with elevated Lp(a) plasma levels.

Safety and Tolerability of PCSK9 Inhibition with mAbs

Overall, the mAbs tested so far have been generally safe and well tolerated, with no major safety issues and no differences in the rate of adverse events (AEs) between treatment and placebo groups from completed phase II and III studies.

In all of the phase 2 studies, alirocumab was generally well tolerated over the treatment period [8–12 weeks]. Injection-site reactions were the most common AEs in two of the phase II trials but were generally mild in severity and transient. However, in the phase II study assessing alirocumab for treatment of FH [77], one patient in the group of 300 mg dose Q4W discontinued treatment after the first dose due to injection-site reaction and generalized pruritus. In another phase II trial [78], one patient receiving atorvastatin 80 mg plus alirocumab 150 mg Q2W discontinued treatment due to a hypersensitivity reaction and rash occurring 12 days after the second injection of mAb. There was a single case of cutaneous leukocytoclastic vasculitis reported in one patient, 9 days after initiation of alirocumab 300 mg [79]. The patient responded rapidly to withdrawal of the drug and initiation of steroid therapy.

Evolocumab was also generally well tolerated throughout the phase II trials, with a similar incidence of drug-related AEs across treatment groups and no

evidence of a relationship between the incidence of any AEs and evolocumab dose [42]. Small numbers of serious adverse events (SAEs) occurred, but none was considered related to the treatment. Injection-site reactions were generally infrequent and mild. Of the 1359 randomized patients in the evolocumab phase II parent studies, 1104 (81 %) elected to enroll in the OSLER study, open trial designed to evaluate mainly longer-term safety. Patients were randomized 2:1 to receive either open-label SC evolocumab 420 mg Q4W with standard of care or standard of care alone [80]. In the OSLER trial, AE occurred in 81.4 % of evolocumab-treated patients and in 73.1 % of patients in the standard of care group. SAE occurred in 7.1 % of patients in the evolocumab group and 6.3 % in the standard of care group. An injection-site reaction was reported in 5.2 % of patients in the evolocumab group. In a specific analysis of the frequency of AEs by LDL-C value on evolocumab treatment, an imbalance appeared in memory impairment in patients with LDL-C <50 mg/dL: four patients (1 %) compared to one patient (0.3 %) in evolocumab subgroup with LDL-C ≥50 mg/dL and zero in the standard of care group. This finding seems at the origin of the request from FDA to make an assessment of potential neurocognitive AEs across the phase III development program for all the mAbs against PCSK9, especially in the longer-term studies.

Indeed, more information on safety and tolerability has been obtained from phase III programs of alirocumab [50–61] and evolocumab [62–67], especially

Table 9.4 Ongoing cardiovascular outcomes phase III trials with PCSK9 monoclonal antibodies

Compound	Trial	Population (main eligibility criteria)	Number of patients	Reference
Alirocumab	ODYSSEY – OUTCOMES (NCT 01663402)	Recent (<52 weeks) ACS requiring hospitalization LDL-C >70 mg/dL	18,000	[81]
Bococizumab	SPIRE-1 (NCT 01975376)	High risk patients on LLT LDL-C ≥70 and <100 mg/dL or non-HDL-C ≥100 and <130 mg/dL	17,000	[82]
	SPIRE-2 (NCT 01975389)	High risk patients on LLT LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL	9000	[83]
Evolocumab	FOURIER (NCT 01764633)	Secondary prevention and high risk of CVD LDL-C ≥70 mg/dL or non-HDL-C ≥ 100 mg/dL	27,500	[84]

ACS acute coronary syndrome, *CVD* cardiovascular disease, *LLT* lipid lowering therapy

from the longer-term ODYSSEY LONG TERM [53] and DESCARTES [63] trials. In the DESCARTES trial conducted in 901 patients (599 on evolocumab 420 mg Q4W, 302 on placebo) during 52 weeks, the overall incidence of AEs was similar in the evolocumab group and the placebo group. The most common AEs in the evolocumab group were nasopharyngitis, upper respiratory tract infection, influenza, and back pain. Injection-site reactions were reported in 5.7 % of patients in the evolocumab group and 5.0 % of patients in the placebo group [63].

In the ODYSSEY LONG TERM trial [53], 2341 patients were randomized to receive either alirocumab 150 mg Q2W (n = 1553) or placebo (n = 788) for 78 weeks: similar percentages of patients experienced AEs in both treatment groups (81 % with alirocumab versus 83 % with placebo). AEs leading to study-drug discontinuation occurred in 7.2 % of alirocumab patients and 5.8 % of placebo patients. There were differences between the alirocumab and placebo groups in rates of injection-site reactions (5.9 % versus 4.2 %, respectively), myalgia (5.4 % versus 2.9 %, respectively), neurocognitive events (1.2 % versus 0.5 %, respectively), and ophthalmologic events (2.9 % versus 1.9 %, respectively). Of note, the utility of the neurocognitive findings in ODYSSEY LONG TERM is limited by the lack of formal neurocognitive testing in this study.

Due to the magnitude of the LDL-C lowering with mAbs against PCSK9, very low LDL-C levels are frequently observed, with putative concerns regarding the long-term safety, especially for cognitive function and hormonal insufficiency. In the ODYSSEY LONG TERM trial [53], 575 patients (38 %) had 2 consecutive LDL-C levels <25 mg/dL. No specific safety signal appeared for this category of patients, including levels of cortisol and fat-soluble vitamins.

PCSK9 Inhibition: Future Perspectives

A number of important questions will need to be resolved in the future. The main objective being the prevention of CV events, it has been interesting to observe in a post hoc analysis of ODYSSEY LONG TERM trial a significant reduction of major CV events (CHD death, myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization) with alirocumab [53]. However, the number of CV events was relatively small. Consequently, the CV benefit in relation to the lowering effect of atherogenic lipoproteins must be evaluated in specific CV outcome trials. Several trials are ongoing, including large populations of high-risk patients (Table 9.4). These large ongoing trials are also critical to obtain long-term safety data, as patients will probably need lifelong treatment. Even if antidrug antibodies were rare in phase II and III trials, experience with other mAbs suggests that the development of antidrug antibodies could reduce clinical efficacy and increase the incidence of AEs [85]. Systematic monitoring of antibody development and AEs will be needed in the large ongoing trials listed in Table 9.4.

Given that PCSK9 is also expressed in organs other than the liver, such as the intestines, nervous system, or pancreas, the potential of AEs associated with PCSK9

inhibition has been raised. For example, it was reported that PCSK9-deficient mice exhibit impaired glucose tolerance and pancreatic islet abnormalities [86]. Other studies have also suggested that PCSK9 inhibition might increase susceptibility to hepatic viruses [87] and visceral adiposity [24]. Beyond the data expected in ongoing outcome trials, the consequence of PCSK9 inhibition in patients with type 2 diabetes, metabolic syndrome, and combined hyperlipidemia should be carefully examined.

PCSK9 Inhibition: Candidate Populations

Before the completion of the ongoing CV outcome studies, it appears important to define the candidate patient populations for PCSK9 inhibition mAbs, mainly in combination with statin therapy.

Undoubtedly, FH should be considered the priority group. Even if a reduction in mortality has been reported for homozygous FH receiving statin therapy [88], it remains very difficult to treat these patients for which the standard treatment should be a combination of LDL apheresis if available and maximum tolerated statin treatment (with or without ezetimibe) [89]. Homozygous FH with at least one defective LDLR allele and also rare homozygous FH with apoB mutation are certainly candidates for PCSK9 inhibitors. At the opposite, patients with negative/negative LDLR mutations do not respond, and other strategies should be proposed such as lomitapide or mipomersen [76].

Severe heterozygous FH is the second category of patient candidates for PCSK9 inhibition. This disease is underdiagnosed and undertreated in the majority of countries [90]. Data from Netherlands (one of the countries with a high percentage of diagnosed FH) have shown that only 21 % of heterozygous FH patients achieved the minimum goal of LDL-C <100 mg/dL (2.5 mmol/L) [91]. Moreover, in recent data from Norway, despite prescription of lipid-lowering drugs, FH patients still had significantly increased CVD mortality compared to the general Norwegian population [92].

The next categories of candidate patients for PCSK9 inhibition are patients in secondary prevention not at LDL-C goals on maximally tolerated lipid-lowering therapy. Even on maximum statin therapy, the proportion of patients not reaching the European goals remains high, with a large variability in response to statin treatment [5]. As a greater progression of atherosclerosis has been observed in patient hyporesponders to statin therapy [93], it seems important to identify this category of patients in routine clinical practice. This category of candidate patients for PCSK9 inhibition includes very high-risk patients (mainly secondary prevention) who experience AEs on high statin dose, and are treated with a usual daily low dose of statin, and also patients who are only able to tolerate an efficacious statin (mainly atorvastatin or rosuvastatin) with alternate day or once/twice weekly dosing regimen. For all these categories of patients in secondary prevention, not at LDL-C goal on maximally tolerated lipid-lowering therapy, the cost/benefit ratio will be an

important issue. The challenge shall be to determine the priorities, especially before the results of CV outcome trials (patients far from the goals, patients with a recurrent CV event, patients with higher residual risk due to associated risk factors such as diabetes, etc.).

Conclusion

PCSK9 is a key player in LDL metabolism mainly by enhancing degradation of LDLR in the liver. The reduced incidence of CVD in patients with PCSK9 LOF mutations provides a strong rationale for the development of PCSK9 inhibitors. The inhibition of PCSK9 is the most attractive new approach to reducing atherogenic lipoproteins and enhancing the efficacy of statins. Phase II and III trials have shown that mAbs are very effective and well tolerated: mAbs against PCSK9 produce a 40–70 % reduction in the LDL-C level when combined with a statin. The ongoing CV outcome trials will provide the needed information on the efficacy of PCSK9 inhibition with mAbs in combination with a statin in reducing CVD events and on the long-term safety of this promising therapeutic approach for the treatment of patients with CVD or at risk for CVD not controlled by conventional lipid-lowering therapies.

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References

1. Baigent C, Keech A, Kearney P, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267–78.
2. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
3. Reiner Z, Catapano AL, De Backer G, et al. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2011;32:1769–818.
4. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerosis cardiovascular risk in adults. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Circulation. 2014;129(25 Suppl 2):S1–S45.
5. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events. A meta-analysis of statin trials. J Am Coll Cardiol. 2014;64:485–94.

6. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy – European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J. 2015;36:1012–22.
7. Seidah NG, Awan Z, Chrétien M, Mbikay M. PCSK9: a key modulator of cardiovascular health. Circ Res. 2014;114:1022–36.
8. Lambert G, Sjouke B, Choque B, Kastelein JJP, Hovingh GK. The PCSK9 decade. J Lipid Res. 2012;53:2515–24.
9. Norata GD, Tibolla G, Catapano AL. PCSK9 inhibition for the treatment of hypercholesterolemia: promises and emerging challenges. Vascul Pharmacol. 2014;62:103–11.
10. Urban D, Pöss J, Böhm M, Laufs U. Targeting the proprotein convertase subtilisin/kexin type 9 (PCSK9) for the treatment of dyslipidemia and atherosclerosis. J Am Coll Cardiol. 2013;62:1401–8.
11. Farnier M. PCSK9: from discovery to therapeutic applications. Arch Cardiovasc Dis. 2014;107:58–66.
12. Marais AD, Kim JB, Wasserman SM, Lambert G. PCSK9 inhibition in LDL cholesterol reduction: genetics and therapeutic implications of very low plasma lipoprotein levels. Pharmacol Ther. 2015;145:58–66.
13. Cui C-J, Li S, Li J-J. PCSK9 and its modulation. Clin Chim Acta. 2015;440:79–86.
14. Seidah NG, Prat A. The biology and therapeutic targeting of the proprotein convertases. Nat Rev Drug Discov. 2012;11:367–83.
15. Abifadel M, Varret M, Rabes JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34:154–6.
16. Cohen J, Pertsemlidis A, Korowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet. 2005;37:161–5.
17. Cohen JC, Boerwinkle E, Mosley Jr TH, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006;354:1264–72.
18. Benn M, Nordestgaard BG, Grande P, Schnohr P, Tybjaerg-Hansen A. PCSK9 R46L, low-density lipoprotein cholesterol levels, and risk of ischemic heart disease: 3 independent studies and meta-analyses. J Am Coll Cardiol. 2010;55:2833–42.
19. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease. J Am Coll Cardiol. 2012;60:2631–9.
20. Surdo PL, Bottomley MJ, Calzetta A, et al. Mechanistic implications for LDL receptor degradation from the PCSK9/LDLR structure at neutral pH. EMBO Rep. 2011;12:1300–5.
21. Rashid S, Curtis DE, Garuti R, et al. Decreased plasma cholesterol and hypersentivity to statins in mice lacking PCSK9. Proc Natl Acad Sci U S A. 2005;102:5374–9.
22. Tavori H, Fan D, Blakemore JL, et al. Serum PCSK9 and cell surface low-density lipoprotein receptor: evidence for a reciprocal regulation. Circulation. 2013;127:2403–13.
23. Tavori H, Rashid S, Fazio S. On the function and homeostasis of PCSK9: reciprocal interaction with LDLR and additional lipid effects. Atherosclerosis. 2015;238:264–70.
24. Roubtsova A, Munkonda MN, Awan Z, et al. Circulating proprotein convertase subtilisin/kexin 9 (PCSK9) regulates VLDLR protein and triglyceride accumulation in visceral adipose tissue. Arterioscler Thromb Vasc Biol. 2011;31:785–91.
25. Le May C, Kourimate S, Langhi C, et al. Proprotein convertase subtilisin/kexin type 9 null mice are protected from postprandial triglyceridemia. Arterioscler Thromb Vasc Biol. 2009;29:684–90.
26. Levy E, Ouadda ABD, Spahis S, et al. PCSK9 plays a significant role in cholesterol homeostasis and lipid transport in intestinal epithelial cells. Atherosclerosis. 2013;227:297–306.
27. Rashid S, Tavori H, Brown P, et al. PCSK9 promotes intestinal overproduction of triglyceride-rich apolipoprotein-b lipoprotein through both LDL-receptor dependent and independent mechanisms. Circulation. 2014;130:431–41.

28. Le May C, Berger JM, Lespine A, et al. Transintestinal cholesterol excretion is an active metabolic process modulated by PCSK9 and statin involving ABCB1. Arterioscler Thromb Vasc Biol. 2013;33:1484–93.
29. Denis M, Marcinkiewicz J, Zaid A, et al. Gene inactivation of PCSK9 reduces atherosclerosis in mice. Circulation. 2012;125:894–901.
30. Al-Mashhadi RH, Sorensen CB, Kragh PM, et al. Familial hypercholesterolemia and atherosclerosis in cloned minipigs created by DNA transposition of a human PCSK9 gain-of-function mutant. Sci Transl Med. 2013;5:166ra1.
31. Kühnast S, van der Hoorn JWA, Pieterman EJ, et al. Alirocumab inhibits atherosclerosis, improves the plaque morphology, and enhances the effects of a statin. J Lipid Res. 2014;55:2103–12.
32. www.clinicaltrials.gov. NCT 01813422. Accessed on March 2015.
33. Dubuc G, Chamberland A, Wassef H, et al. Statins upregulate PCSK9, the gene encoding the proprotein convertase neural apoptosis-regulated convertase-1 implicated in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2004;24:1454–9.
34. Careskey HE, Davis RA, Alborn WE, Troutt JS, Cao G, Konrad RJ. Atorvastatin increases human serum levels of proprotein convertase subtilisin/kexin type 9. J Lipid Res. 2008;49:394–8.
35. Welder G, Zineh I, Pacanowski MA, Troutt JS, Cao G, Konrad RJ. High-dose atorvastatin causes a rapid sustained increase in human serum PCSK9 and disrupts its correlation with LDL cholesterol. J Lipid Res. 2010;51:2717–21.
36. Farnier M. The role of proprotein convertase subtilisin/kexin type 9 in hyperlipidemia. Focus on therapeutic implications. Am J Cardiovasc Drugs. 2011;11:145–52.
37. Berge KE, Ose L, Leren TP. Missense mutations in the PCSK9 gene are associated with hypocholesterolemia and possibly increased response to statin therapy. Arterioscler Thromb Vasc Biol. 2006;26:1094–100.
38. Hedrick JA. Targeting PCSK9 for the treatment of hypercholesterolemia. Curr Opin Investig Drugs. 2009;10:938–46.
39. Rhainds D, Arsenault BJ, Tardif J-C. PCSK9 inhibition and LDL cholesterol lowering: the biology of an attractive therapeutic target and critical review of the latest clinical trials. Clin Lipidol. 2012;7:621–40.
40. Seidah NG. PCSK9 as a therapeutic target of dyslipidemia. Expert Opin Ther Targets. 2009;13:19–28.
41. Hooper AJ, Burnett JR. Anti-PCSK9 therapies for the treatment of hypercholesterolemia. Expert Opin Biol Ther. 2013;13:429–35.
42. Farnier M. PCSK9 inhibitors. Curr Opin Lipidol. 2013;24:251–8.
43. Dadu RT, Ballantyne CM. Lipid lowering with PCSK9 inhibitors. Nat Rev Cardiol. 2014;11:563–75.
44. Frank-Kamenetsky M, Grefhorst A, Anderson NN, et al. Therapeutic RNAi targeting PCSK9 acutely lowers plasma cholesterol in rodents and LDL cholesterol in nonhuman primates. Proc Natl Acad Sci U S A. 2008;105:11915–20.
45. Ason B, Tep S, Davis Jr HR, et al. Improved efficacy for ezetimibe and rosuvastatin by attenuating the induction of PCSK9. J Lipid Res. 2011;52:679–87.
46. Fitzgerald K, Frank-Kamenetsky M, Shulga-Morskaya S, et al. Effect of a RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomized, single-blind, placebo-controlled, phase 1 trial. Lancet. 2014;383:60–8.
47. Mayne J, Dewpura T, Raymond A, et al. Novel loss-of-function PCSK9 variant is associated with low plasma LDL cholesterol in a French-Canadian family and with impaired processing and secretion in cell culture. Clin Chem. 2011;57:1415–23.
48. Chan JCY, Piper DE, Cao Q, et al. A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates. Proc Natl Acad Sci U S A. 2009;106:9820–5.

49. Galabova G, Brunner S, Winsauer G, et al. Peptide-based anti-PCSK9 vaccines-an approach for long-term LDL-C management. PLoS One. 2014;9, e114469.
50. www.clinicaltrials.gov. NCT 01623115. Accessed on March 2015.
51. www.clinicaltrials.gov. NCT 01709500. Accessed on March 2015.
52. www.clinicaltrials.gov. NCT 01617655. Accessed on March 2015.
53. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of Alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1489–99.
54. www.clinicaltrials.gov. NCT 01644175. Accessed on March 2015.
55. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J. 2015;36:1186–94.
56. Roth EM, Taskinen MR, Ginsberg HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. Int J Cardiol. 2014;176:55–61.
57. www.clinicaltrials.gov. NCT 01709513. Accessed on March 2015.
58. Bays H, Gaudet D, Weiss R, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS 1 randomized trial. J Clin Endocrinol Metab 2015; June 1: online. www.clinicaltrials.gov. NCT 01730040. Accessed on March 2015.
59. www.clinicaltrials.gov. NCT 01730053. Accessed on March 2015.
60. www.clinicaltrials.gov. NCT 01926782. Accessed on March 2015.
61. www.clinicaltrials.gov. NCT 02023879. Accessed on March 2015.
62. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolemia (RUTHERFORD-2): a randomized, double-blind, placebo-controlled trial. Lancet. 2015;385:331–40.
63. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014;370:1809–19.
64. Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia – the MENDEL-2 randomized, controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014;63:2531–40.
65. Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014;63:2541–8.
66. Robinson JG, Nedergaard BS, Rogers WJ, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in Patients with hypercholesterolemia. JAMA. 2014;311:1870–82.
67. Raal FJ, Honarpour N, Blom DK, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B); a randomized, double-blind, placebo-controlled trial. Lancet. 2015;385:341–50.
68. www.clinicaltrials.gov. NCT 01588496. Accessed on March 2015.
69. www.clinicaltrials.gov. NCT 01968980. Accessed on March 2015.
70. www.clinicaltrials.gov. NCT 01968954. Accessed on March 2015.
71. www.clinicaltrials.gov. NCT 01968967. Accessed on March 2015.
72. www.clinicaltrials.gov. NCT 02100514. Accessed on March 2015.
73. www.clinicaltrials.gov. NCT 02135029. Accessed on March 2015.
74. Stein EA, Honarpour N, Wasserman SM, XU F, Scott R, Raal FJ. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. Circulation. 2013;128:2113–20.
75. Raal FJ, Giugliano RP, Sabatine MS, et al. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials. J Am Coll Cardiol. 2014;63:1278–88.

76. Rader DJ, Kastelein JJ. Lomitapide and mipomersen: two first-in-class drugs for reducing low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. Circulation. 2014;129:1022–32.
77. Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, REG727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Lancet. 2012;380:29–36.
78. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med. 2012;367:1891–900.
79. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J Am Coll Cardiol. 2012;59:2344–53.
80. Koren MJ, Giugliano P, Raal FJ, et al. Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia. 52-week results from the open-label study of long term evaluation against LDL-C (OSLER) randomized trial. Circulation. 2014;129:234–43.
81. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY Outcomes trial. Am Heart J. 2014;168:682–9. e1.
82. www.clinicaltrials.gov. NCT 01975376. Accessed on March 2015.
83. www.clinicaltrials.gov. NCT 01975389. Accessed on March 2015.
84. www.clinicaltrials.gov. NCT 01764633. Accessed on March 2015.
85. Catapano AL, Papadopoulos N. The safety of therapeutic monoclonal antibodies: Implications for cardiovascular disease and targeting the PCSK9 pathway. Atherosclerosis. 2013;228:18–28.
86. Mbikay M, Sirois F, Mayne J, et al. PCSK9-deficient mice exhibit impaired glucose tolerance and pancreatic islet abnormalities. FEBS Lett. 2010;584:701–6.
87. Labonte P, Begley S, Guevin C, et al. PCSK9 impedes hepatitis C virus infection in vitro and modulates liver CD81 expression. Hepatology. 2009;50:17–24.
88. Raal FJ, Pilcher GJ, Panz VR, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation. 2011;124:2202–7.
89. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolemia of the European Atherosclerosis Society. Eur Heart J. 2014;35:2146–57.
90. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholestrolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Eur Heart J. 2013;34:3478–90.
91. Pijlman AH, Huijgen R, Verhagen SN, et al. Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: a large cross-sectional study in The Netherlands. Atherosclerosis. 2010;209:189–94.
92. Mundal L, Sarancic M, Ose L, et al. Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992–2010. J Am Heart Assoc. 2014;3:e001236.
93. Kataoka Y, St John J, Wolski K, et al. Atheroma progression in hyporesponders to statin therapy. Arterioscler Thromb Vasc Biol. 2015;35:990–5. Doi:10.1161.

Chapter 10
Other Possible Drug Combinations for Dyslipidemia

Karam Kostner

Introduction

Statin therapy has become a cornerstone to stabilize, reduce, and prevent atherosclerosis. Despite the success of the statins very few additional agents have been successfully developed and introduced for LDL-C lowering, ezetimibe as a cholesterol absorption inhibitor being the exception [1]. Other promising lipid lowering agents such as fibrates and niacin have failed to provide mortality benefits in large clinical trials and are only used in selected clinical settings such as severe hypertriglyceridemia and residual diabetic dyslipidemia.

Since most of the clinical benefit has been shown for LDL reduction, new and additional LDL-C lowering agents are needed for the following reasons:

(a) Several clinical end point trials have confirmed that greater LDL-C reduction results in more CVD risk reduction [2].
(b) Clinical and practice guidelines continue to propose aggressive LDL-C reduction in high and even lower risk CHD patients and with current therapies many patients cannot achieve these goals [3].
(c) Special patient groups, such as those with genetic hypercholesterolemia or elevated Lp(a), often require significantly greater LDL-C reductions [4].
(d) There are a growing number of statin-intolerant patients in whom there are limited alternatives to achieving acceptable LDL-C reductions [5].

In addition, therapies targeting HDL and Lp(a) are also being developed for residual risk reduction. Currently several of these therapies have made it into clinical trials. Whereas traditionally these drugs have been small molecules for oral therapy, a significant amount of these new drugs are biologicals such as antisense

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oligonucleotides and monoclonal antibodies etc. If these novel therapies prove to be safe and effective they can be combined with currently available lipid lowering therapies in patients with significant residual hyperlipidemia or intolerances to currently available drugs.

Mipomersen, PCSK9 inhibitors, and CETP inhibitor combinations have been discussed in previous chapters of this book. This chapter will focus on possible combinations of currently available lipid lowering agents with MTP inhibitors, thyromimetics, squalene synthase inhibitors, and Lp(a) lowering therapies.

Microsomal Triglyceride Transfer Protein Inhibitors (MTPi)

Microsomal triglyceride transport protein (MTP) is a lipid transfer protein localized in the endoplasmatic reticulum (ER) of hepatocytes and enterocytes, which plays a critical role in lipoprotein lipidation of Apo B. It is vital to the formation of chylomicrons, VLDL, and their downstream lipoproteins including remnants, IDL, and LDL.

Since the discovery of MTP deficiency as the cause of a rare inherited disorder associated with very low levels of LDL-C, called abetalipoproteinemia [6], this enzyme has been a therapeutic target. Abetalipoproteinemia is also characterized by fat malabsorption, steatorrhea, and hepatic steatosis.

Systemic MTPi

Early animal and human studies confirmed that MTP-inhibition reduces hepatic secretion of VLDL as well as intestinal secretion of chylomicrons [7]. Initial MTPi compounds were systemically active and inhibited the enzyme in both the liver and intestine. Although there may have been some modest differences between agents, all impacted both Apo B100 and B48 lipoprotein formation.

The first MTPi to be studied in humans, implitapide (BAY 13-9952) demonstrated significant effects on enzymes in the liver and intestine within 10 days [7]. In 2001 Farnier et al. reported a large, phase 2, dose-ranging, 4 week, double-blind, placebo-controlled and parallel-group design study, MISTRAL, comparing the efficacy and the safety of four doses of implitapide (20, 40, 80, and 160 mg/day), placebo and cerivastatin (0.3 mg/day) in patients with primary hypercholesterolemia [8]. LDL-C reductions with implitapide ranged from 8.2 % with 20 mg to 55.1 % on 160 mg ($p < 0.001$ compared to placebo), compared to a 33.3 % reduction for 0.3 mg cerivastatin and 0.2 % for placebo. In addition dose-related reductions were seen in other Apo B-related lipids, other than Lp(a). However there were also dose-related reductions in HDLc from 1.8 to 17.9 % and in Apo A1 lipoprotein from 2 to 22.3 % [8]. Adverse events increased with the dose of implitapide with an unacceptably high incidence (mainly diarrhea) in those receiving 80 and 160 mg. The percentages of patients with elevations in ALT >3 times the ULN-were 8 %, 8 %, 27 %, and

25 % in the groups receiving 20, 40, 80, and 160 mg of implitapide, respectively [8]. Subsequently further development of the compound was abandoned.

BMS-201038 was reported in a 7-day ascending-dose, phase 1 study to produce large reductions in LDL-C ranging from 54 to 86 % with doses of 25–100 mg [9]. However there was a high rate of hepatosteatosis and adverse gastrointestinal effects, although the 25 mg dose was further studied in a longer phase 2 trial. Phase 2 data has not been reported for either the BMS or Pfizer compounds but both were apparently not carried into further development for similar reasons.

After being abandoned by major pharmaceutical companies, both implitapide and BMS-201038 were provided to individual academic investigators and small studies in HoFH and severe HeFH were continued [10]. In 2005 BMS-201038 was licensed to Aegerion, and renamed AEGR-733. In 2006 the same company obtained implitapide and renamed it AEGR-427. AEGR-733 entered new phase 2 trials at significantly lower doses, 5, 7.5, and 10 mg daily than the 25 mg dose originally investigated. It was administered for 4 weeks in a dose-escalating study with two other arms, ezetimibe only and a combination of ezetimibe and AEGR-733 [11]. Dose-related reductions in Apo B and LDL-C were found; 30 % for LDL-C with 10 mg dose. Triglyceride reductions were very modest, up to 10 % with the 10 mg dose. In addition there were significant reductions from 6.5 to 9.2 % in HDL-C and 9–11 % for Apo A1 with all doses [11]. Thirty two percent of patients receiving AEGR-733 monotherapy discontinued, mainly for frequent gastrointestinal side-effects. Elevated transaminases were also common.

Similar findings have also been reported with BMS-201038/AEGR-733 in HoFH patients. Significant reductions in LDL-C up to approximately 50 % were found with the 55–80 mg dose. Again significant elevations of hepatic ALT were observed in more than 55 % of subjects even at lower starting doses. Hepatic magnetic resonance imaging (MRI) showed hepatic fat accumulation in nearly all patients, even at lower doses.

In a phase III clinical trial with lomitapide, an average LDL reduction of up to 80 % was achieved with 40–60 mg daily in homocygous FH patients, in addition triglycerides were reduced by up to 54 %. Side effects in this trial were abdominal discomfort, diarrhea, and nausea [12].

In 2012 the FDA approved lomitapide for the treatment of patients with homocygous FH.

Intestinal MTPi

SurfaceLogix developed a MTPi, SLx-4090, that was minimally absorbed with effects only in the intestinal tract. SLx-4090 is a first-in-class inhibitor of enterocytic microsomal triglyceride transfer protein (MTP), designed to overcome or reduce the inherent in systemic MTP inhibition. By inhibiting only MTP in enterocytes, the drug reduces triglycerides and cholesterol transport into the lymphatic circulation and subsequent delivery to the liver.

Results of a phase II clinical trial in combination with metformin in diabetics indicate a significant reduction of plasma triglycerides by 35 % and also found reduction in postprandial free fatty acids and HbA1c and a weight loss of 1.3 % [13].

If these trials show clinical benefit, MTP inhibitors could be combined with statins in patients with elevated LDL and Lp(a) but also with various other currently available lipid lowering agents such as ezetimibe and fibrates in cases of statin intolerance and mixed dyslipidemia.

Thyromimetics

Thyroid hormones have profound effects on lipids, mainly via stimulation of cholesterol conversion to bile acids, increase in hepatic LDL receptor expression, and stimulation of reverse cholesterol transport.

After initial trials with natural thyroid hormones, liver selective thyromimetics were developed.

Eprotirome was the first compound trialed in humans. In a 12-week phase III trial in 189 patients on statin therapy, 25–100 microg of eprotirome reduced LDL-C, TG, and Lp(a) by 22–32, 27–43, and 16–33 % respectively [14]. There was also a small reduction in HDL and no significant side effects were observed [15]. The development of the compound was, however, terminated due to safety concerns due to cartilage damage in a 12-week toxicology study in dogs.

Another thyroid hormone receptor antagonist soberitome was investigated in a phase I clinical trial and showed LDL reductions up to 41 % in healthy volunteers but the compound is no longer available [16].

Two other thyromimetic compounds VIA-3196 and ZYT1 are currently in phase I clinical trials. If these trials show clinical benefit, thyromimetics could be combined with statins in patients with elevated LDL and Lp(a) but also with various other currently available lipid lowering agents such as ezetimibe and fibrates in cases of statin intolerance and mixed dyslipidemia.

Squalene Synthase Inhibitors

While cholesterol synthesis inhibition with statins remains the most important approach to lower cholesterol to date, there are other potential opportunities for inhibition of the cholesterol synthesis but these must be prior to the cyclization and formation of squalene, a nonrecyclable compound.

One of these, squalene synthase, has been a desired target since the 1970s. However only one, lapaquistat (TAK-475) has entered advanced development [17].

In addition to lowering plasma LDL-C by upregulation of the LDL receptor, as do statins, squalene synthase inhibitors (SSI) may have the potential to reduce myalgias and other muscle-related side effects with statins. This is because SSIs

inhibit the synthetic pathway further downstream after formation of a number of key mevalonate-derived compounds involved in intracellular energy utilization. While significantly metabolized via the cytochrome P450 3A4 system, lapaquistat does not appear to have significant interactions with statins, such as simvastatin and atorvastatin which are metabolized through the same CYP 3A4 system.

Lapaquistat has been extensively studied in a large, phase 3, global development program involving well over 4,000 patients exposed to the drug mainly in a dose of 100 mg daily for up to 3 years. These have included a wide variety of hypercholesterolemic patients including those with severe homozygous and heterozygous familial hypercholesterolemia in whom lapaquistat 100 mg was added to maximal dose statin and in many patients also to ezetimibe and even bile acid sequestrants and niacin. A robust phase 2 dose-ranging trial evaluating the drug as monotherapy in approximately 60 patients per treatment arm (placebo, lapaquistat 25, 50, and 100 mg, and atorvastatin 10 mg) has been presented [18]. Significant dose-related reductions in LDL-C of 16 %, 18 %, and 26 %, respectively, compared to placebo were seen. Similar reductions were seen in Apo B lipoprotein, total cholesterol, and triglycerides, with modest increases in HDL-C [18]. When assessed in a placebo-controlled trial in combination with stable doses of atorvastatin an additional 20 % decrease in LDL-C was found [19].

Initial safety and tolerability appeared good with the 100 mg dose, even in combination with the highest dose of the most efficacious statins. However one or possibly two, patients developed both a sustained increase of >3 times the upper normal range (ULN) for ALT/AST and an increase in total bilirubin to 2 ×pULN. This combination, is viewed seriously by the FDA as an indirect indication of drug-associated hepatitis with the potential to lead to liver failure in approximately 10 % of such patients. Subsequently, Takeda terminated development in early 2008. Whether the cause of the liver abnormalities can be determined, were directly related to the compound and can be overcome, or whether other SSI will enter future clinical development remains uncertain. However lapaquistat has clearly demonstrated that inhibition of squalene synthase can achieve significant additional LDL-C reductions of approximately 20 % on top of both the highest dose of rosuvastatin and atorvastatin, even when they are combined with ezetimibe. This clearly indicates further capacity to upregulate the LDL receptor and achieve meaningful reductions in plasma LDL-C.

These drugs have the potential to be combined with statins and or ezetimibe in patients with elevated LDL and Lp(a) and can potentially also be used in patients with statin intolerance.

New Therapies Affecting Lp(a)

Recent reports on large prospective epidemiological studies strongly suggest that Lp(a) is one of the strongest risk factor for atherosclerosis and myocardial infarction and that the association might be causal [4]. Lp(a) belongs to the cholesterol ester

rich, apoB containing lipoproteins, yet its metabolism is distinct from that of LDL for the in vivo metabolism remains to be established [20].

Lp(a) plasma concentrations are influenced by numerous factors. In first instance genetic factors in the gene of apo(a) but also of other apolipoproteins strongly influence Lp(a) levels. In fact plasma Lp(a) is to >90 % inherited where the best studied kringle-4 size polymorphism accounts for >50 % of inheritance. Other factors like steroid hormones, dietary fatty acids, and vitamins have minor effects on Lp(a) levels [4]. Concerning secondary factors we know that kidney diseases cause a two to three fold increase of Lp(a) whereas liver disease is mostly associated with grossly reduced plasma Lp(a) [20].

Few established therapeutic options exist in patients with increased plasma Lp(a). In high-risk patients with elevated Lp(a), it is usually recommended to lower LDL to levels below 1.8 mmol/L [4]. Niacin and LDL apheresis are options for some patients [4]. Some newer LDL lowering therapies such as PCSK9 inhibitors and mipomersen as well as MTP inhibitors do have a significant effect on Lp(a) [4].

A novel approach to reduce Lp(a) based on our own research seems possible with agonists of the farnesoid X receptor and is currently being investigated [4].

Some of these Lp(a) lowering therapies could be combined with currently available lipid lowering drugs.

I conclude that possible combinations of currently available lipid lowering agents with MTP inhibitors, thyromimetics, squalene synthase inhibitors, and novel Lp(a) lowering therapies may be available in the future to treat residual dyslipidemias and patients with intolerance to currently available drugs.

References

1. Stein EA, Ose L, Retterstol K, et al. Further reductions in low-density lipoprotein cholesterol and C-reactive protein with the addition of ezetimibe to maximum dose rosuvastatin in patients with severe hypercholesterolemia. J Clin Lipidol. 2007;1:280–6.
2. LaRosa JC, Grundy SM, Waters DD, et al. Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425–35.
3. Davidson MH, Maki KC, Pearson TA, et al. Results of the National Cholesterol Education (NCEP) Program Evaluation ProjecT Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. Am J Cardiol. 2005;96:556–63.
4. Kostner KM, Maerz W, Kostner GM. When should we measure Lp(a)? Eur Heart J. 2013; 34:3268–76.
5. Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients – the PRIMO study. Cardiovasc Drugs Ther. 2005;19:403–14.
6. Wetterau JR, Aggerbeck LP, Bouma ME, et al. Absence of microsomal triglyceride transfer protein in individuals with abetalipoproteinemia. Science. 1992;258:999–1001.
7. Zaiss S, Gruetzmann R, Ulrich M. BAY 13-9952, an inhibitor of the microsomal triglyceride transfer protein (MTP), dose-dependently blocks the formation of atherosclerotic plaques and renders them more stable in apoE knockout mice. Circulation. 1999;100(18 Suppl 1):Abst 1343.

8. Farnier M, Stein E, Megnien S, et al. Efficacy and safety of implitapide, a microsomal triglyceride transfer protein inhibitor in patients with primary hypercholesterolemia. Abstract book of the XIV international symposium on drugs affecting lipid metabolism in New York, 9–12 Sept 2001. p. 46.
9. Chandler CE, et al. CP-346086: an MTP inhibitor that lowers plasma total, VLDL, and LDL cholesterol and triglycerides by up to 70% in experimental animals and in humans. J Lipid Res. 2003;44:1887–901.
10. Cuchel M, Bloedon LT, Szapary PO, et al. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med. 2007;356:148–56.
11. Samaha FF, McKenney J, Bloedon LT, et al. Inhibition of microsomal triglyceride transfer protein alone or with ezetimibe in patients with moderate hypercholesterolemia. Nat Clin Pract Cardiovasc Med. 2008;5:497–505.
12. Cuchel M, Meagher EA, Du Toit theron H. Efficacy and Safety of a microsomal triglyceride transfer protein inhibitor in patients with homocygous familial hypercholesterolemia: a single-arm, openlabel, phase 3 study. Lancet. 2013;381:40–6.
13. Surface logix achieves big objectives with SLx-4090 in Phase 2a clinical trial. 2008. http://www.surfacelogix.com/news/news_080129.htm. 29 Jan 2008.
14. Chennamsetty I, Claudel T, Kostner K, et al. Farnesoid X receptor represses hepatic apolipoprotein (a) gene expression: studies in humans and transgenic mice. J Clin Invest. 2011;9:45277.
15. Ladenson PH, Kristensen JD, Ridgeway EC, et al. Use of the thyroid hormone analogue eprotirome in statin treated dyslipidemia. N Engl J Med. 2010;362:906–16.
16. Scanlan TS. A case history of bench to clinic drug discovery and development. Heart Fail Rev. 2010;15:177–82.
17. Amano Y, Nishimoto T, Tozawa R, et al. Lipid-lowering effects of TAK-475, a squalene synthase inhibitor, in animal models of familial hypercholesterolemia. Eur J Pharmacol. 2003; 466:155–61.
18. Piper E, Price G, Chen Y. TAK-475, a squalene synthase inhibitor improves lipid profile in hyperlipidemic subjects. Circulation. 2006;114(18 Suppl):II-288. Abstract 1493.
19. Piper E, Price G, Munsaka M, Karim A. TAK-475, a squalene synthase inhibitor, coadministered with atorvastatin: a pharmacokinetic study. American Society for Clinical Pharmacology and Therapeutics Annual Meeting March 21–24, 2007 Anaheim. (PI-75). Clin Pharmacol Ther. 2007;91(Suppl 1):S37. Abstract.
20. Kostner K. Treatment of elevated Lp(a). Handbook of experimental pharmacology atherosclerosis, vol. 170. Springer; Berlin: 2005. p. 519–36.

Chapter 11
Statins and Nutraceuticals/Functional Food: Could They Be Combined?

Arrigo F.G. Cicero and Alessandro Colletti

Introduction

It is well known that statins are the gold standard among lipid-lowering drugs, both in primary and secondary prevention of cardiovascular disease; however they usually reduce LDL cholesterolemia of no more than 50–55 % at maximal dosage, the high dosages are often not well tolerated, and they have a limited efficacy on other lipid fractions like TG and HDL-C. For these reasons, their assumption could be associated to other natural or chemical drugs to improve their efficacy and tolerability, and to reach more ambitious therapeutic targets. The recent literature suggest that a number of nutraceuticals and functional foods have a significant lipid-lowering effect and potentially they could be associated to statin treatment in order to improve its efficacy. Of course, to choose which nutraceutical could be associated to statin treatment, it is needed to know the mechanism of action, the clinical efficacy, and obviously the tolerability for long-term use [18].

Recent preclinical and clinical evidence support the use of a certain number of lipid-lowering nutraceuticals in every day practical management of dyslipidemias.

Some nutraceuticals could also be associated to lipid-lowering drugs in order to potentiate the last ones or to reduce the dosage of non-fully tolerated drugs.

There have been studied over 40 lipid-lowering nutraceuticals and numerous clinical trials have confirmed their benefits on lipid metabolism and, consequently, on cardiovascular prognosis [55].

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The ratio and pitfalls of combination of statins and niacin and statins and omega-3 fatty acids have been deeply described in this book, respectively in Chaps. 4 and 5. So, in this chapter the available evidence on those nutraceuticals potentially effective to improve statin efficacy in a safe way.

Natural Inhibitors of Cholesterol Absorption from the Bowel

From a pharmacological point of view, the inhibition of cholesterol and biliary salt absorption by the bowel is one of the main cholesterol-lowering mechanism associated to significant reduction in statin-treated patients, typically achieved with exchange-anion resins (cholestyramin, cholestipol) or ezetimibe. Nutraceuticals with similar mechanisms of action are soluble fibers and plant sterols.

Soluble Fibers

Soluble fibers, in particular psyllium husk (but also guar, pectin, oat), lower LDL cholesterol by decreasing bowel cholesterol absorption and increasing the fractional turnover of both chenodeoxycholic acid and cholic acids [59]. Animal studies also suggest that psyllium increases activity of cholesterol 7-alpha hydroxylase, which is the rate-limiting enzyme for bile acid synthesis. Psyllium increases this activity two times faster than cellulose or oat bran and pectines [84], although this effect has never been adequately investigated in humans.

Different meta-analyses suggest that psyllium supplementation has a mild but significant dose- and time-dependent cholesterol lowering effect in hypercholesterolemic patients, with a final effect of mean decrease of LDL-cholesterolemia by 7 % for 10 g/day of supplemented fiber, without significant effect on other lipid fractions [88]. Psyllium also increases the efficacy of bile acid sequestrant drugs (even reducing their bowel side effects) [54], and phytosterols [75]. However, there are also some trials demonstrating its additive effect to the one of statins [64].

All available trials and meta-analysis confirm the overall safety of psyllium supplements. However, they could have transient gastrointestinal side effects, which are usually not severe and only mildly decrease compliance to the treatment, especially when micronized fiber is used. Entire seeds, used for the treatment of constipation, did not demonstrate lipid-lowering action, but they could exacerbate diverticulitis in patients affected by chronic diverticulosis.

A main safety concern regarding soluble fibers used as cholesterol lowering agents is the risk of interaction with the absorption of orally assumed drugs, in particular the ones with a narrow therapeutic range; some reports of reduced bioavailability are in fact available for oral antidiabetic drugs, digoxin, warfarin, lithium, iron, oral steroids, tricyclic antidepressants, carbamazepin, and other molecules [60]. For this reason it is usually suggested to assume fibers far (at least 2 h) from other medications.

Glucomannan

Glucomannan is a peculiar dietary fiber derived from tubers of the *Amorphophallus konjac* plant, commonly referred to as konjac root. It is found primarily in the tropical, sub-tropical, and temperate zones of Asia and contains large amounts of mannan, known as "Konjac mannan" or glucomannan. Glucomannan is an unabsorbable polysaccharide, composed of glucose and mannose in 1:1.6 ratio, bound through beta-1,4-glycosidic linkages [41]. It has been consumed in the Orient, especially in Japan, for at least 1000 years.

Like other gel forming fibers, it interferes with the motility and absorption of nutrients from the gut, slowing absorption of fats and glucose and interfering with gut hormones [65]. However, the activity of konjac mannan cannot be explained by a simple interaction with bile acids because it shows no in vitro or in vivo bile acid–binding activity. Rather, it appears to inhibit the active transport of cholesterol in the jejunum and the absorption of bile acids in the ileum, yielding improvements in plasma LDL and apolipoprotein B levels [86]. It has also been suggested that glucomannan increases the activity of 7-alpha-hydroxylase, an enzyme required for cholesterol conversion to bile acids [58].

A meta-analysis evaluating 14 randomized clinical trials including 531 patients concluded that glucomannan significantly reduces total cholesterol levels (weighted mean difference [WMD], −19.28 mg/dL; 95 % CI, −24.30 to −14.26), LDL cholesterol (WMD, −15.99 mg/dL; 95 % CI, −21.31 to −10.67), and triglycerides (WMD, −11.08 mg/dL; 95 % CI, −22.07 to 0.09) when compared to the placebo. However, it has no effect on HDL-cholesterol and blood pressure [78]. Glucomannan's cholesterol-lowering effects have also been evaluated in children. In a clinical study of 40 children with hypercholesterolemia, patients underwent a 1-week diet run-in phase followed by randomization to either glucomannan 1–1.5 g twice daily plus diet or diet alone for 8 weeks. Treatment with glucomannan caused a significant reduction in LDL cholesterol values from baseline compared with the control group. Specifically, significant reductions were noted in favor of girls compared with boys (LDL-C: −30 % vs −9 %, $P=0.046$) [57]. This gender-related effect has also been observed with other fibers and seems to be mediated by an interaction between sexual hormones and lipoprotein metabolism, although this has yet to be fully clarified [83].

Kojac glucomannan may reduce fat-soluble vitamin absorption while removing bile acids in humans. The absorption of vitamin E was reduced following administration of glucomannan. However, glucomannan did not interfere with the absorption of water soluble, fat-insoluble vitamin B-12 [41].

In one study measuring the effect of unavailable carbohydrates on the gastrointestinal absorption of calcium in rats during a 7–8 week period, calcium absorption was also compromised by nearly 20 %, partially by calcium-binding protein caused by the gastrointestinal transit of large amounts of undigested food [13].

As for psyllium, glucomannan may reduce the bioavailability of some oral medications, as well. Thus, it is recommended to take other medications 1 h before or 4 h after glucomannan administration [41]. The association of glucomannan with statin has now yet never directly evaluated in clinical trials.

Plant Sterols

Phytosterols are plant derived sterols or stanols (saturated sterols) with cholesterol-like chemical structure. Vegetable oils, cereals, breads, spreads, margarines, vegetables, and fruit are rich in plant sterols, while the intake of plant stanols depends mainly from cereals. The most commonly consumed phytosterols in the human diet are β-sitosterol, campesterol, stigmasterol, stanols sitostanol, and campestanol. Having a similar structure to cholesterol, phytosterols compete with cholesterol of dietary and biliary origin for incorporation into micelles in the gastrointestinal tract. Besides inhibition of bowel cholesterol absorption, they indirectly increase de novo hepatic synthesis of cholesterol, decrease hepatic and lipoprotein lipase activities, and increase serum lechitin:cholesterol acyl-transferase activity [62]. The average daily intake of plant stanols is 17–24 mg and that of plant sterols is 300 mg: these levels are too low for any significant LDL-lowering effect [79].

Recent results produced new information concerning relative efficacy of various mixtures and dose-response relationships [31]: a 2 g supplementation in phytosterols is sufficient to produce significant reduction of plasma LDL-C concentrations (around −10 %) both in normo- and hypercholesterolemic subjects. A 3 g supplementation in both plant sterols and stanols have a LDL-cholesterol lowering effect of 12 % [70]. However, their cholesterol lowering action increases in dose-dependent manner; phytostSerol consumption up to 9 g reduces serum LDL-cholesterol concentrations linearly up to 17.4 % [61], also in subjects affected by familial hypercholesterolemia [66]. The use of plant sterols/stanols in combination with statin therapy was evaluated in a meta-analysis of eight randomized clinical trials including a total of 306 patients: their addition to statins showed a favorable significant reduction in LDL cholesterol, but not HDL cholesterol or triglycerides [73].

The reduction of LDL-cholesterol mediated by sterols and stanols in combination with statin therapy is relevant, equivalent to doubling the dose of statin [35].

On the other side, miming the effect of dietary cholesterol, plant sterols could down-regulate the expression of the Niemann-Pick C1-like 1 protein, thus reducing the efficacy of ezetimibe [94]. On the short-term, plant sterols have been safely tested as lipid-lowering agents, also in children [32].

The main concern about phytosterols is their use in patients with very rare genetic phytosterolemia where the phytosterols are abnormally absorbed in the bowel. However, recent epidemiological data show that phytosterolemia is associated to cardiovascular disease risk in a linear manner, also for values strongly inferior to those observed in genetic phytosterolemia [89, 90]. In particular, recent preclinical data suggest that in apo E −/− mice serum phytosterols impaired endothelial vasodilation [91]. Moreover, since phytosterols mainly act on inhibition of lipid absorption and they are not very specific to cholesterol, they may also reduce absorption of carotenoids and fat-soluble vitamins [34]. Therefore, people using phytosterols may be advised to use adequate dosages (no more than 2 g/day) and to increase their diet intake of carotene-rich vegetables.

Probiotics

Probiotics could have a direct lipid-lowering effect, but also improving statin absorption in patients with inflammatory bowel disease or irritable bowel disease in inflammatory phase [8]. A recent meta-analysis of 13 clinical trials including 485 participants concluded that some probiotics could cause net changes in plasma total cholesterol by −6.40 mg/dL, LDL by −4.90 mg/dL, triglycerides by −3.95 mg/dL, and HDL −0.11 mg/dL [33]. Studies in the last decades have discussed the role of intestinal flora on energy metabolism and metabolic balance, specifically focusing on the balance between Bacteroidetes and Firmicutes species, the two dominant groups of beneficial bacteria in gut flora [8].

The cholesterol lowering activities of Lactobacillus, Enterococci and Bifidobacterium are not clearly defined. Supposed mechanisms are: (1) their co-precipitation with bile salts, (2) effects on bowel pH, (3) deconjugation of bile acids to be easily excreted as free bile acids by the body or binding to lipopolysaccharides on the surface of microorganisms, (4) incorporation of cholesterol into the cellular membrane, (5) microbial absorption of cholesterol, (6) fermentation of carbohydrates by microorganisms causing propanoic acid which inhibits hepatic cholesterol synthesis, (7) down regulation of NPC1L1 gene expression of cells, and (8) disruption of cholesterol micelles [7, 30, 43, 46]. On the other side, experimental studies suggest that specific improvement of microflora by supplementation of selected prebiotics could improve the lipid metabolism by activating the proglucagon-derived peptide (GLP2) [10]. Usually no safety concerns have been raised.

Inhibitors of Liver Cholesterol Synthesis

It is well known that about 90 % of circulating LDL-cholesterol depends on the liver cholesterol synthesis, and this is the reason why statins, inhibiting this process, are particularly efficacious LDL-cholesterol agents. Some nutraceuticals also exert some LDL-lowering effects related to liver inhibition of cholesterol synthesis as well, and they could have an additive effect to statins.

Monacolins

Monacolins are statin-like molecules derived by the mycotic fermentation of yeast rice from *Monascus purpureus*. Monacolins inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMGCoA) reductase. Monacolin K is in fact lovastatin. It has been used to make rice wine and as a food preservative to maintain the color and taste of fish and meat. Among all the Chinese herbal medicine with lipid-lowering activity, it is the one with the largest literature support [52].

The lipid-lowering efficacy of *M. purpureus* was tested in different clinical settings, from the general practice on relatively healthy subjects [15] to high-risk patients, such as those under antiretroviral therapy [42] or chronic kidney disease [27]. In a meta-analysis evaluating 93 randomized clinical trials (including 9625 participants), red yeast rice preparations showed short-time cholesterol lowering effects similar to those of low-dose statins [51]. In the same meta-analysis, no relevant side effects were highlighted. It is well tolerated also in statin intolerant subjects, at the dosage of 0.6–1.2–2.4 g/day red yeast rice form, with a 0.2 % monacolin K content [36]. Moreover, red yeast rice has pleiotropic effects similar than statins, such for instance antiinflammatory effect and improvement of serum level of vascular remodeling biomarkers [20].

Acting through a direct inhibition of the HMGCoA reductase, red yeast extract could potentially have the same side effects as the statins: myopathy, rhabdomyolysis, and hepatotoxiciy. In fact some cases reported occurrences of symptomatic myopathy, rhabdomyolisis in a renal transplant patient, and acute toxic hepatitis [68]. Other more common and relatively mild adverse reactions associated with red yeast rice consumption are headache, abdominal discomfort, heartburn, gas, bloating, muscle pain or damage, dizziness, and asthma. Those with liver damage and kidney problems, pregnant or lactating women, children, and people with bleeding tendency should avoid monacolins, due to lack of safety data. It also recommended that co-administration with gemfibrozil, cyclosporine, azole-antifungals, erythromycin, clarithromycin, and protease inhibitors be avoided [50], since monacolins are mostly metabolized by the cytochrome P3A4. The majority of these effects appear with the use of high red yeast rice dosages. Finally, issues with long-term safety, the wide variability of active ingredients in available formulations, and the potential toxic by-products such as mycotoxin citrinin in some cultivation conditions make it difficult for physicians to justify its use in treating hyperlipidemia [25].

Overall, at comparable dosages, the monacolin efficacy and safety profile is similar to that of statins. Because of the statin-like mechanism of action the possibility to add red yeast rice to statin treatment is limited because the risk to increase the dose-related statin adverse event risk and because the increase in statin dose is usually not associated to a linear improvement in LDL-reduction effect.

Policosanols

Policosanols are aliphatic primary alcohols mainly extracted from sugarcane (*Saccharum officinarum* L) wax. Cuban studies claim policosanol supplements significantly reduce LDL cholesterolemia by modulation of HMGCoA reductase transcription and bile acid absorption inhibition [56]. In this context, theoretically policosanols would be a favorite nutraceutical to be associated to statin treatment. However, this effect has not been confirmed by some recent randomized controlled trials carried out on more severe hypercholesterolemic patients [6]. Beyond the

characteristics of the enrolled patients, one of the reasons is most likely due to the largely variant ability of the different components of policosanols to reduce cholesterol synthesis in liver cell [76].

Garlic

Several placebo-controlled randomized clinical trials have been carried out confirming the potential antihypercholesterolemic, and antihypertriglyceridemic properties of aged garlic powder. The main mechanism of action is the inhibition of the 3-hydroxy-3-methyl-coenzyme A reductase activity, with an additive effect on the statins [1]. Recent and well-designed clinical studies reveal conflicting results about the effects of commercial garlic supplementations on lipid parameters.

A recent meta-analysis, which has been performed on 22 trials reporting total cholesterol, 17 trials reporting LDL cholesterol, and 18 trials reporting HDL cholesterol, demonstrates that garlic powder intake reduces cholesterol and LDL cholesterol significantly [47].

Another meta-analysis performed on 39 clinical trials about the effect of garlic preparations on total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides shows an 8 % reduction in total serum cholesterol after 2 months of therapy, which is associated with a 38 % reduction in risk of coronary events at 50 years of age [71].

Even if in vitro and in animal experimental models garlic extract has a significant antiplatelet effect, its use has been proven to be relatively safe in patients under warfarin treatment [53]. However, it is recommended to be discontinued at least 7–10 days prior to surgical interventions. Garlic may also trigger gastroesophageal reflux in patients with a reflux tendency and may cause mild gastrointestinal side effects. Halitosis caused by allyl-methyl-sulphite is common complaint of natural garlic ingested subjects. It should also be avoided during lactation as it may also alter the odor of the milk, thus affecting infant sucking behavior. People with an allergy to plants in the allium family may also experience allergic reactions, including anaphylaxis [39]. Garlic may also interact with saquinavir and darunavir, antiretroviral drugs used in HIV therapy, decreasing their blood levels [5].

Bergamot

Bergamot (*Citrus bergamia*) is a citrus fruit spread in Italy in the region of Calabria; its juice is characterized by high content of some flavonoid glycosides, including neoeriocitrina, neohesperidin, and naringin. It remains unclear the mechanism by which the fraction of juice to achieve its lowering-cholesterol effect, but it is likely that some derivatives of it competitively inhibit the HMG-CoA reductase enzyme, producing a decrease in the synthesis of cholesterol.

Mollace et al. observed the cholesterol-lowering efficacy of bergamot extract in diet-induced hyperlipemia in Wistar rats and in 237 patients suffering from hyperlipemia. After 30 days of treatment, the results showed that bergamot extract reduces total and LDL cholesterol levels, increases HDL cholesterol, and reduces triglycerides [63].

Furthermore, a prospective, placebo-controlled study on 77 patients with elevated serum LDL-C and triglycerides demonstrates the significant addictive effect of bergamot extract to rosuvastatin [28].

Bergamot's cholesterol-lowering properties were so tested with significant results, but the number of studies regarding these effects are yet limited and further studies are needed to confirm its properties.

Inducer of LDL-Cholesterol Excretion

One of the most physiological ways to improve the efficacy of statins is to increase the liver ability to re-uptake the circulating LDL-cholesterol and to increase its excretion with bile in the bowel. There are some nutraceutical with this mechanism of action, and in particular berberine.

Berberine

Berberine is a natural alkaloid with lipid-lowering, antidiabetic, antiinflammatory, and antiproliferative effects [24].

A 3-month treatment of 400 mg of berberine extracted from *Coptis chinensi*s reduced plasma LDL-C by 25 % and TG by 35 % in a preliminary clinical trial carried out on 91 mixed hyperlipidemic subjects [45].

Another trial evaluated a 3-month treatment with berberine (500 mg/tab) and monacolins (3 mg/tab) in 84 patients with LDL-C increased above normal value after the use of at least two different oral estroprogestins treatments: the results showed that berberine and monacolins are able also to improve lipid metabolism in oral contraceptive induced hypercholesterolemia [22].

The supposed mechanism of action is the increased expression of the liver receptor for LDL. Besides its up regulation effect on the LDL receptor, berberine could also reduce triglycerides by AMP kinase activation and MAPK/ERK pathway blocking [93]. Due to its peculiar mechanism of action not directly involving the HMCGCoA reductase, berberine has been observed to increase the cholesterol-lowering action of both simvastatin and monakolines [16, 45].

The LD50 of berberine sulfate is 25 mg/kg in mice while the one of *Berberis vulgare* is moderately high (LD50 = 2.6 ± 0.22 g/kg b.w. in mice) [14]; this data supports the use of highly purified and concentrated berberine formulations only.

Standard doses of berberine (500–1000 mg/day) are usually well tolerated and adverse reactions are rare and mild (mainly gastrointestinal discomfort). On the

contrary, high doses (>1000 mg/day) have been associated to arterial hypotension, dyspnea, flu-like symptoms, gastrointestinal discomfort, constipation, and cardiac damage [24].

The main safety issue of berberine involves the risk of some pharmacological interaction. In fact, berberine displaces bilirubin from the albumin about ten-fold more than phenylbutazone. Thus, any herb containing large amounts of berberine should be avoided in jaundiced infants and pregnant woman [11]. Thus, berberine could warfarin, thiopental, and tolbutamide from their protein binding sites, thus increasing their plasma levels [24]. However, until now, no clinical report of a significant pharmacological interaction is yet available.

Berberine can also markedly increase blood levels of cyclosporine A due to CYP3A4 and P-glycoprotein inhibition in the liver and gut wall respectively and because of an increase in gastric emptying time, thus causing increased cyclosporine A bioavailability and reduced metabolism. In renal transplant recipients taking cyclosporine 3 mg/kg twice daily, the co-administration of berberine (0.2 g/day for three times a day for 3 months) increases the mean cyclosporine A AUC by 34.5 % and its mean half-life by 2.7 h [92].

Although the main mechanism of pharmacological interaction of berberine involves CYP3A4 and intestinal P-glycoprotein, it also inhibits CYP1A1 in vitro, therefore potentially interacting with drugs metabolized by this cytochrome isoform as well [85]. The impact of this observation in clinical practice has to yet to be evaluated since the CYP1A1 metabolized drugs are relatively rare.

Soybean Proteins

Soybeans contain high-quality proteins and have been consumed for approximately 5000 years in Asian countries. The role of vegetable proteins in reducing cardiovascular risk was postulated as much as a century ago and soy products were found to be effective cholesterol-lowering agents in the last three to four decades. Several mechanisms for the lipid-lowering action of soy protein have been proposed and include increased bile acid synthesis, increased apolipoprotein B receptor activity, but also decreased cholesterol synthesis, and decreased hepatic lipoprotein secretion and cholesterol content, both associated with an increased clearance of cholesterol from the blood [29, 69]. Soy protein also reduces the insulin/glucagon ratio, which in turn down-regulates the expression of the hepatic transcription factor sterol regulatory element binding protein (SREBP)-1. The SREBP-1 reduction in turn decreases the expression of several lipogenic enzymes, thus reducing serum and hepatic triglycerides as well as LDL-C and VLDL triglycerides and liver lipotoxicity [81]. Additionally, soy components also induce the SREBP-2 regulated gene expression, which increases serum cholesterol clearance [67].

The soybean protein cholesterol lowering effect is clearly dose-related [77]. In an old, but complete, meta-analysis of 38 randomized clinical trials carried out by Anderson et al., it was estimated that, after adjustments for initial serum cholesterol

concentrations and other variables were made, the ingestion of 25 or 50 g (mean 47 g/day) of soy protein per day decreases serum cholesterol by 0.23 or 0.45 mmol/dL, respectively [4]. Thus, it was recommended to include four servings of at least 6.25g each (25 g/day) of soy protein into a low saturated fat and cholesterol diet to reduce the risk of heart disease [48]. In a more recent meta-analysis of 30 randomized clinical trials including data from 2913 subjects, 25 g (range 15–40 g/day) of soy protein reduced LDL by 6 %. Further analysis, however, showed no dose response relationship between 15 and 40 g/day [37]. The smaller effect observed in this meta-analysis is most likely due to the exclusion of studies using higher soy protein dosages and including patients with higher cholesterol level. In fact, the cholesterol-lowering effect of soy protein seems to be proportional to the baseline cholesterolemia level.

Both meta-analyses conclude that soy protein can be safely used for cholesterol reduction.

In patients with lipid abnormalities, the effects of dietary proteins have to be confirmed, for formulation of dietary alternatives for the treatment of lipid disturbances [26].

Moreover, soy proteins with 0.25–0.5 g/kg body weight dosage were also safely tested in children/adolescents [87] and hemodialysis patients [12], where the safety of high dosage statins is not so clear.

The main risk associated with the use of a high dosage of isolated soy protein is the dietary unbalance due to excessive protein intake. If the overall protein intake is not adequately controlled, some patients, such as those with advanced chronic renal failure, may have excessive dietary protein load. Although the thyramine content of soy protein is not higher than 0.6 mg per serving, it should be considered in patients using monoamine oxidase inhibitor antidepressant medications [38]. Only one report suggests an interaction between soy milk and warfarin [9]. In vitro, unhydrolyzed soy extract produces very little inhibition of CYP1A2, CYP2A6, and CYP2D6 and a trend of activation of CYP3A4, while hydrolyzed soy extract shows mild inhibition of CYP2C9 and CYP3A4, but the clinical relevance of these observations is yet to be defined [3].

Green Tea

Different researches carried out on rats also suggest that green tea antihypercholesterolemic activity is related to an increased excretion of bile acids [49]. A Japanese epidemiological study carried out on 13,916 healthy workers (age = 40–69 years) concludes that high consumption of green tea (*Cammelia sinensis*) is associated with significantly lower serum concentration of total cholesterol [80]. Green tea may decrease the risk of coronary heart disease by inhibiting the development of atherosclerosis, protecting LDL against oxidation and foam cell formation via catechins similar to blacktea theaflavins [21]. Despite conflicting results on lipid-lowering effects of green tea catechins, in recent meta-analyses consumption of

green tea catechins 145–3000 mg/day for 3–24 weeks were found to be associated with a significant reduction in total and LDL cholesterol levels (ranging from −5.46 mg/dL to −7.20 mg/dL, and −2.19 to −5.30 mg/dL compared to controls, respectively), but no effect on HDL or triglyceride levels were found [44, 95]. Besides discussions regarding effects on iron absorption [72], large doses may be related with folate deficiency in pregnancy and may lead to neural tube defects [74].

Discussion and Conclusion

The largest part of the most widely marketed lipid-lowering nutraceuticals was not clearly demonstrated to have positive additive cardiometabolic effects. The reasons could be different, among the others low bioavailability, scarce tolerability of efficacious dosages, short duration of the studies, low methodology quality of the available clinical trials. The low interest of industries to invest large amount of money in outcome study on products that could not be exclusive is probably an important reason, as well. Moreover, these compounds, usually easily available in the market, need to be long-term tested and evaluated on larger patient samples in clinical practice setting. Another concern is the efficacy and safety of lipid-lowering nutraceuticals when differently combined for marketing purposes without being directly tested in clinical trials. In fact, a perspective could be the association of more active nutraceuticals in order to improve their efficacy maintaining dosages not associated to potential side effects. In this context, an example of a good practice has been applied to the study of a registered association of Monacolins, Berberine, and Policosanols (Armolipid Plus), which has been tested for its efficacy in more than 1700 subjects in clinical practice [82] and for a period longer than 1 year [17] (Fig. 11.1), clearly showed to improve Flow-mediated vasodilation [2] and pulse wave velocity in mildly hypercholesterolemic subjects [19].

More clinical research is needed to clarify the potential role in therapy of some interesting nutraceuticals with strong preclinical evidence of efficacy, such as guggulipid (*Commiphora mukul*) [23] and curcumin (*Curcuma longa*) [40]. The most convincing evidence suggest that the association of a bowel cholesterol inhibitor nutraceutical and a cholesterol excreting natural molecule (in particular, berberine) to a statin could be an efficient and safe approach to improve cholesterolemia control in a large number of patients.

However, some nutraceuticals could exert a significant reduction in LDL-cholesterol (Table 11.1), thus clinicians should be informed about their efficacy and safety, in order to use them as preventive tools as additive tools to potentiate more conventional treatments in high-risk subjects. They should also be able to give the consumer full information about the product they are assuming. Further clinical research is advisable to individuate between the available lipid-lowering nutraceuticals with the best cost-effectiveness and risk-benefit ratio for large use in the general population, and in particular in statin treated patients.

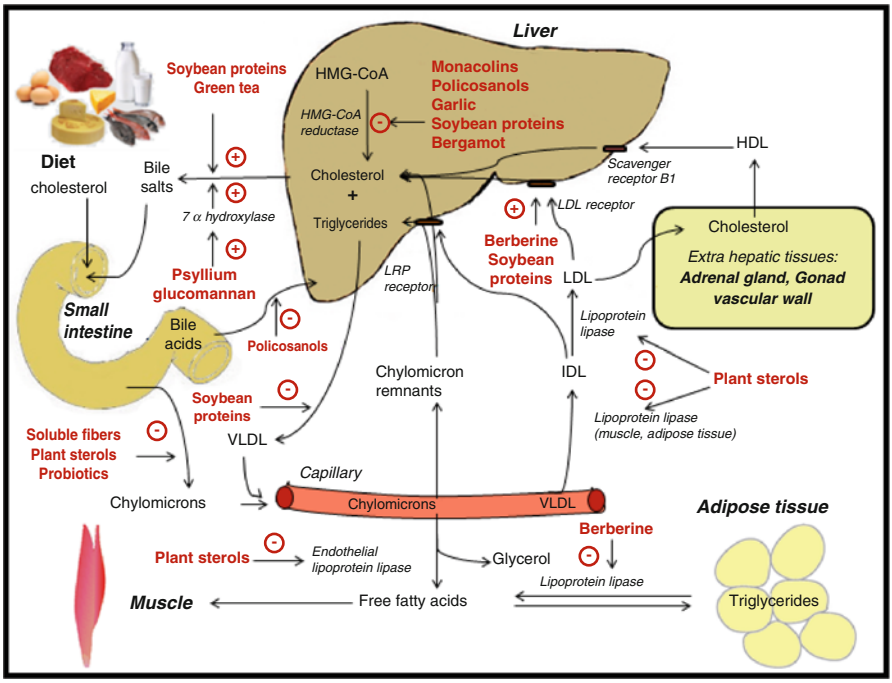

Fig. 11.1 Mechanism of action of the main lipid-lowering nutraceuticals

Table 11.1 Estimated percentage LDL-C reduction obtainable with different lipid-lowering nutraceuticals

Product	Expected % LDL-C reduction (%)
Red yeast rice	~ −10 to 20
Berberine	~ −15
Soluble fibers/glucomannan/plant sterols/probiotics	~ −8 to 12
Soy proteins/garlic/bergamot oil	~ −6 to 10
Policosanols/green tea	~ −5

References

1. Ackermann RT, et al. Garlic shows promise for improving some cardiovascular risk factors. Arch Intern Med. 2001;161:813–24.
2. Affuso F, et al. A nutraceutical combination improves insulin sensitivity in patients with metabolic syndrome. World J Cardiol. 2012;4:77–83.
3. Anderson GD, et al. Drug interaction potential of soy extract and Panax ginseng. J Clin Pharmacol. 2003;43:643–8.
4. Anderson JW, et al. Meta-analysis of the effects of soy protein intake on serum lipids. N Engl J Med. 1995;333:276–82.

5. Berginc K, et al. Garlic flavonoids and organosulfur compounds: impact on the hepatic pharmacokinetics of saquinavir and darunavir. Drug Metab Pharmacokinet. 2010;25(6):521–30.
6. Berthold HK, et al. Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: a randomized, controlled trial. JAMA. 2006;295:2262–9.
7. Brashears MM, et al. Bile salt deconjugation and cholesterol removal from media by Lactobacillus casei. J Dairy Sci. 1998;81:2103–10.
8. Burcelin R, et al. The gut microbiota ecology: new opportunity for the treatment of metabolic diseases? Front Biosci. 2009;14:5107–17.
9. Cambria-Kiely JA. Effect of soy milk on warfarin. Ann Pharmacother. 2002;36:1893–6.
10. Cani PD, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut. 2009;58(8):1091–103.
11. Chan E. Displacement of bilirubin from albumin by berberine. Biol Neonat. 1993;63:201–8.
12. Chen ST, et al. Variable effects of soy protein on plasma lipids in hyperlipidemic and normolipidemic hemodialysis patients. Am J Kidney Dis. 2005;46:1099–106.
13. Chua M, et al. Traditional uses and potential health benefits of Amorphophallus konjac K. Koch ex N.E.Br. J Ethnopharmacol. 2010;128:268–78.
14. Cicero AFG, Ertek S. Metabolic and cardiovascular effects of berberine: from preclinical evidences to clinical trial results. Clin Lipidol. 2009;4(5):553–63.
15. Cicero AFG, et al. Antihyperlipidaemic effect of a Monascus purpureus brand dietary supplement on a large sample of subjects at low risk for cardiovascular disease: a pilot study. Complement Ther Med. 2005;13:273–8.
16. Cicero AFG, et al. Eulipidemic effects of berberine administered alone or in combination with other natural cholesterol-lowering agents in humans. Arzneimittelforschung. 2007;57:26–30.
17. Cicero AFG, et al. Long-term efficacy and tolerability of a largely marketed multicomponent nutraceutical in overweight and normoweight dyslipidaemic patients. Nutrafoods. 2012;11(2):15–21.
18. Cicero AFG, et al. Tolerability and safety of commonly used dietary supplements and nutraceuticals with lipid-lowering effects. Expert Opin Drug Saf. 2012;11(5):753–66. doi:10.1517/14740338.2012.705827.
19. Cicero AFG, et al. Effect of a lipid-lowering nutraceutical on pulse-wave-velocity in hypercholesterolemic patients with or without chronic kidney disease. Open Hypertens J. 2013;5:18–22.
20. Cicero AFG, et al. Red yeast rice improves lipid pattern, high-sensitivity C-reactive protein, and vascular remodeling parameters in moderately hypercholesterolemic Italian subjects. Nutr Res. 2013;33(8):622–8. doi:10.1016/j.nutres.2013.05.01.
21. Cicero AFG, et al. Nutraceuticals for metabolic syndrome management: from laboratory to benchside. Curr Vasc Pharmacol. 2014;12(4):565–71.
22. Cicero AFG, et al. Berberine and monacolin effects on the cardiovascular risk profile of women with oestroprogestin-induced hypercholesterolemia. High Blood Press Cardiovasc Prev. 2014;21(3):221–6. doi:10.1007/s40292-014-0052-5.
23. Deng R. Therapeutic effects of guggul and its constituent guggulsterone: cardiovascular benefits. Cardiovasc Drug Rev. 2007;25(4):375–90.
24. Derosa G, et al. Berberine on metabolic and cardiovascular risk factors: an analysis from preclinical evidences to clinical trials. Expert Opin Biol Ther. 2012;12(8):1113–24.
25. Eisenbrand G. Toxicological evaluation of red mould rice. Mol Nutr Food Res. 2006;50:322–7.
26. El Khoury D, Anderson GH. Recent advances in dietary proteins and lipid metabolism. Curr Opin Lipidol. 2013;24(3):207–13. doi:10.1097/MOL.0b013e3283613bb7.
27. Gheit O, et al. Efficacy and safety of Monascus purpureus Went rice in subjects with secondary hyperlipidemia. Eur J Intern Med. 2009;20:e57–61.
28. Gliozzi M, et al. Bergamot polyphenolic fraction enhances rosuvastatin-induced effect on LDL-cholesterol, LOX-1 expression and protein kinase B phosphorylation in patients with hyperlipidemia. Int J Cardiol. 2013;170(2):140–5. doi:10.1016/j.ijcard.2013.08.125.
29. Grieco A, et al. A cute hepatitis caused by a natural lipid-lowering product: when “alternative” medicine is no “alternative” at all. J Hepatol. 2009;50:1273–7.

30. Grill JP, et al. Effects of Lactobacillus amylovorus and Bifidobacterium breve on cholesterol. Lett Appl Microbiol. 2000;31:154–6.
31. Grundy SM. Stanol esters as a component of maximal dietary therapy in the National Cholesterol Education Program Adult Treatment Panel III report. Am J Cardiol. 2005;96(suppl):47D–50.
32. Guardamagna O, et al. Primary hyperlipidemias in children: effect of plant sterol supplementation on plasma lipids and markers of cholesterol synthesis and absorption. Acta Diabetol. 2011;48:127–33.
33. Guo Z, et al. Influence of consumption of probiotics on the plasma lipid profile: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2011;21:844–50.
34. Gylling H, et al. The effect of a very high daily plant stanol ester intake on serum lipids, carotenoids, and fat soluble vitamins. Clin Nutr. 2010;29:112–8.
35. Gylling H, et al. Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease. Atherosclerosis. 2014;232(2):346–60. doi:10.1016/j.atherosclerosis.2013.11.043.
36. Halbert SC, et al. Tolerability of red yeast rice (2,400 mg twice daily) versus pravastatin (20 mg twice daily) in patients with previous statin intolerance. Am J Cardiol. 2010; 105(2):198–204.
37. Harland JI, Haffner TA. Systematic review, meta-analysis and regression of randomized controlled trials reporting an association between an intake of circa 25 g soya protein per day and blood cholesterol. Atherosclerosis. 2008;200:13–27.
38. Hutchins AM, et al. Hypertensive crisis associated with high dose soy isoflovane supplementation in a post-menopausal woman; a case report. BMC Womens Health. 2005;5:9.
39. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs. A systematic review. Drugs. 2001;61:2163–75.
40. Kang Q, Chen A. Curcumin suppresses expression of low-density lipoprotein receptor, leading to the inhibition of LDL-induced activation of hepatic stellate cells. Br J Pharmacol. 2009;157:1354–67.
41. Keithley J, Swanson B. Glucomannan and obesity: a critical review. Altern Ther Health Med. 2005;11:30–4.
42. Keithley J, et al. A pilot study of the safety and efficacy of cholestin in treating HIV-related dyslipidemia. Nutrition. 2002;18:201–4.
43. Klaver FA, Van der Meer V. The assumed assimilation of cholesterol by Lactobacilli and Bifidobacterium bifidum is due to their bile salt –deconjugating activity. Appl Environ Microbiol. 1993;59:1120–4.
44. Kim A, et al. Green tea catechins decrease total and low-density lipoprotein cholesterol: a systematic review and meta-analysis. J Am Diet Assoc. 2011;111:1720–9.
45. Kong W, et al. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nat Med. 2004;10:1344–51.
46. Kumar M, et al. Cholesterol-lowering probiotics as potential biotherapeutics for metabolic diseases. Exp Diabetes Res. 2012;2012:902917.
47. Kwak JS, et al. Garlic powder intake and cardiovascular risk factors: a meta-analysis of randomized controlled clinical trials. Nutr Res Pract. 2014;8(6):644–54. doi:10.4162/nrp.2014.8.6.644.
48. Lenz TL. Therapeutic lifestyle changes and pharmaceutical care in the treatment of dyslipidemias in adults. J Am Pharm Assoc. 2005;45(4):492–9.
49. Li G, et al. A tea catechin, epigallocatechin-3-gallate, is a unique modulator of the farnesoid X receptor. Toxicol Appl Pharmacol. 2012;258(2):268–74.
50. Lin YL, et al. Biologically active components and nutraceuticals in Monascus-fermented rice: a review. Appl Microbiol Biotechnol. 2008;77:965–73.
51. Liu J, et al. Chinese red yeast rice (monascus purpureus) for primary hyperlipidemia: a meta-analysis of randomized controlled trials. Chin Med. 2006;1:4.
52. Liu ZL, et al. Chinese herbal medicines for hypercholesterolemia. Cochrane Database Syst Rev. 2011;(7):CD008305.

53. Macan H, et al. Aged garlic extract may be safe for patients on warfarin therapy. J Nutr. 2006;136(3 Suppl):793S–5.
54. Maciejko JJ, et al. Psyllium for the reduction of cholestyramine-associated gastrointestinal symptoms in the treatment of primary hypercholesterolemia. Arch Fam Med. 1994;3:955–60.
55. Mannarino MR, et al. Nutraceuticals for the treatment of hypercholesterolemia. Eur J Intern Med. 2014;25(7):592–9. doi:10.1016/j.ejim.2014.06.008.
56. Marinangeli CP, et al. Policosanols as nutraceuticals: fact or fiction. Crit Rev Food Sci Nutr. 2010;50:259–67.
57. Martino F, et al. Effect of dietary supplementation with glucomannan on plasma total cholesterol and low density lipoprotein cholesterol in hypercholesterolemic children. Nutr Metab Cardiovasc Dis. 2005;15:174–80.
58. McCarty MF. Glucomannan minimizes the postprandial insulin surge: a potential adjuvant for hepatothermic therapy. Med Hypotheses. 2002;58(6):487–90.
59. McGowan MP, Proulx S. Nutritional supplements and serum lipids: does anything work? Curr Atheroscler Rep. 2009;11:470–6.
60. Mechanick JI, et al. AACE Nutrition Guidelines Taskforce. American Association of Clinical Endocrinologists medical guidelines for the clinical use of dietary supplements and nutraceuticals. Endocr Pract. 2003;9:417–70.
61. Mensink RP, et al. Plant stenols dose dependently decrease LDL cholesterol concentrations but not cholesterol standardized fat soluble antioxidant concentrations, at intakes up to 9g/d. Am J Clin Nutr. 2010;92:24–33.
62. Mogadishian MH, et al. Proatherogenic and antiatherogenic effects of probucol and phytosterols in apolipoprotein E-deficient mice: possible mechanisms of action. Circulation. 1999;99:1733–9.
63. Mollace V, et al. Hypolipemic and hypoglycaemic activity of bergamotpolyphenols: from animal models to human studies. Fitoterapia. 2011;82(3):309–16. doi:10.1016/j.fitote.2010.10.014.
64. Moreyra AE, et al. Effect of combining psyllium fiber with simvastatin in lowering cholesterol. Arch Intern Med. 2005;165:1161–6.
65. Morgan LM, et al. The effect of soluble- and insoluble-fibre supplementation on post-prandial glucose tolerance, insulin and gastric inhibitory polypeptide secretion in healthy subjects. Br J Nutr. 1990;64:103–10.
66. Moruisi KG, et al. Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis. J Am Coll Nutr. 2006;25:41–8.
67. Mullen E, et al. Soy isoflavones affect sterol regulatory element binding proteins (SREBPs) and SREBP-regulated genes in HepG2 cells. J Nutr. 2004;134:2942–7.
68. Nijjar PS, et al. Role of dietary supplements in lowering low-density lipoprotein cholesterol: a review. J Clin Lipidol. 2010;4(4):248–58.
69. Potter SM. Overview of proposed mechanisms for the hypocholesterolemic effect of soy. J Nutr. 1995;125(3 Suppl):606S–11.
70. Ras RT, et al. LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies. Br J Nutr. 2014;112(2):214–9. doi:10.1017/S0007114514000750.
71. Ried K, et al. Effect of garlic on serum lipids: an updated meta-analysis. Nutr Rev. 2013;71(5):282–99. doi:10.1111/nure.12012.
72. Samman S, et al. Green tea or rosemary extract added to foods reduces nonheme-iron absorption. Am J Clin Nutr. 2001;73:607–12.
73. Scholle JM, et al. The effect of adding plant sterols or stanols to statin therapy in hypercholesterolemic patients: systematic review and meta-analysis. J Am Coll Nutr. 2009;28:517–24.
74. Shirashi M, et al. Association between serum folate levels and tea consumption during pregnancy. Biosci Trends. 2010;4:225–30.
75. Shrestha S, et al. A combination of psyllium and plant sterols alters lipoprotein metabolism in hypercholesterolemic subjects by modifying the intravascular processing of lipoproteins and increasing LDL uptake. J Nutr. 2007;137:1165–70.

76. Singh DK, et al. Policosanol inhibits cholesterol synthesis in hepatoma cells by activation of AMP-kinase. J Pharmacol Exp Ther. 2006;318:1020–6.
77. Sirtori CR, Lovati MR. Soy proteins and cardiovascular disease. Curr Atheroscler Rep. 2001;3:47–53.
78. Sood N, et al. Effect of glucomannan on plasma lipid and glucose concentrations, body weight, and blood pressure: systematic review and meta-analysis. Am J Clin Nutr. 2008; 88(4):1167–75.
79. Stock J. Focus on lifestyle: EAS Consensus Panel Position Statement on Phytosterol-added Foods. Atherosclerosis. 2014;234(1):142–5. doi:10.1016/j.atherosclerosis.2014.01.047.
80. Tokunaga S, et al. Green tea consumption and serum lipids and lipoproteins in a population of healthy workers in Japan. Ann Epidemiol. 2002;12:157–65.
81. Torres N, et al. Regulation of lipid metabolism by soyprotein and its implication in diseases mediated by lipid disorders. J Nutr Biochem. 2006;17:365–73.
82. Trimarco B, et al. Clinical evidence of efficacy of red yeast rice and berberine in a large controlled study versus diet. Med J Nutrition Metab. 2011;4:133–40.
83. Vega-López S, et al. Sex and hormonal status modulate the effects of psyllium on plasma lipids and monocyte gene expression in humans. J Nutr. 2003;133:67–70.
84. Vergara-Jimenez M, et al. Hypolipidemic mechanisms of pectin and pysllium in guinea pigs fed high fat-sucrose diets: alterations on hepatic cholesterol metabolism. J Lipid Res. 1998;39:1455–65.
85. Vrzal R, et al. Activation of the arylhydrocarbon receptor by berberine in HepG2 and H4IIEcells: Biphasic effect on CYP1A1. Biochem Pharmacol. 2005;70:925–36.
86. Vuksan V, et al. Konjac-Mannan and American ginsing: emerging alternative therapies for type 2 diabetes mellitus. J Am Coll Nutr. 2001;20(S5):370S–80.
87. Weghuber D, Widhalm K. Effect of 3 month treatment of children and adolescents with familial and polygenic hypercholesterolemia with a soy-substituted diet. Br J Nutr. 2008;99: 281–6.
88. Wei ZH, et al. Time- and dose-dependent effect of psylium on serum lipids in mild- to- moderate hypercholesterolemia: a meta—analysis of controlled trials. Eur J Clin Nutr. 2009;63: 821–7.
89. Weingärtner O, et al. Vascular effects of diet supplementation with plant sterols. J Am Coll Cardiol. 2008;51(16):1553–61.
90. Weingärtner O, et al. Controversial role of plant sterol esters in the management of hypercholesterolaemia. Eur Heart J. 2009;30(4):404–9.
91. Weingärtner O, et al. Differential effects on inhibition of cholesterol absorption by plant stanol and plant sterol esters in apoE−/− mice. Cardiovasc Res. 2011;90(3):484–92.
92. Xin HW, et al. The effects of berberine on the pharmacokinetics of cyclosporine A in healthy volunteers. Methods Find Exp Clin Pharmacol. 2006;28:25–9.
93. Yin J, et al. Efficacy of berberine in patients with type 2 diabetes mellitus. Metabolism. 2008;57:712–7.
94. Yu L. The structure and function of Niemann-Pick C1-like 1 protein. Curr Opin Lipidol. 2008;19(3):263–9.
95. Zheng XX, et al. Green tea intake lowers fasting serum total and LDL cholesterol in adults: a meta-analysis of 14 randomized controlled trials. Am J Clin Nutr. 2011;94:601–10.

Chapter 12
Lipid-Lowering Therapy and Apheresis: Indications and Outcomes

Patrick M. Moriarty and Audrey E. McCalley

Introduction

Seventy-one million Americans have elevated LDL-cholesterol (LDL-C), and only a third of these Americans have been able to control their LDL-C [1]. Due to this large number of patients, research has continued in the development of newer lipid-modifying therapy (LMT). Additionally, combinations of LMT are often needed to lower plasma cholesterol levels and decrease cardiovascular risk. Patients with familial hypercholesterolemia (FH), statin intolerance, or elevated lipoprotein (a) [Lp(a)] have a particularly difficult time controlling cholesterol levels and cardiovascular disease (CVD), and thus combination therapies including lipoprotein apheresis (LA) may be necessary. FH is a commonly inherited (1:200–1:500) autosomal dominant genetic condition resulting in extreme elevation of serum cholesterol levels, thus leading to early onset of CVD. Aggressive and early lipid-lowering therapy is vital for the prevention of cardiovascular events, but goals are often not reached. Since most FH patients have a lack of or a defective LDL-C receptor, statins are only slightly or not effective in this population. Currently, the only therapy that significantly reduces LDL-C is LA, which is almost exclusively limited to treating patients with FH, although exceptions and cases are made by physicians for patients with statin intolerance, uncontrolled serum cholesterol, elevated Lp(a), or a limited number of other medical problems.

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Lipoprotein Apheresis (LA)

Apheresis, derived from the Greek word *aphairein*, meaning to take away, is the process of removing components from plasma/blood via an extracorporeal procedure. Using nonselective plasma exchange for FH was first reported in a case study by de Gennes in 1967 [2]. In 1975, Thompson et al. again using plasma exchange found a reduction of anginal symptoms and an influx of tissue cholesterol into the plasma in a group of FH patients [3]. In 1978, membrane apheresis was developed and allowed for semiselective or selective plasma-cell separation removal of particles by methods such as filtration, adsorption, or precipitation [4]. This pioneering work led to a vast amount of research and creation of new technology beginning in the 1980s.

Presently five selective and semiselective LA systems are used for the removal of plasma lipoproteins:

Semiselective

1. Membrane differential filtration

Selective

2. Immunoadsorption (Plasmaselect; Teterrow, Germany)
3. Heparin-induced extracorporeal LDL precipitation (HELP; Melsungen, Germany)
4. Dextran sulfate LDL adsorption (Liposorber LA-15 system; Kaneka, Osaka, Japan)
5. Hemoperfusion (direct adsorption of lipoproteins, DALI; Fresenius, St. Wendel, Germany; Liposorber D; Kaneka, Osaka, Japan)

The first four systems separate the plasma from the red blood cells (RBCs) while hemoperfusion allows for the direct adsorption from whole blood.

Membrane filtration (MF) was developed in 1980 by Agishi et al. and uses a double-membrane system to filter the plasma [5]. The double membrane allows for semi-selection of particles based on size and geometric shape.

In 1981, Stoffel et al. developed immunoadsorption (IA); the first LDL-specific machine uses apolipoprotein-B (apoB) antibodies to attract apoB-containing particles, which includes LDL-C [6]. The Pocard IA machine (Moscow, Russia) was developed using sheep anti-Lp(a) antibodies to attract lipoprotein (a) particles without altering LDL-C levels [7]. Another IA-like device is the fibrinogen adsorption system (Rheosorb), which reduces plasma/blood viscosity and improves microvascular flow by using a peptide with a high affinity for fibrinogen, a major protein associated with rheology [8].

The heparin-induced extracorporeal LDL precipitation (HELP) machine was introduced by Weiland and Seidel in 1983 [9]. The HELP system uses a low ph (5.1) buffer solution and negatively charged heparin precipitation to remove the positively charged apoB of LDL-C and other apoB containing particles.

In 1987, Mabuchi et al. developed the dextran sulfate apheresis (DSA) system, which, similar to the HELP machine, uses electrostatic interaction to

Table 12.1 Mean percentage reduction of plasma proteins with different methods of lipoprotein-apheresis

Lipid (mg/dL)	MDF (%)	HELP (%)	DALI (%)	DSA (%)	IA (%)
LDL-C	56–62	55–61	53–76	49–75	62–69
Triglycerides	37–49	20–53	29–40	26–60	34–49
HDL-C	25–42	5–17	5–29	4–17	9–27
Lp(a)	53–59	55–68	28–74	19–70	51–71

High variation of values is partially due to differences in treated plasma and blood volumes
MDF membrane differential filtration, *HELP* heparin-induced extracorporeal LDL precipitation, *DALI* direct adsorption of lipoproteins, *DSA* dextran sulfate adsorption, *IA* immunoadsorption

capture apoB lipoproteins. Plasma is exposed to a column of cellulose beads coated with negatively charged dextran sulfate cellulose, thus attracting apoB-containing particles [10].

Hemoperfusion (HP) was introduced in 1993 by Bosch with the direct adsorption of lipoproteins (DALI) blood perfusion system (Fresenius, St. Wendel, Germany), which requires no blood separation [11]. Blood is perfused through a column of negatively charged polyanions called polyacrylate-coated polyacrylamide beads, which, similar to the HELP and DSA systems, attract apoB-containing lipoproteins. In 2002, Kaneka developed their own whole-blood LDL apheresis system (KLD01) [12]. The mechanism for apoB lipoprotein reduction is similar to the DSA except the abdsorber's bead size has increased from 170 to 240 um, resulting in minimal side effects in terms of blood cell activation and RBC loss [13].

Only the HELP and the DSA systems are approved in North America. Table 12.1 shows the previously mentioned LA devices and their ability to lower serum lipoprotein levels.

Guidelines

Guidelines for the initiation of LA therapy vary throughout the world. Before initiating therapy, patients need to have exhausted their usage of LMT. In the United States, approved patients are separated into two major groups: (1) Preexisting coronary heart disease (CHD) and LDL-C >200 mg/dL and (2) without CAD and LDL-C >300 mg/dL. In Japan, LA may be initiated if the total cholesterol is above 250 mg/dL with pre-existing CHD. Germany allows LA if the patient has existing CHD and an LDL-C above 130 mg/dL, and as of 2010, the German Government has approved treatment of elevated Lp(a) with LA for patients with progressive CHD and an Lp(a) above 60 mg/dL. The rest of Europe, Russia, Israel, Lebanon, and Canada have variations of the German and American guidelines with some only allowing LA therapy for homozygote FH patients. For most of the world, simple plasma exchange is the method of choice for LA.

Table 12.2 LA therapy for elevated Lp(a)

	Jaeger [22]		Rosada [23]		Leebmann [24]	
	Pre-	Post-	Pre-	Post-	Pre-	Post-
Patients #	120	120	37	37	170	166
Duration years	5.5	5.0	5.2	6.8	2	2
LDL-C mg/dL	125	45 (−65 %)	84	34 (−60 %)	100	33 (−60 %)
Lp(a) mg/dL	118	33 (−72 %)	112	36 (−68 %)	87	26 (−70 %)
MACE[a] total	297	57 (−81 %)	67	20 (−70 %)	142	31 (−78 %)
MACE[a] per year	1.05	0.14 (−86 %)	2.80	0.08 (−97 %)	0.41	0.09 (−78 %)

Percentages are mean percent change
[a]*MACE* Major coronary event

Patient Population: Elevated Lp(a)

Lp(a) is an independent cardiovascular risk factor for CAD, stroke, myocardial infarctions, restenosis, venous thromboembolism and the progression of diabetic nephropathy [14–18]. Lp(a) elevations are more common in FH patients than in the general population [19]. This patient population has limited treatment options with LA currently as the only therapy capable of consistently lowering Lp(a) by at least 50 % [20]. The European Atherosclerosis Society has recommended the use of LA for patients with ongoing symptomatic CHD and elevated Lp(a) levels [21], but presently only Germany is allowed to treat this particular patient population. In the United States, a handful of patients (<20) receive regular LA therapy for an elevated Lp(a). Since initiating LA for elevated Lp(a), German apheresis centers have published three retrospective/prospective studies demonstrating the therapy's ability in reducing cardiovascular events (Table 12.2). Due to ethical reasons, the studies have used the individual patient's preapheresis data as the control group.

As previously mentioned, Pokrovsky introduced Lp(a) apheresis (POCARD Ltd., Moscow, Russia), which reduces Lp(a) by greater than 70 % without altering LDL-C levels [7]. In a recent trial, patients with stable CHD and elevated Lp(a) levels (103 ± 23 mg/dL) with near-normal LDL-C (77 ± 23 mg/dL), despite taking atorvastatin, were randomized to apheresis and statin or statin alone. Following 18 months, the apheresis group demonstrated a significant regression of coronary atherosclerosis when compared to the control group [25].

Combination Therapies with LA

The use of statins and LA has been shown to be a safe and effective manner of cholesterol reduction [26]. Following a treatment of LA, there is an acute rebound of plasma cholesterol through an increase of cholesterol biosynthesis and influx of extravascular cholesterol [27, 28]. The mechanism of influx of extravascular cholesterol may explain the reduction of arterial wall inflammation seen shortly after one

treatment of LA [29]. Statins, when used with LA, markedly decrease cholesterol synthesis following a single treatment [30]. In a group of 14 FH patients receiving weekly LA, LDL-C was reduced another 39 % after adding a daily dose of atorvastatin 80 mg/qd [31].

The use of statins with LA has provided a significant regression of coronary calcium and plaque volume [31–34]. The Low-Density Lipoprotein Apheresis Coronary Morphology and Reserve Trial (LACMART), a 1-year study involving 18 FH patients, 7 receiving atorvastatin and 11 receiving atorvastatin plus LA, found no significant change of LDL-C from baseline in the statin-treated group, while the LA and statin group reduced LDL-C by 34 %. Using coronary angiography and intravascular ultrasound (IVUS), the authors found a significant increase in the minimal lumen diameter ($p = 0.004$) and plaque area ($p = 0.008$) between the medication group compared to the LA and statin group [33].

Hemorheology is the study of flow dynamics for blood and its components. Alteration of these properties can impair vascular hemodynamics resulting in atherosclerosis and CVD [35]. Since blood is a non-Newtonian fluid, its resistance to flow or viscosity is altered by shear stress/rate, erythrocyte deformability/aggregation, temperature, and plasma viscosity [36]. In regard to FH patients, studies have demonstrated the abnormal coronary blood flow reserve seen with hyperlipidemia due to increased blood viscosity [37]. LA, following a single treatment, reduces blood viscosity by more than 20 % [38], which persists for at least 7 days [39]. Statins, such as atorvastatin, have demonstrated improvement in blood viscosity [40]. To determine the effects of atorvastatin on blood viscosity for FH patients receiving regular LA therapy, Banyai et al. found, following an 8 week period of adding the maximum dose of atorvastatin (80 mg/qd), a significant reduction of low–shear rate blood viscosity ($p = 0.03$, >10 %) when compared to baseline [41].

A large percentage of patients receiving LA have a history of statin intolerance [42]. Other therapeutic options including ezetimibe, niacin, bile acid sequestrants, phytosterols, fibrate, and omega-3-fatty acids should be considered with or without statins. The recent Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) involving more than 18,000 individuals with acute coronary disease who had ezetimibe added to a statin (simvastatin) over a period of ~6 years demonstrated the drug's ability to safely reduce LDL-C by 24 % and reduce CVD by 8–9 % [43]. Geiss et al. in 2005 found when ezetimibe was added to LA and statins, the LDL-C was further reduced by 16 % [44]. The Low-Density Lipoprotein Apheresis Coronary Atherosclerosis Prospective Study (L-CAPS) in 1999 by Nichimura et al. investigated the use of multiple lipid-lowering therapies along with or without LA in 36 FH patients. Pravastatin, probucol (not available in the United States), and a resin (cholestyramine) were used for each patient. When compared to the medication-only group, minimal lumen diameter regression was significantly improved ($P < 0.0001$) in the medication-and-LA group [34]. More importantly, this study demonstrated the safety and benefits of using multiple LMT along with LA.

In the past few years, lomitapide and mipomersen have been approved as therapy for the HoFH population. Lomitapide, an inhibitor of the microsomal triglyceride transport protein (MTP), was tested on a group of 29 HoFH patients in which 18

Table 12.3 Lipid lowering therapies

Class	Primary and secondary mechanism of action	LDL-lowering response	
		HeFH[a]	HoFH[b]
Statins	↑ LDLR activity (1°)	>35 %	Up to 28 %
Resins	↓ Bile acid re-absorption (1°), ↑ LDLR activity (2°)	15 %	<10 %
Ezetimibe	↓ Cholesterol absorption (1°), ↑ LDLR activity (2°)	15 %	<10 %
Stanol esters	↓ Cholesterol absorption (1°), ↑ LDLR activity (2°)	10 %	<10 %
Nicotinic acid	↓ VLDL synthesis (1°)	20 %	<10 %
Lomitapide	Inhibits microsomal triglyceride transfer protein	NA[c]	50 %
Mipomersen	Antisense oligonucleotide against apoB-100	NA[c]	28 %
Lipoprotein-apheresis	Removes LDL-c and Lp(a)	Up to 76 % acutely 20–40 % chronically	

Table adapted from Radar DJ, et al. *J Clin Invest*. 2003;111(12):1796–1803; [46–52]
[a]*HeFH* heterozygous familial hypercholesterolemia
[b]*HoFH* homozygous familial hypercholesterolemia
[c]*NA* not approved

were receiving periodic apheresis treatments. After 26 weeks, lomitapide (40 mg a day) reduced LDL-C by 50 %, and three patients had permanently discontinued LA therapy based on their LDL-C response [45]. Mipomersen, an antisense oglionucleotide that inhibits ApoB and lowers LDL-C by 28 %, has not been studied in combination with LA. Of note, unlike lomitapide, mipomersen does consistently lower Lp(a) levels by 26 %.

Understanding the outcomes and benefits of other alternative medications to statins for patients receiving LA is vital for those with statin intolerance and other high-risk populations (Table 12.3). Unfortunately, there is a severe lack of research on the efficacy and safety of using these alternative drug therapies along with LA.

Current and Future Uses for LA

As previously discussed, LA is mostly indicated for those with FH and/or elevated Lp(a) but has also been applied, when standard therapy has failed, for other vascular diseases such as idiopathic sudden hearing loss (ISHL), age-related macular degeneration (MD), nonarteritic acute ischemic anterior optic neuropathy (NAION), primary focal segmental glomerulosclerosis (FSGS), diabetic nephrotic syndrome, preeclampsia, cardiac transplantation, acute coronary syndrome, and peripheral and cerebral vascular disease [53–59]. Microcirculation disturbances may be a potential etiology for these diseases, and the possible improvement of symptoms following LA therapy may be based on its complex modification of vascular physiology [60, 61].

Future Combination Therapy

Proprotein convertase subtilisin kexin type 9 (PCSK9) is an enzyme which induces LDL receptor degradation resulting in hypercholesterolemia. Since the discovery of this protein, pharmaceutical companies have been developing antibodies, peptide mimics, and gene silencing techniques to inhibit PCSK9's activity. The PCSK9 inhibitor companies are leading in attaining their drug first to market. Recent studies with PCSK9 inhibitor drugs have shown LDL-C reductions by 53–57 % and have provided evidence that the drug is safe, effective, and more tolerable than statin drugs [62–64]. FH patients receiving LA therapy would be the population to benefit the most from this class of lipid-lowering therapy. As of March 2015, the REGN727/SAR236553 ODYSSEY ESCAPE study is underway to evaluate the effect of an PCSK9 inhibitor (Alirocumab), compared to placebo, on the frequency of LA treatments in patients with HeFH [65].

Conclusion

For patients with FH, LA therapy has been an effective means of lowering plasma cholesterol levels and CVD. The use of LMT with LA offers an additional reduction of LDL-C levels. Future LMTs appear to be favorable adjuncts to LA therapy with an added value of potentially reducing or eradicating treatments.

References

1. Centers for Disease Control and Prevention. Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol–United States, 1999–2002 and 2005–200. MMWR Morb Mortal Wkly Rep. 2011;60(4):109–14.
2. de Gennes JL, Touraine R, Maunand B, et al. Homozygous cutaneo-tendinous forms of hypercholesteremic xanthomatosis in an exemplary familial case. Trial of plasmapheresis and heroic treatment. Bull Mem Soc Med Hop Paris. 1967;118(15):1377–402.
3. Thompson GR, Lowenthal R, Myant NB. Plasma exchange in the management of homozygous familial hypercholesterolaemia. Lancet. 1975;1(7918):1208–11.
4. Solomon BA et al. Continuous flow membrane filtration of plasma from whole blood. Trans Am Soc Artif Intern Organs. 1978;24:21–6.
5. Agishi T et al. Double filtration plasmapheresis. Trans Am Soc Artif Intern Organs. 1980; 26:406–11.
6. Stoffel W, Borberg H, Greve V. Application of specific extracorporeal removal of low density lipoprotein in familial hypercholesterolaemia. Lancet. 1981;2(8254):1005–7.
7. Pokrovsky SN et al. Development of immunosorbents for apoB-containing lipoproteins apheresis. Artif Organs. 1995;19(6):500–5.
8. Koll R, Klinkmann J, Richter W. RheoSorb: a specific adsorber for fibrinogen elimination in clinical situations with impaired rheology. Artif Organs. 2002;26(2):145–51.
9. Wieland H, Seidel D. A simple specific method for precipitation of low density lipoproteins. J Lipid Res. 1983;24(7):904–9.

10. Mabuchi H et al. A new low density lipoprotein apheresis system using two dextran sulfate cellulose columns in an automated column regenerating unit (LDL continuous apheresis). Atherosclerosis. 1987;68(1–2):19–25.
11. Bosch T et al. Lipid apheresis by hemoperfusion: in vitro efficacy and ex vivo biocompatibility of a new low-density lipoprotein adsorber compatible with human whole blood. Artif Organs. 1993;17(7):640–52.
12. Otto C et al. Effects of direct adsorption of lipoproteins apheresis on lipoproteins, low-density lipoprotein subtypes, and hemorheology in hypercholesterolemic patients with coronary artery disease. Ther Apher. 2002;6(2):130–5.
13. Kobayashi J et al. Single LDL apheresis improves serum remnant-like particle-cholesterol, C-reactive protein, and malondialdehyde-modified-low-density lipoprotein concentrations in Japanese hypercholesterolemic subjects. Clin Chim Acta. 2002;321(1–2):107–12.
14. Gudnason V. Lipoprotein(a): a causal independent risk factor for coronary heart disease? Curr Opin Cardiol. 2009;24(5):490–5.
15. Milionis HJ, Winder AF, Mikhailidis DP. Lipoprotein (a) and stroke. J Clin Pathol. 2000; 53(7):487–96.
16. Keller C. Apheresis in coronary heart disease with elevated Lp (a): a review of Lp (a) as a risk factor and its management. Ther Apher Dial. 2007;11(1):2–8.
17. Song KH et al. Prospective study of lipoprotein(a) as a risk factor for deteriorating renal function in type 2 diabetic patients with overt proteinuria. Diabetes Care. 2005;28(7):1718–23.
18. von Depka M et al. Increased lipoprotein (a) levels as an independent risk factor for venous thromboembolism. Blood. 2000;96(10):3364–8.
19. Utermann G et al. Defects in the low density lipoprotein receptor gene affect lipoprotein (a) levels: multiplicative interaction of two gene loci associated with premature atherosclerosis. Proc Natl Acad Sci U S A. 1989;86(11):4171–4.
20. Bambauer R. Is lipoprotein (a)-apheresis useful? Ther Apher Dial. 2005;9(2):142–7.
21. Catapano AL et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis. 2011;217(1):3–46.
22. Jaeger BR et al. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. Nat Clin Pract Cardiovasc Med. 2009;6(3):229–39.
23. Rosada A. Does regular lipid apheresis in patients with isolated elevated lipoprotein (a) levels reduce the incidence of cardiovascular events? (vol 38, pg 135, 2014). Artif Organs. 2014; 38(2):177.
24. Leebmann J et al. Lipoprotein apheresis in patients with maximally tolerated lipid-lowering therapy, lipoprotein(a)-hyperlipoproteinemia, and progressive cardiovascular disease: prospective observational multicenter study. Circulation. 2013;128(24):2567–76.
25. Safarova MS et al. Effect of specific lipoprotein(a) apheresis on coronary atherosclerosis regression assessed by quantitative coronary angiography. Atheroscler Suppl. 2013;14(1):93–9.
26. Masaki N et al. Ten-year follow-up of familial hypercholesterolemia patients after intensive cholesterol-lowering therapy. Int Heart J. 2005;46(5):833–43.
27. Thompson GR, Myant NB. Low density lipoprotein turnover in familial hypercholesterolaemia after plasma exchange. Atherosclerosis. 1976;23(2):371–7.
28. Kano M et al. Plasma exchange and low density lipoprotein apheresis in Watanabe heritable hyperlipidemic rabbits. Arteriosclerosis. 1987;7(3):256–61.
29. van Wijk DF et al. Nonpharmacological lipoprotein apheresis reduces arterial inflammation in familial hypercholesterolemia. J Am Coll Cardiol. 2014;64(14):1418–26.
30. Pfohl M et al. Acute and chronic effects on cholesterol biosynthesis of LDL-apheresis with or without concomitant HMG-CoA reductase inhibitor therapy. J Lipid Res. 1994;35(11): 1946–55.
31. Goldammer A et al. Atorvastatin in low-density lipoprotein apheresis-treated patients with homozygous and heterozygous familial hypercholesterolemia. Metabolism. 2002;51(8): 976–80.

32. Hoffmann U et al. Effects of combined low-density lipoprotein apheresis and aggressive statin therapy on coronary calcified plaque as measured by computed tomography. Am J Cardiol. 2003;91(4):461–4.
33. Matsuzaki M et al. Intravascular ultrasound evaluation of coronary plaque regression by low density lipoprotein-apheresis in familial hypercholesterolemia: the Low Density Lipoprotein-Apheresis Coronary Morphology and Reserve Trial (LACMART). J Am Coll Cardiol. 2002;40(2):220–7.
34. Nishimura S et al. Effects of intensive lipid lowering by low-density lipoprotein apheresis on regression of coronary atherosclerosis in patients with familial hypercholesterolemia: Japan Low-density Lipoprotein Apheresis Coronary Atherosclerosis Prospective Study (L-CAPS). Atherosclerosis. 1999;144(2):409–17.
35. Angelkort B, Amann B, Lawall H. Hemorheology and hemostatis in vascular disease. A pathophysiological review. Clin Hemorheol Microcirc. 2002;26:145–54.
36. Kensey K, Cho Y. The origin of atherosclerosis, An introduction to hemodynamics, vol. 1. 1st ed. Haddonfield: EPP Medica; 2001.
37. Rim S-J et al. Decrease in coronary blood flow reserve during hyperlipidemia is secondary to an increase in blood viscosity. Circulation. 2001;104:2704–9.
38. Moriarty P, et al. LDL apheresis and its effect on whole blood viscosity. In: 3rd Annual Conference on Arteriosclerosis, Thrombosis, and Vascular Biology, Salt Lake; 2002.
39. Rubba P et al. Hemodynamic changes in the peripheral circulation after repeat low density lipoprotein apheresis in familial hypercholesterolemia. Circulation. 1990;81:610–6.
40. Szapary L et al. Hemorheological disturbances in patients with chronic cerebrovascular diseases. Clin Hemorheol Microcirc. 2004;31(1):1–9.
41. Banyai S et al. Atorvastatin improves blood rheology in patients with familial hypercholesterolemia (FH) on long-term LDL apheresis treatment. Atherosclerosis. 2001;159(2):513–9.
42. Raper A, Kolansky DM, Cuchel M. Treatment of familial hypercholesterolemia: is there a need beyond statin therapy? Curr Atheroscler Rep. 2012;14(1):11–6.
43. Blazing MA et al. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population. Am Heart J. 2014;168(2):205–12.e1.
44. Geiss HC et al. Effects of ezetimibe on plasma lipoproteins in severely hypercholesterolemic patients treated with regular LDL-apheresis and statins. Atherosclerosis. 2005;180(1):107–12.
45. Cuchel M et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet. 2013;381(9860):40–6.
46. Kastelein JJ et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008;358(14):1431–43.
47. Raal FJ et al. Inhibition of cholesterol synthesis by atorvastatin in homozygous familial hypercholesterolaemia. Atherosclerosis. 2000;150(2):421–8.
48. Konrad RJ, Troutt JS, Cao G. Effects of currently prescribed LDL-C-lowering drugs on PCSK9 and implications for the next generation of LDL-C-lowering agents. Lipids Health Dis. 2011;10:38.
49. Vohl MC et al. Influence of LDL receptor gene mutation and apo E polymorphism on lipoprotein response to simvastatin treatment among adolescents with heterozygous familial hypercholesterolemia. Atherosclerosis. 2002;160(2):361–8.
50. Chaves FJ et al. Genetic diagnosis of familial hypercholesterolemia in a South European outbreed population: influence of low-density lipoprotein (LDL) receptor gene mutations on treatment response to simvastatin in total, LDL, and high-density lipoprotein cholesterol. J Clin Endocrinol Metab. 2001;86(10):4926–32.
51. Gordon BR et al. Long-term effects of low-density lipoprotein apheresis using an automated dextran sulfate cellulose adsorption system. Liposorber Study Group. Am J Cardiol. 1998; 81(4):407–11.
52. Ito MK et al. Management of familial hypercholesterolemias in adult patients: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):S38–45.

53. Schuff-Werner P et al. The HELP-LDL-apheresis multicentre study, an angiographically assessed trial on the role of LDL-apheresis in the secondary prevention of coronary heart disease. II. Final evaluation of the effect of regular treatment on LDL-cholesterol plasma concentrations and the course of coronary heart disease. The HELP-Study Group. Heparin-induced extra-corporeal LDL-precipitation. Eur J Clin Invest. 1994;24(11):724–32.
54. Ullrich H et al. Improved treatment of sudden hearing loss by specific fibrinogen aphaeresis. J Clin Apher. 2004;19(2):71–8.
55. Balletshofer BM et al. Acute effect of rheopheresis on peripheral endothelial dysfunction in patients suffering from sudden hearing loss. Ther Apher Dial. 2005;9(5):385–90.
56. Pulido JS, Multicenter Investigation of Rheopheresis for AMD (MIRA-1) Study Group. Multicenter prospective, randomized, double-masked, placebo-controlled study of Rheopheresis to treat nonexudative age-related macular degeneration: interim analysis. Trans Am Ophthalmol Soc. 2002;100:85–106; discussion 106–7.
57. Koss MJ et al. Prospective, randomized, controlled clinical study evaluating the efficacy of Rheopheresis for dry age-related macular degeneration. Dry AMD treatment with Rheopheresis Trial-ART. Graefes Arch Clin Exp Ophthalmol. 2009;247(10):1297–306.
58. Moriarty PM, Whittaker TJ. Treatment of acute occlusion of the retinal artery by LDL-apheresis. J Clin Apher. 2005;20(2):88–92.
59. Ramunni A et al. LDL-apheresis accelerates the recovery of nonarteritic acute anterior ischemic optic neuropathy. Ther Apher Dial. 2005;9(1):53–8.
60. Ohinata Y et al. Blood viscosity and plasma viscosity in patients with sudden deafness. Acta Otolaryngol. 1994;114(6):601–7.
61. Mosges R et al. Rheopheresis for idiopathic sudden hearing loss: results from a large prospective, multicenter, randomized, controlled clinical trial. Eur Arch Otorhinolaryngol. 2009; 266(7):943–53.
62. Blom DJ et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014;370(19):1809–19.
63. Koren MJ et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014;63(23): 2531–40.
64. Stroes E et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014;63(23):2541–8.
65. ClinicalTrials.gov. Study of Alirocumab (REGN727/SAR236553) in Patients With Heterozygous Familial Hypercholesterolemia (HeFH) Undergoing Low-density Lipoprotein (LDL) Apheresis Therapy. 2015.

Chapter 13
Combination of Lipid-Lowering Agents with Antihypertensive Drugs: A Joint Fight Against the Two Most Important Risk Factors?

Yanglu Zhao and Nathan D. Wong

Risk Prevalence and Impact on Disease Burden

Prevalence of Hypertension and Its Impact on CVD

Some 40 % of adults aged 25 and over have hypertension globally. Elevated blood pressure is estimated to cause 7.5 million deaths annually worldwide, accounting for 12.8 % of total mortality and ranking the first among all the global risk factors for mortality. Hypertension also contributes to 57 million disability-adjusted life years (DALYs) or 3.7 % of total DALYs. In addition, it is the major risk factor for coronary heart disease (CHD) and stroke and is responsible for 45 % of deaths due to heart disease and 51 % of deaths due to stroke [1]. The harm of elevated blood pressure can start as low as 115/75 mmHg in some age-groups, and the risk of cardiovascular disease (CVD) death doubles per each increment of 20/10 mmHg of blood pressure [2].

Hypertension and Dyslipidemia Are Frequently Concomitant Risk Factors

Hypertension is frequently accompanied by other risk factors. Kannel et al. found that 82 % of offspring from the Framingham Study present one or more risk factors clustering with hypertension [3]. Among them, dyslipidemia is a very common one. Approximately one out of five people have both hypertension and dyslipidemia in

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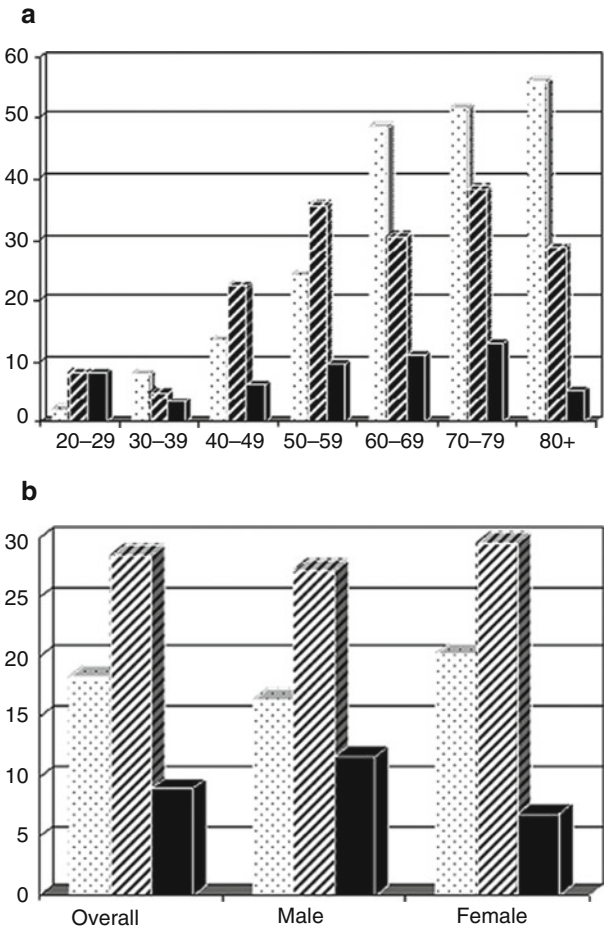

Fig. 13.1 Prevalence, treatment and control of combined hypertension and hypercholesterolemia in UC adults by age group (**a**) and sex (**b**). Hypertension and hypercholesterolemia: prevalence (*dotted bars*), treatment (*slashed bars*), and control (*black bars*) by age group. Prevalence indicates percentage with hypertension (blood pressure ≥140/90 or ≥130/80 mmHg if DM was present or on antihypertensive medication) and with hypercholesterolemia (LDL cholesterol >130 or >100 mg/dL if DM or coronary heart disease was present or on lipid-lowering medications). Treatment indicates percentage on treatment among those with hypertension and hypercholesterolemia. Control indicates percentage controlled to below previously mentioned cutpoints of those with hypertension and hypercholesterolemia (Adapted from Wong et al. [4] with permission)

the USA and UK [4]. Wong et al. have shown in US adults the prevalence of combined hypertension and dyslipidemia to range from 2 % in those aged 20–29 to 56 % in those aged 80 and over and to be particularly high (69 %) in those with both CVD plus diabetes or metabolic syndrome (Fig. 13.1a). Besides, females seem to have higher percentage of combined condition than males and poorer control rate (Fig. 13.1b) [4]. The situation in European countries is no better: data from UK

showed the prevalence of combined hypertension and dyslipidemia to be 15 % in 1990 and 20 % in 2001 [5, 6]. The 2005 data from Belgium revealed that both risk factors occurred simultaneously in 38 % of men and 32 % of women aged 35–74 years old [7]. Asian populations seem to have lower prevalence: in Turkey, approximately one in six people suffered combined hypertension and dyslipidemia [8].

Hypertension-Dyslipidemia Aggregate Risk for CVD

Multiple observational cohort studies, either single or pooled, have been conducted to explore the association of combined hypertension-dyslipidemia and future CVD incidence and consistently found that individuals with both hypertension and dyslipidemia have a greater risk of CVD than those with either hypertension or dyslipidemia alone in a variety of populations [9–13]. One of the earliest studies involved 316,099 white men screened for the Multiple Risk Factor Intervention Trial (MRFIT). The study showed that high cholesterol levels (>180 mg/dL), elevated systolic BP (>110 mmHg), and diastolic BP (>70 mmHg) were strongly correlated with increased risk of CHD-related death [9]. Also, the impact of LDL-C seems weaker among older patients based on data from the Cardiovascular Health Study (CHS), which revealed that in those≥65 years, elevated BP was associated with increased risk across all lipid levels while increased LDL-C added risk mainly when BP <140/90 mmHg [10]. On the contrary, a French study including subjects under 55 years of age showed a combination of high systolic blood pressure and high serum cholesterol dramatically increased cardiovascular disease and coronary heart disease risk, especially in men [11]. One recent large pooled cohort study from Japan additionally found the synergistic increase in risk for coronary heart disease death in the Asian population: the adjusted hazard ratios of systolic increase with increases in total cholesterol categories and similar increase hazard ratios of total cholesterol was seen with increases in systolic BP categories (Fig. 13.2) [12]. The Turkish study compared the risk of CVD between dyslipidemic hypertension and simple hypertension and found that the dyslipidemic hypertensions have 58 % higher risk [8]. Besides, those with dyslipidemic hypertension also have 47 % higher risk of CVD than those with MetS but no dyslipidemic hypertension, indicating that the coexistence of hypertension and dyslipidemia may aggregate the risk of future CVD.

Control Rate of the Combined Hypertension-Dyslipidemia

Although clinical trials have proved the efficacy of combined therapy and guidelines are continuously updated, control of hypertension-dyslipidemia remains inadequate. It was estimated that among the 78 million Americans with hypertension, although 81 % of them were aware of the disease and 75 % received treatment, only 53 % were under control [14]. The control rate of both hypertension and

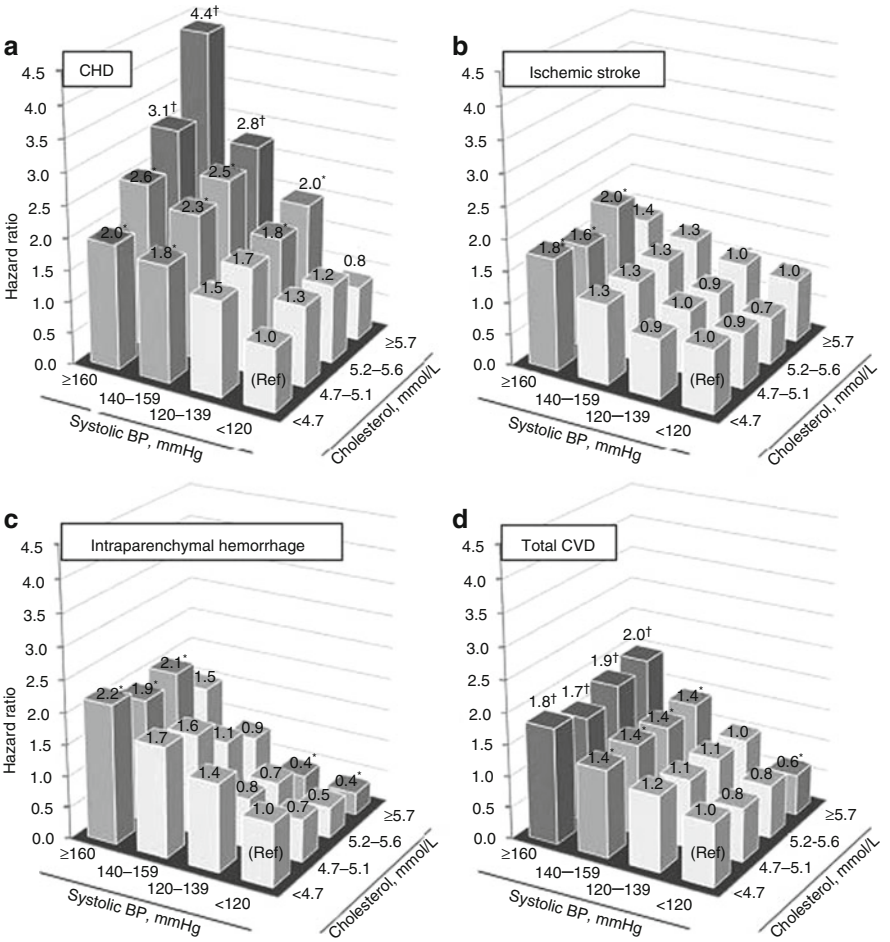

Fig. 13.2 Adjusted hazard ratios for death from (**a**) coronary heart disease (*CHD*), (**b**) ischemic stroke, (**c**) intraparenchymal hemorrhage, and (**d**) total cardiovascular disease (*CVD*) in each group according to the levels of systolic blood pressure (*BP*) and total cholesterol were calculated using cohort-stratified Cox proportional hazards models. All analyses were stratified by cohort. The analyses included 73,916 Japanese people from 11 cohorts. Covariates were sex, age, body mass index, former smoking, current smoking, former drinking, and current drinking. *$P<0.05$, †$P<0.0001$ vs group with systolic BP <120 mmHg with total cholesterol <4.7 mmol/L (Reprinted from Satoh et al. [12] with permission)

dyslipidemia is even lower. Wong et al. found that among those with the two conditions, the control of both was as low as 9 % [4]. Control of HTN-DYS was worse in women, nonwhites, and those with DM or CVD [4, 15]. From 1988 to 2010 in the USA, control of concomitant high blood pressure and LDL-C increased from 5.0 to 30.7 % (and from 1.8 to 26.9 % if non-high-density lipoprotein cholesterol control was added) [16].

Combined Therapy Aimed to Address Joint Hypertension-Dyslipidemia

Individual antihypertensive therapy and lipid-lowering drugs reduce CVD events by approximately 25 % and 30 %, respectively [17]. But the combined therapy can more rapidly control blood pressure and lipids to target levels compared to single therapies alone due mainly to better adherence of a single fixed-dose combination agent [18]. Trials of combined therapy of amlodipine and atorvastatin showed comparable control rates (Table 13.1). Within the designed study period, which varies from 8 weeks to 20 weeks, the control rate of both risks ranged from 48.3 to 67.8 %. It is consistent across all the studies that LDL-C level is better controlled than blood pressure. In addition, there is no obvious trend that higher blood pressure/LDL-C level corresponds with poorer control rates, indicating the control of risk factors, either combined or single, might be influenced by other reasons. Combined valsartan/simvastatin in different titrations were also investigated and showed similar (50%) control rate

Table 13.1 Trial of combined therapy of amlodipine and atorvastatin

Study	No. of participants	Baseline BP, mmHg	Baseline LDL-C, mmol/L	Patients achieving BP and LDL-C goals, %	Patients achieving BP goals, %	Patients achieving LDL-C Goals, %
AVALON [18]	847	147/92	4.25	67.1	51	82.1
CAPABLE [19]	499	147/91	3.68	48.3	56.8	73.7
CRUCIAL [20]	1,461	150/90	3.64	50	58	83
CUSP [21]	63	147/91	3.44	47.6	65.1	74.6
GEMINI [22]	1,220	146/88	3.96	57.7	65.5	74.7
GEMINI-AALA [23]	1,649	146/88	3.4	55.2	61.3	87.1
IMPACT [24]	62	156/89	3	48.7	65.8	85.3
JAWEL I [25]	1,138	152/90	5	62.9	66.8	90.7
JAWEL II [25]	1,107	152/90	5	50.6	65.7	73.1
TOGETHER [26]	244	132/81	3.39	67.8	79.9	84

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(a) Treatment goals for BP in the AVALON and CUSP studies were defined according to the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 6), in the CAPABLE, CRUCIAL, and IMPACT studies according to the JNC 7, in the JAWEL study according to the European, Canadian, and UK guidelines; and in the CUSP and TOGETHER studies BP goal was <140/90 mmHg
(b) Treatment goals for LDL-C levels in all the studies, except in the CUSP and TOGETHER studies, were defined according to the National Cholesterol Education Program Adult Treatment Panel III. Only in the CUSP and TOGETHER studies, LDL-C goal was <100 mg/dL (2.6 mmol/L) for all the participants
Abbreviations: *DBP* diastolic blood pressure, *LDL-C* low-density lipoprotein cholesterol, *SBP* systolic blood pressure

of both risk factors. However, the results also showed that increasing the dose of simvastatin does not help improve the combined control rate [28].

Treating hyperlipidemia in hypertensive patients significantly reduces future CHD risk compared to single medication strategy or placebo [29, 30]. The Anglo-Scandinavian Cardiac Outcomes Trial--Lipid-Lowering Arm (ASCOT-LLA) demonstrated that adding atorvastatin will result in an additional 29 % risk reduction for CHD and 21 % for CVD events [30]. Observed CHD event rates reduced by 79 % in those assigned amlodipine-based treatment and atorvastatin, compared to the estimates of CHD risk by Framingham algorithm at baseline [31]. If patients present more risk factors, for example, in those with metabolic syndrome, controlling blood pressure, LDL-C, and HDL-C to normal levels will prevent 51.3 % of events for men and 42.6 % for women and prevent 80.5 and 82.1 % of events if controlling to optimal levels, respectively [32]. Emberson J et al. used estimates of the relative risk reductions from meta-analyses of randomized trials in combination with data from a prospective observational study of CVD (the British Regional Heart Study) to analyze the impact of different risk reduction strategies in primary prevention [33]. The study examined the effects of prevention strategies based on single risk factor assessment or total risk assessment. They concluded that assessment of overall risk leads to more effective intervention than assessment based on single risk factors. Furthermore, multiple interventions have considerably greater benefits than interventions based on targeting single risk factors. A 10 % reduction in long-term mean blood cholesterol and BP could have reduced major CVD by 45 %.

But the additional prognostic benefit beyond the blood-pressure-lowering and cholesterol-lowering effects in the combined treatment in secondary prevention seems still questionable. The Japanese Coronary Artery Disease (JCAD) study of 13,812 patients with angiographically demonstrable significant coronary narrowing showed no statistically significant difference in the cardiovascular event rate between those on the combined therapy of calcium channel blocker (CCB) plus statin and those with neither CCB nor statin [13]. Another meta-analysis also found that compared with placebo, single drug active component, or usual care, the effects of fixed-dose combination therapy on all-cause mortality or CVD events are still uncertain, although most of them reached prescribed control targets [34]. Statins and some hypertension medications are also believed to have pleiotropic actions beyond their lipid-lowering and antihypertensive effects.

Some studies have also examined the mechanism of combined therapy, such as the effect of statin on the antihypertensive drug activity. Both antihypertensive drugs and statins are believed to have additional effects, beyond lowering blood pressure or lipid level. Combined therapy of lipid-lowering medication and antihypertensive treatment leads to a variety of pathophysiological change including improvement in nitric oxide release, reduction in inflammation markers, improvement in fibrinolytic balance, decreased plasminogen activator inhibitor plasma levels, increased tissue plasminogen activator activity, decreased atherosclerotic plaque size and calcification, normalization atherosclerotic plaque protein secretion profile, improved vascular compliance, decreased left ventricular mass index, decreased carotid systolic BP, and improved insulin sensitivity [27].

Implications for Older Patients Who Frequently Have Multiple Risk Factors

Older patients are merited to benefit more from the combined treatment given the following two reasons. First, aging is independently related to higher CVD incidence. Since the absolute event rates are higher in older populations, the numbers needed to treat will be less than the young ones whose CVD event rates are relatively low. Second, older patients tend to present multiple risk factors, including hypertension and dyslipidemia. It was found that the joint prevalence of hypertension and hypercholesterolemia positively correlates with age, and among those aged >80 years, the percentage of population with both is as high as 56 % [4]. Wong et al. examined the joint association of blood pressure and lipid (HDL-C and LDL-C) in older American adults and found blood pressure is positively related to increased risk of CVD across all lipid levels while LDL-C was only predictive when BP ≤140/90 mmHg. The coexistence of multiple risk factors in older adults emphasizes the need for greater individual and combined risk factor control that makes a strong case for combination therapeutic agents for hypertension and dyslipidemia and beyond (e.g., polypill).

While the benefit of combined therapy should be emphasized in the high-risk elderly caused either by age or by comorbidity, there is no direct evidence from randomized trials showing the efficacy of combined therapy among older subjects is as high as in young ones. In addition, few have been done to evaluate the overall effectiveness (including adherence, dose tolerance, adverse effect, etc.) of combined therapy in the elderly. It is generally agreed that the initiation of therapy should be from low dose and a slower uptitration for older patients due to the above considerations.

Practical Issues and Future Perspective

Beyond the Drug Efficacy

Many trials of combined therapy, including some of the earliest ones, focused not only on drug efficacy but also on pragmatic issues including safety, drug tolerance and adherence, etc. However, not all the components to evaluate the overall effectiveness have been sufficiently investigated, such as cost-effectiveness and the variation of drug efficacy among different populations, which will influence the postulation of integrated prevention strategies in individuals with hypertension-dyslipidemia. The AVALON trial investigated the drug tolerance and safety by comparing the proportion of samples that discontinued the trial due to adverse events as well as the number of adverse events in each treatment group and found no significant difference between coadministration of amlodipine/atorvastatin and single drug therapy or placebo [18].

Adherence is believed to be the biggest challenge of concomitant therapy. Most hypertensive patients need multiple medications for effective management, yet adherence to concomitant therapy decreases as number of medications increases. The reduction in adherence was greatest in patients with the fewest preexisting prescriptions [35]. Correspondingly, it was found that concurrently starting two medications improved adherence [36]. Other factors that may influence adherence include time interval of therapy initiation, a history of CVD, and more outpatient physician visits in the prior year [37]. A more efficient way is the single-pill strategy, which has been adopted in many trials and was found to improve adherence than two-pill administration [38].

However, few standard comparative effectiveness studies have ever been done in real-world settings to solve all the practical problems, e.g., a head-to-head comparison among various antihypertensive drugs or statins in combined therapy or an investigation of the long-term effect vs. short-term one. Although a single-pill strategy is believed to help achieve treatment goal largely due to improved adherence, no direct evidence is currently available to prove its superiority in adherence.

Integrated Strategy Toward the Goal of Overall Risk Reduction

Although lifestyle change, education, and risk factor monitoring are the first steps for control of patients with combined hypertension-dyslipidemia, this is often not sufficient for most patients with these conditions. Management of hypertension-dyslipidemia should integrate both lifestyle and pharmacological approaches since the potential benefits of medication might be largely jeopardized or attenuated by the negative impact of bad behavior, such as smoking. On the other hand, evidence of the incremental protective effect of supplementary management regarding behavioral and lifestyle interventions is still limited except for one randomized trial that found the self-monitoring had no significant incremental effect on reducing future CV events in addition to medication, which results in the strong focus of pharmacological management in guidelines [39].

While the strategies of CVD prevention are being integrated, the goal to prevent CVD events is to reduce the overall CVD risk rather than targeting single risk factors. Jackson et al. conducted a review of the randomized trials of BP or blood cholesterol–lowering treatments and outlined the rationale for targeting BP and blood cholesterol–lowering therapy to patients at high absolute CV risk. They concluded that separate management guidelines for raised BP and blood cholesterol need to be replaced by integrated CV risk management guidelines. They also posited that because CV risk factors interact with each other, moderate reductions in several risk factors can be more effective than major reductions in one.

Conclusion

While there have been substantial improvements over recent decades in the management of single risk factors including hypertension and dyslipidemia, control of composite risk factors such as concomitant hypertension and dyslipidemia remain particularly low, even among those on medication. Yet, reduction of overall CVD risk decreases CVD events greater than single risk factor reduction, which emphasizes the importance of integrated management of CVD risk. The benefit is believed to be even more among those with particular high-risk populations, such as the elderly. Although combined therapy postulates big challenges on adherence, greater adherence is possible with fewer medications or a single pill to treat hypertension-dyslipidemia or overall CVD risk. Current guidelines recognize the importance of total cardiovascular risk management, and overall CV risk management is the ultimate goal in order to maximize CVD event reduction.

References

1. World Health Organization. World health statistics 2012. Geneva: WHO; 2012.
2. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA. 2003;289:2560–72.
3. Kannel WB. Risk stratification in hypertension: new insights from the Framingham Study. Am J Hypertens. 2000;13:3S–10.
4. Wong ND, Lopez V, Tang S, Williams GR. Prevalence, treatment, and control of combined hypertension and hypercholesterolemia in the United States. Am J Cardiol. 2006;98:204–8.
5. Eaton CB, Feldman HA, Assaf AR, et al. Prevalence of hypertension, dyslipidemia, and dyslipidemic hypertension. J Fam Pract. 1994;38:17–23.
6. Williams B, Wilson K, Lacey L, et al. The prevalence and management of patients with coexisting hypertension and hypercholesterolaemia in the UK. Eur Heart J. 2004;25:528–9.
7. De Bacquer D, De Backer G. The prevalence of concomitant hypertension and hypercholesterolaemia in the general population. Int J Cardiol. 2006;110:217–23.
8. Onat A, Hergenç G, Sari I, Türkmen S, Can G, Sansoy V. Dyslipidemic hypertension: distinctive features and cardiovascular risk in a prospective population-based study. Am J Hypertens. 2005;18:409–16.
9. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med. 1992;152:56–64.
10. Wong ND, Lopez VA, Roberts CS, et al. Combined association of lipids and blood pressure in relation to incident cardiovascular disease in the elderly: the cardiovascular health study. Am J Hypertens. 2010;23:161–7.
11. Thomas F, Bean K, Guize L, et al. Combined effects of systolic blood pressure and serum cholesterol on cardiovascular mortality in young (<55 years) men and women. Eur Heart J. 2002;23:528–35.
12. Satoh M, Ohkubo T, Asayama K, et al. Combined effect of blood pressure and total cholesterol levels on long-term risks of subtypes of cardiovascular death: evidence for cardiovascular prevention from observational cohorts in Japan. Hypertension. 2015;65:517–24.

13. Kohro T, Fujita M, Sasayama S, et al. Prognostic effects of combined treatment with calcium channel blockers and statins in patients with coronary narrowing: from the Japanese Coronary Artery Disease study. Int Heart J. 2010;51:299–302.
14. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: a report from the american heart association. Circulation. 2015;131:e29–322.
15. Johnson ML, Pietz K, Battleman DS, et al. Therapeutic goal attainment in patients with hypertension and dyslipidemia. Med Care. 2006;44:39–46.
16. Egan BM, Li J, Qanungo S, Wolfman TE. Blood pressure and cholesterol control in hypertensive hypercholesterolemic patients: national health and nutrition examination surveys 1988–2010. Circulation. 2013;128:29–41.
17. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA. 2003;289:2534–44.
18. Messerli FH, Bakris GL, Ferrera D, et al. Efficacy and safety of coadministered amlodipine and atorvastatin in patients with hypertension and dyslipidemia: results of the AVALON trial. J Clin Hypertens (Greenwich). 2006;8:571–81.
19. Flack JM, Victor R, Watson K, et al. Improved attainment of blood pressure and cholesterol goals using single-pill amlodipine/atorvastatin in African Americans: the CAPABLE trial. Mayo Clin Proc. 2008;83:35–45.
20. Zamorano J, Erdine S, Pavia A, et al; CRUCIAL Investigators. Proactive multiple cardiovascular risk factor management compared with usual care in patients with hypertension and additional risk factors: the CRUCIAL trial. Curr Med Res Opin. 2011;27:821–33.
21. Neutel JM, Bestermann WH, Dyess EM, et al. The use of a single-pill calcium channel blocker/statin combination in the management of hypertension and dyslipidemia: a randomized, placebo-controlled, multicenter study. J Clin Hypertens (Greenwich). 2009;11:22–30.
22. Blank R, LaSalle J, Reeves R, et al. Single-pill therapy in the treatment of concomitant hypertension and dyslipidemia (the amlodipine/atorvastatin GEMINI study). J Clin Hypertens (Greenwich). 2005;7:264–73.
23. Erdine S, Ro YM, Tse HF, et al. Single-pill amlodipine/atorvastatin helps patients of diverse ethnicity attain recommended goals for blood pressure and lipids (the Gemini-AALA study). J Hum Hypertens. 2009;23:196–210.
24. Oliver S, Jones J, Leonard D, Crabbe A, Delkhah Y. Improving adherence with amlodipine/atorvastatin therapy: IMPACT study. J Clin Hypertens (Greenwich). 2011;13:598–604.
25. Richard Hobbs FD, Gensini G, John Mancini GB. International open-label studies to assess the efficacy and safety of single-pill amlodipine/atorvastatin in attaining blood pressure and lipid targets recommended by country-specific guidelines: the JEWEL programme. Eur J Cardiovasc Prev Rehabil. 2009;16:472–80.
26. Grimm R, Malik M, Yunis C, Sutradhar S, Kursun A, TOGETHER Investigators. Simultaneous treatment to attain blood pressure and lipid goals and reduced CV risk burden using amlodipine/atorvastatin single-pill therapy in treated hypertensive participants in a randomized controlled trial. Vasc Health Risk Manag. 2010;6:261–71.
27. Ivanovic B, Tadic M. Fixed combination of amlodipine/atorvastatin: from mechanisms to trials. J Cardiovasc Pharmacol Ther. 2013;18:544–9.
28. Rump LC, Baranova E, Okopien B, Weisskopf M, Kandra A, Ferber P. Coadministration of valsartan 160 and 320 mg and simvastatin 20 and 40 mg in patients with hypertension and hypercholesterolemia: a multicenter, 12-week, double-blind, double-dummy, parallel-group superiority study. Clin Ther. 2008;30:1782–93.
29. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. JAMA. 1998;279:1615–22.
30. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361:1149–58.

31. Sever PS, Poulter NR, Mastorantonakis S, et al. Coronary heart disease benefits from blood pressure and lipid-lowering. Int J Cardiol. 2009;135:218–22.
32. Wong ND, Pio JR, Franklin SS, et al. Preventing coronary events by optimal control of blood pressure and lipids in patients with the metabolic syndrome. Am J Cardiol. 2003;91:1421–6.
33. Emberson J, Whincup P, Morris R, et al. Evaluating the impact of population and high-risk strategies for the primary prevention of cardiovascular disease. Eur Heart J. 2004;25:484–91.
34. de Cates AN, Farr MR, Wright N, et al. Fixed-dose combination therapy for the prevention of cardiovascular disease. Cochrane Database Syst Rev. 2014;(4):CD009868.
35. Benner JS, Chapman RH, Petrilla AA, et al. Association between prescription burden and medication adherence in patients initiating antihypertensive and lipid-lowering therapy. Am J Health Syst Pharm. 2009;66:1471–7.
36. Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med. 2005;165:1147–52.
37. Chapman RH, Petrilla AA, Benner JS, et al. Predictors of adherence to concomitant antihypertensive and lipid-lowering medications in older adults: a retrospective, cohort study. Drugs Aging. 2008;25:885–92.
38. Patel BV, Leslie RS, Thiebaud P, et al. Adherence with single-pill amlodipine/atorvastatin vs a two-pill regimen. Vasc Health Risk Manag. 2008;4:673–81.
39. Tiessen AH, Smit AJ, Broer J, Groenier KH, Van der Meer K. Which patient and treatment factors are related to successful cardiovascular risk score reduction in general practice? Results from a randomized controlled trial. BMC Fam Pract. 2013;14:123.

Chapter 14
The Cardiovascular Polypill in the Prevention of Cardiovascular Disease

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The June 2003 edition of the *British Medical Journal* introduced Wald and Law's concept of a polypill, also known as a fixed-dose combination (FDC) pill. Wald and Law proposed "a strategy to reduce cardiovascular disease by more than 80 %" by simultaneously addressing four cardiovascular risk factors regardless of pretreatment levels in a low-risk population. They stated, "the polypill strategy could largely prevent heart attacks and strokes if taken by everyone aged 55 and older, and everyone with existing cardiovascular disease," and "widespread use would have a greater impact on the prevention of disease in the Western world than any other single intervention." [1] Criticism of the polypill strategy is based on the view that the use of aspirin, statin, and blood pressure (BP)-lowering agents would largely be promoted in a primary prevention setting in a population at a low absolute risk of cardiovascular disease. It was argued that a large proportion of the population would be medicalized unnecessarily, inducing a sense of protection and deflecting attention from healthy behaviors. Although this strategy raised high hopes that a polypill-based treatment could reduce the incidence of atherosclerotic cardiovascular disease exceptionally, the bare truth is that cardiovascular disease is still the major cause of mortality and morbidity worldwide and the polypill has still not largely entered the market.

In the Western world, cardiovascular disease affects half of all individuals over their lifetimes [2]. More strikingly, the burden of cardiovascular disease is increasing disproportionate in low- and middle-income countries (LMICs), in which over 80 % of the global cardiovascular deaths occur [3, 4]. Risk factors cluster in patients, combining dyslipidemia, increased blood pressure (BP), and insulin resistance. To call a halt to the epidemic of cardiovascular disease will require simultaneously

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addressing the societal determinants of the root causes of cardiovascular disease, the development of risk factors among individuals, and the use of medication to treat cardiovascular risk factors in order to prevent cardiovascular diseases [5].

Current Guideline Recommendations for Long-Term Use of Aspirin, a Statin, and BP-Lowering Agents

In patients with established cardiovascular disease, current guidelines recommend the use of aspirin, a statin, and BP-lowering agents with little constraints. This reflects the enormous body of evidence that such treatments reduce the risk of cardiovascular events and mortality, regardless of the initial levels of risk factors and independent of other treatments [6–9]. Among people without established cardiovascular disease, there has been a transition in recent decades from treatment recommendations for statin and BP treatment being based on single risk factors, e.g., BP thresholds, to treatment based on predicted absolute risk of cardiovascular disease [10]. Also in high-risk patients, such as those with dyslipidemia and high BP, statin and BP-lowering agents are recommended to be used unless clear contraindications exist. The reduction of risk factors is proportional to the clinical benefits [7, 8]. The use of aspirin in primary prevention is still under debate, although recent evidence, demonstrating a potential reduction in cancer deaths with long-term use, might be expected to further change the risk/benefit equation [6, 11].

Current Treatment Gaps in High-Risk Groups

Given the evidence that reductions in any level of cholesterol and BP reduce cardiovascular risk, pharmacological treatment should be prescribed to the vast majority of high-risk patients. However, a substantial gap exists between recommended treatment and clinical practice. Several reports indicate inadequate prescription rates of antiplatelet lipid- and BP-lowering agents and nonachievement of treatment goals. The EUROASPIRE III survey has shown that in patients with established coronary artery disease (CAD) cholesterol was on target in 54 % and BP in 39 % of the patients. Antiplatelet agents were used in 91 %, statins in 78 %, beta-blockers in 80 %, and angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor blockers (ARBs) in 71 % of the patients [12]. A survey performed in LMICs showed that patients with CAD and ischemic cerebrovascular disease received aspirin in 80 and 71 %, statins in 30 and 14 %, beta-blockers in 48 and 23 %, and ACEis in 40 and 38 % of the cases respectively [13]. These data indicate that even larger prescription gaps exist in LMICs compared to suboptimal prescription rates in high-income countries. It should also be emphasized that prescription rates exceed consumption or individual dosing rates. Various barriers may underlie suboptimal prescribing rates and low treatment continuation rates in high-risk patients, which

include the complexity of preventive treatment regimens for both doctors and patients, inequities in health care delivery, and medication costs.

Furthermore, nonadherence to therapy is one of the main obstacles for the unsatisfactory reduction of risk factors. Nonadherence is characterized by premature cessation of treatment together with suboptimal use of medication and is correlated with an increased risk of mortality [14]. Patients usually do not understand the importance of taking long-term preventive medication. Long-term adherence is low, with only 70 % adherence to aspirin therapy and 45 % to lipid- and BP-lowering therapy after 12 months [15]. The problem gets worse as the number of prescribed drugs per day increases. Increasing age, established cardiovascular disease, and/or type 2 diabetes mellitus usually indicate the use of more than five drugs per day, called polypharmacy [16]. Treating high-risk patients often requires prescription of multiple medications even though this is known to be associated with diminishing adherence, inadequate prescription, and drug interactions.

High drug costs largely affect treatment gaps in LMICs where most healthcare services are paid for out of pocket with little or no subsidy through health insurances or the government. In this setting, the economic burden of secondary prevention of cardiovascular diseases is enormous [17]. Consequently, preventive drugs are unaffordable for the majority of individuals in developing countries. Although the efficacy concerns of preventive strategies may be recognized at a high scientific level, access and supply for the target population remains the major challenge.

Polypill in High-Risk Groups

Combining multiple well-established cardiovascular drugs into a single polypill may be likely to result in a significant reduction of cardiovascular events when implemented in a low-risk population. However, the use of the polypill in high-risk populations could be seen as the “low-hanging fruit” for research and implementation of FDC pills for several reasons. Patients with established cardiovascular disease are at the highest absolute risk. In these patients, there is no doubt that the multiple components are indicated and the margin of benefit is high. By avoiding complex decision algorithms and enhancing the simplicity of prescribing medication, the polypill may well help in closing current substantial treatment gaps in this group. The polypill could be considered as baseline therapy providing the minimum standard therapy for high-risk individuals. The principal goal of the polypill strategy is reducing the risk of cardiovascular events and mortality and not normalizing risk factors. It should be noted that this strategy does not rule out tailored care as every individual can be treated with additional cholesterol- and/or BP-lowering agents if the treatment goals are not achieved.

Improvement of adherence in patients at high cardiovascular risk is an important principle of the polypill. The World Health Organization (WHO) suggested that increasing the effectiveness of adherence to therapy may have greater impact on the health of the population than any new interventions [18].

One further issue is cost-effectiveness. The use of aspirin, a statin, a beta-blocker, and an ACEi in the secondary prevention of cardiovascular disease is well accepted and part of standard care in most LMICs. Current standards qualify these treatments as highly cost effective [19]. A major advantage of the polypill, with tremendous consequences on health care in developing countries, relates to the low costs and improved affordability. By dispensing a single generic pill instead of the individual drugs, packaging, dispensing, and pharmacy expenditure can be reduced enormously. The intended pricing, motivated by public health considerations, would increase equitable access in LMICs and has the potential to bring an effective preventive strategy within the financial reach of poorer individuals and governments in LMICs.

Limitations of the Polypill

Even though the polypill strategy is conceptually simple, there are certain drawbacks to a combination pill meaning that a polypill strategy will not be applicable in every individual. Due to fixed combinations in the polypill, there is no flexibility in being able to change the class of BP-lowering drugs due to unacceptable side effects or contraindications. This may be addressed in the future by the marketing of several polypills with various components, thereby giving the clinician greater choice of drug class while retaining the convenience of the polypill.

In addition, because of the combination of agents at a fixed dose in a polypill, it may not be suitable for all the patients, as, for example, it may cause adverse events like orthostatic hypotension or dizziness in those requiring lower doses of BP-lowering agents. Alternatively, if the doses of some agents in a polypill are insufficient for some patients and treatment goals are not reached, then additional doses of those agents may be prescribed in addition to the polypill.

Trialing the Polypill

Although the effectiveness and efficacy of the individual agents of polypills have been demonstrated widely, the effectiveness of this strategy of providing treatment needs to be assessed. Currently, several academic collaborations have been launched for performing randomized clinical trials, assessing the efficacy of the polypill in various patient populations, from pharmacodynamic and pharmacokinetic studies to clinical end-point trials.

Pharmacodynamic and Pharmacokinetic Studies

One of the first clinical studies compared the effect of an FDC formulation to the components of the polypill on risk factor levels and safety parameters [20, 21]. In “The Indian Polycap Study” (TIPS), 2053 individuals aged 45–80 years with one

cardiovascular risk factor were randomized to a 12 week treatment with the polycap (aspirin 100 mg, simvastatin 20 mg, atenolol 50 mg, hydrochlorothiazide 12.5 mg, and ramipril 5 mg) or to one of the eight other treatment groups (aspirin, simvastatin, hydrochlorothiazide, three combinations of the two BP-lowering drugs, three BP-lowering drugs, or three BP-lowering drugs plus aspirin). After 12 weeks of treatment, a mean LDL-cholesterol reduction of 0.70 mmol/L and 7.4 mmHg systolic BP reduction was observed when using the polycap compared to placebo. The trial demonstrated that the risk factor reductions and number of adverse events from each treatment modality were similar in the presence and absence of other treatments. Only simvastatin in the polypill reduced the LDL-cholesterol slightly less compared to the single drug (0.70 mmol/L versus 0.83 mmol/L; $p = 0.04$), although this could be the play of chance [22].

The bioavailability of the ingredients of the polycap was compared with that of identical capsules with each of the ingredients separately in a five-arm clinical trial in 195 healthy individuals. Plasma concentrations of each drug and, where applicable, its active metabolite were measured. The plasma concentration of simvastatin was significantly lower (3–4 %) than the allowed 80 % bound. However, the concentration of the active metabolite, simvastatin acid, was significantly higher, which appeared to compensate for the loss of bioavailability of simvastatin. Comparative bioavailability was computed for all other components, and no drug-drug interactions and no difference in comparative bioavailability were concluded for each ingredient [23].

The effect of the polypill in the morning or the evening (aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and hydrochlorothiazide 12.5 mg) on LDL-cholesterol and 24-h systolic ambulatory BP was compared to the administration of individual, identical dosed components of the polypill. "The Evening versus Morning Polypill Utilization Study" (TEMPUS) was a randomized cross-over trial in which 78 participants were included. When the polypill was administered in the evening, the reduction of LDL-cholesterol (mean difference:−0.1 mmol/L; 95 %-CI: −0.1 to 0.0) and mean 24-h systolic BP (mean difference: 1.0 mmHg; 95 %-CI:−0.8 to 2.8) was not different than when using the individual agents. However, compared to the individual agents, the mean LDL-cholesterol was 0.2 mmol/L (95 %-CI: 0.1 to 0.3) higher when using the polypill in the morning, while the mean 24-h systolic BP was similar (mean difference: 0.4 mmHg; 95 %-CI: −1.5 to 2.3). Importantly, therapy with a polypill was highly preferred over treatment with the individual, identical dosed agents of the polypill supporting the role for the polypill in the prevention of cardiovascular disease [24].

Efficacy and Safety

An FDC formulation corresponds closely to combinations that are already in widespread use. Remarkably, the generic drugs used as components of the polypill have been marketed for many years in the prevention of cardiovascular disease. It may very well be that many patients use the identical components as polypill administered at the same time, although not in one pill or capsule. However, substantially

different from when using the polypill, each of the individual components was prescribed at the discretion of the treating physician for a specific indication and taking into account contraindications. The concept of the polypill includes promoting widespread use of cardiovascular risk-lowering treatments regardless of risk factor levels leaving limited potential for flexibility.

In a double-blind, randomized, placebo-controlled trial in Iran, 475 low-risk participants, aged 50–79 years, were randomized to a polypill (aspirin 81 mg, atorvastatin 20 mg, enalapril 2.5 mg, and hydrochlorothiazide 12.5 mg) or placebo for a period of 12 months. The trial showed that the polypill achieved modest reductions of LDL-cholesterol (mean difference: 0.46 mmol/L) and BP levels (mean difference systolic: 4.5 and diastolic: 1.6 mmHg) [25].

In the randomized, double-blind, placebo-controlled "Programme to Improve Life and Longevity" (PILLpilot) trial, 378 individuals at intermediate risk of cardiovascular disease were randomized to using a polypill (aspirin 75 mg, simvastatin 20 mg, lisinopril 10 mg, and hydrochlorothiazide 12.5 mg) or placebo during 12 weeks. Using the polypill resulted in a 0.9 mmol/L (95 %- CI: 0.8–1.0) lower mean LDL-cholesterol and 10 mmHg (95 %-CI: 8–12) lower mean systolic BP compared to using placebo [26]. The effect of the polypill on risk factor levels was modified by the baseline levels of these risk factors. Yet, the achieved cardiovascular relative risk reduction was only modestly modified by the baseline levels of these risk factors. Although mild adverse events such as cough and hypotension were reported more often in the polypill group, these were not related to baseline risk factor levels, suggesting that patients with mildly increased risk factor levels, but an overall raised cardiovascular risk, would also benefit from being treated with a polypill (unpublished data).

The dose of each substance within the combination must be such that the combination is safe and effective for the targeted population and the benefit/risk assessment of the novel FDC formulation is equal or exceeds that of each substance taken alone. In concept, the initial doses of the components of a polypill should be low to increase tolerability [27]. Recently, a dosage study has been performed in which the polycap (aspirin 100 mg, simvastatin 20 mg, atenolol 50 mg, hydrochlorothiazide 12.5 mg, and ramipril 5 mg) was used. "The Second Indian Polycap Study" (TIPS-2) with 518 patients demonstrated that a double-dosed polycap with potassium supplementation resulted in a 0.2 mmol/L additional mean LDL-cholesterol reduction and 2.8 mmHg additional systolic BP reduction compared to a single-dosed polycap. Both treatments had similar discontinuation rates (7.8 % in the double-dosed group versus 6.9 % in the single-dosed group), suggesting also a potential role for a high-dosed polypill [28].

Comparative Clinical Trial

As one of the most fundamental evidence are comparative clinical studies of a polypill -based treatment strategy versus reference treatment, these trials are needed to put into perspective the improvement obtained with a polypill-based treatment

strategy. Only confirmatory trials are able to show the net effect of the various hypothesized benefits of a polypill in a real-life population. The acceptability, efficacy, and economic impact of a polypill-based strategy for the prevention of cardiovascular events are likely to vary substantially between countries, as these will be greatly influenced by the existing health care systems, i.e., usual care and the subsidies offered for drug therapy. Hence, information about these healthcare system parameters for implementing a polypill-based strategy from both developed and developing countries in high-risk patients is imperative. It could be hypothesized that implementation of the polypill strategy would be most beneficial in LMICs. A large international initiative to address the effects of polypill versus usual care was undertaken by the "Single Pill to Avert Cardiovascular Events" (SPACE) Collaboration. The Collaboration was initiated in 2009 and comprises a group of academic investigators from Australia, New Zealand, India, China, South Africa, Brazil, Canada, United Kingdom, Ireland, and The Netherlands. Currently, three trials with similar design have been published [29–31]. Each trial is as similar to "real life" as possible within each national setting, while maintaining as much uniformity between all trials as possible to facilitate the final pooling of data. The "Use of a Multidrug Pill In Reducing cardiovascular Events" (UMPIRE) trial was the first randomized, clinical trial comparing a polypill-based treatment strategy for delivery of medication (aspirin, a statin, and two BP-lowering agents) to usual care among participants with established cardiovascular disease or at equivalent high risk (an estimated 5 year cardiovascular risk of ≥15 %) in India and three European countries (the United Kingdom, Ireland, and the Netherlands). In the polypill group, physicians could use a polypill that contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and either atenolol 50 mg or hydrochlorothiazide 12.5 mg. In the usual care group, treatment continued according to the physicians' discretion. In total, 2004 participants were randomized in India and Europe. After a median follow-up of 15 months, the polypill group showed to have an improved adherence (relative risk of being adherent: 1.33; 95 %-CI: 1.26–1.41) with a concurrent 0.11 mmol/L (95 %-CI: 0.05–0.17) lower mean LDL-cholesterol and 2.6 mmHg (95 %-CI: 1.1–4.0) lower mean clinical systolic BP compared to the usual care group [29]. The size of these benefits was regarded as modest in the relatively well-treated high-risk population. As participants were randomized to continuing usual care or a polypill, the consequences of switching to a polypill were likely to be influenced by medications and doses used at baseline [29]. In the "IMProving Adherence using Combination Therapy" (IMPACT) trial, 513 patients in New Zealand were randomized to an FDC-based care or usual care, similar to the UMPIRE trial. In this trial, there was no statistically significant improvement in LDL-cholesterol (mean difference: −0.05 mmol/L; 95 %-CI: −0.17 to 0.08) or in systolic BP (mean difference:−2.2 mmHg; 95 %-CI: −5.6 to 1.2) after 12 months of treatment with the polypill or usual care [30]. In the "Kanyini-Guidelines Adherence with the Polypill' (GAP) trial, 623 Australian patients were included. After a median of 18 months, the polypill-based strategy did not show a difference in total cholesterol (mean difference: 0.08 mmol/l; 95 %-CI: −0.06 to 0.22) or systolic blood pressure (mean difference: −1.5 mmHg; 95 %-CI: −4.0 to 1.0) [31]. It is anticipated that

a prespecified meta-analysis will provide substantial power to examine the effects of the intervention on clinical outcomes, including cardiovascular events such as myocardial infarction, stroke, and mortality [32].

Additionally, an open-label, parallel-group, randomized trial has been published, which enrolled 216 high-risk patients without established cardiovascular disease in Sri Lanka. The trial compared a polypill (aspirin 75 mg, simvastatin 20 mg, lisinopril 10 mg, and hydrochlorothiazide 12.5 mg) to usual care after 3 months of treatment. Both polypill treatment and usual care resulted in marked reductions in total cholesterol, systolic BP, and 10 year risk of cardiovascular disease. These reductions in risk factor levels were not significantly different between the two treatment groups. However, it has been stated that the prescribed therapies in regular care comprised more use of statins and BP-lowering agents than was to be expected due to dilution bias underestimating the effect of the polypill. Additionally, also adverse events were similar in both groups [33].

Marketing the Polypill

Licensing is an essential step for marketing combination therapy in any population. Regulatory agencies are faced with new issues when evaluating novel FDC formulations. The United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved various two- and a couple of three-drug combinations, but neither has granted a marketing license for four- or five-drug formulations [34]. Additionally, previous combination treatments only addressed one risk factor, complicating decision-making as in the polypill concept multiple risk factors are addressed simultaneously, irrespective of risk factor levels. Currently, the effect of FDC formulations has been shown in various comparative trials powered on risk factors. Although the emerging opinion suggests that cardiovascular end-point trial studies are not required, this is not yet undoubtedly adopted by the regulators. Treatment effects on established surrogate end points that are reasonably likely to predict clinical benefit, such as LDL-cholesterol and systolic BP, may result in marketing authorization [35].

High-Risk Patients: The Near Future!

Given the present data on the effect of a polypill in high-risk patients, it is highly likely that a polypill-based treatment strategy will be adopted in the forthcoming years. Especially in LMICs, a polypill is, in general, the best alternative treatment to hardly any treatment. Yet, similarly in the Western countries, the polypill has shown to have beneficial effects on adherence and cardiovascular risk factor levels, indicating a role for the polypill as complementary treatment strategy in the

prevention of cardiovascular disease. However, if FDC formulations are licensed and a polypill-based treatment strategy is to be successfully implemented, health care professionals will need to be convinced of the benefits of this approach.

Low-Risk Population: More Reservations?

There is a theoretical rationale for a polypill-based treatment in low-risk populations, in which imperfect and expensive screening is avoided. While the low-risk population has a small absolute risk of cardiovascular events, this population includes most of those who will experience cardiovascular events due to the great size of low-risk group [1]. Additionally, with the present increasing incidence of cardiovascular disease, there would be insufficient physicians and healthcare workers worldwide to screen and treat every individual at risk. Instead of aiming at lifestyle first and pharmaceutical treatment only if required, a multifactorial approach addressing the societal determinants of the root causes of cardiovascular disease, the development of risk factors among individuals, and the use of medicines to prevent and treat cardiovascular diseases is far more efficient. Although lifestyle modification is natural and safe, it is generally not low cost, not simple, and not sustainable [36]. Yet, even a decade later since the introduction of the concept, there appears to be little, though growing, support for a polypill-based preventive strategy in a low-risk population. Possibly if trials involving high- and intermediate-risk individuals show clear beneficial effects, the idea of offering treatment to everybody older than 50 years might raise widespread interest.

Some trials have been initiated in a low-risk population with regard to risk factor reductions [25, 33]. Nevertheless, licensing a polypill for a low-risk population will undoubtedly require large clinical end-point trials. The "Heart Outcomes Prevention and Evaluation 4" (HOPE-4) study aims to evaluate the effect of a polypill-based treatment strategy (simvastatin 20 mg, ramipril 5 mg, atenolol 50 mg, and hydrochlorothiazide 12.5 mg) on major cardiovascular end points compared to usual care in approximately 9,500 participants aged 50 years and older. Similarly, "The International Polycap Study 3" (TIPS-3) aims to evaluate the effect of the polycap in double strength (simvastatin 40 mg, ramipril 10 mg, atenolol 100 mg, and hydrochlorothiazide 25 mg), aspirin and cholecalciferol on major cardiovascular events in 5,500 participants at intermediate risk aged 55 years and older in a factorial design. The results of both trials are anticipated to become available in 2020.

As an alternative option for a licensed polypill-based treatment strategy, alternatives have been marketed. Early in 2012, Wald and Law performed a randomized cross-over trial including 86 individuals aged older than 50 years. All participants received (simvastatin 40 mg, losartan 25 mg, amlodipine 2.5 mg and hydrochlorothiazide 12.5 mg) or placebo during a period of 12 weeks the polypill, and switched to the alternative treatment for another 12 weeks. Use of the polypill resulted in a 1.4 mmol/L (95 %-CI: 1.2–1.6) lower mean LDL-cholesterol and 17.9 mmHg

(95 %-CI: 15.7–20.1) lower mean systolic BP. They suggested that long-term reduction of this magnitude would have substantial effect on preventing cardiovascular disease [37]. Most strikingly, they put the Polypill Prevention Programme online after failing to get backing from the pharmaceutical industry [38]. This program includes a daily preventive treatment with a polypill (simvastatin 20 mg, losartan 25 mg, amlodipine 2.5 mg, and hydrochlorothiazide 12.5 mg) for individuals aged 50 years and older [39].

Conclusion

Currently, large treatment gaps exist among high-risk individuals, in whom the guidelines recommend concomitant treatment with aspirin, statin, and BP-lowering drugs. The polypill could be an important tool to help close these treatment gaps. Recent data indicate that combination pills can produce sizable risk factor reductions, with a halving of predicted cardiovascular risk. Results from ongoing trials that are further assessing the effectiveness of combination pills in reducing cholesterol and BP levels, effects on adherence to indicated medications, and clinical outcomes would provide clear evidence on the role of polypill-based treatment strategy in the long run. It would also hold implications for policymaking to address both primary and secondary cardiovascular prevention globally.

References

1. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003;326(7404):1419.
2. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113(6):791–8. CIRCULATIONAHA.105.548206 [pii]. doi:10.1161/CIRCULATIONAHA.105.548206 [published Online First: Epub Date].
3. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128. doi:10.1016/S0140-6736(12)61728-0 [published Online First: Epub Date].
4. World Health Organization. Global status report on non-communicable diseases 2010. Geneva: World Health Organization; 2011.
5. Browne JL, Grobbee DE. Cardiovascular prevention and international health: time for action. Eur J Cardiovasc Prev Rehabil. 2011;18(4):547–9. doi:10.1177/1741826711414116 [published Online First: Epub Date].
6. Antithrombotic Trialists Collaboration, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373(9678):1849–60. doi:10.1016/S0140-6736(09)60503-1 [published Online First: Epub Date].
7. Cholesterol Treatment Trialists Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000

participants in 26 randomised trials. Lancet. 2010;376(9753):1670–81. doi:10.1016/S0140-6736(10)61350-5 [published Online First: Epub Date].
8. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
9. Thompson AM, Hu T, Eshelbrenner CL, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. JAMA. 2011;305(9):913–22. 305/9/913 [pii]. doi:10.1001/jama.2011.250 [published Online First: Epub Date].
10. Jackson R, Lawes CM, Bennett DA, et al. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet. 2005;365(9457):434–41. S0140-6736(05)17833-7 [pii]. doi:10.1016/S0140-6736(05)17833-7 [published Online First: Epub Date].
11. Rothwell PM, Fowkes FGR, Belch JFF, et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011;377(9759):31–41.
12. Kotseva K, Wood D, De Backer G, et al. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. Lancet. 2009;373(9667):929–40.
13. Mendis S, Abegunde D, Yusuf S, et al. WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE). Bulletin of the World Health Organization. 2005;83(11):820–9. S0042-96862005001100011 [pii]/S0042-96862005001100011 [published Online First: Epub Date].
14. Gehi AK, Ali S, Na B, et al. Self-reported medication adherence and cardiovascular events in patients with stable coronary heart disease: the heart and soul study. Arch Intern Med. 2007;167(16):1798–803. 167/16/1798 [pii]. doi:10.1001/archinte.167.16.1798 [published Online First: Epub Date].
15. Newby LK, LaPointe NM, Chen AY, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. Circulation. 2006;113(2):203–12. CIRCULATIONAHA.105.505636 [pii]. doi:10.1161/CIRCULATIONAHA.105.505636 [published Online First: Epub Date].
16. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001;23(8):1296–310.
17. Mendis S, Fukino K, Cameron A, et al. The availability and affordability of selected essential medicines for chronic diseases in six low- and middle-income countries. Bulletin of the World Health Organization. 2007;85(4):279–88. S0042-96862007000400013. [pii] [published Online First: Epub Date].
18. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
19. Gaziano TA, Opie LH, Weinstein MC. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. Lancet. 2006;368(9536):679–86. S0140-6736(06)69252-0 [pii]. doi:10.1016/S0140-6736(06)69252-0 [published Online First: Epub Date].
20. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical development of fixed combination medicinal products. London: European Medicines Agency; 2009.
21. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry: codevelopment of two or more new investigational drugs for use in combination. Silver Spring: Food and Drug Administration; 2013.
22. Yusuf S, Pais P, Afzal R, et al. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. Lancet. 2009;373(9672):1341–51.
23. Patel A, Shah T, Shah G, et al. Preservation of bioavailability of ingredients and lack of drug-drug interactions in a novel five-ingredient polypill (polycap): a five-arm phase I crossover

trial in healthy volunteers. Am J Cardiovasc Drugs. 2010;10(2):95–103. doi:10.2165/11532170-000000000-00000 [published Online First: Epub Date].
24. Lafeber M, Grobbee DE, Schrover IM, et al. Comparison of a morning polypill, evening polypill and individual pills on LDL-cholesterol, ambulatory blood pressure and adherence in high-risk patients; a randomized crossover trial. Int J Cardiol. 2014;181C:193–9. doi:10.1016/j.ijcard.2014.11.176 [published Online First: Epub Date].
25. Malekzadeh F, Marshall T, Pourshams A, et al. A pilot double-blind randomised placebo-controlled trial of the effects of fixed-dose combination therapy ('polypill') on cardiovascular risk factors. Int J Clin Pract. 2010;64(9):1220–7. IJCP2412 [pii]. doi:10.1111/j.1742-1241.2010.02412.x [published Online First: Epub Date].
26. Rodgers A, Patel A, Berwanger O, et al. An international randomised placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk. PloS one. 2011;6(5):e19857. doi:10.1371/journal.pone.0019857. PONE-D-11-02253 [pii] [published Online First: Epub Date].
27. Lafeber M, Spiering W, Singh K, et al. The cardiovascular polypill in high-risk patients. Eur J Cardiovasc Prev Rehabil. 2012;19(6):1234–42. doi:10.1177/1741826711428066 [published Online First: Epub Date].
28. Yusuf S, Pais P, Sigamani A, et al. Comparison of risk factor reduction and tolerability of a full-dose polypill (with potassium) versus low-dose polypill (polycap) in individuals at high risk of cardiovascular diseases: the Second Indian Polycap Study (TIPS-2) investigators. Circ Cardiovasc Qual Outcomes. 2012;5(4):463–71. doi:10.1161/CIRCOUTCOMES.111.963637 [published Online First: Epub Date].
29. Thom S, Poulter N, Field J, et al. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. JAMA. 2013;310(9):918–29.
30. Selak V, Elley CR, Bullen C, et al. Effect of fixed dose combination treatment on adherence and risk factor control among patients at high risk of cardiovascular disease: randomised controlled trial in primary care. BMJ. 2014;348:g3318. doi:10.1136/bmj.g3318 [published Online First: Epub Date].
31. Patel A, Cass A, Peiris D, et al. A pragmatic randomized trial of a polypill-based strategy to improve use of indicated preventive treatments in people at high cardiovascular disease risk. Eur J Prev Cardiol. 2014. doi:10.1177/2047487314530382 [published Online First: Epub Date].
32. Webster R, Patel A, Billot L, et al. Prospective meta-analysis of trials comparing fixed dose combination based care with usual care in individuals at high cardiovascular risk: the SPACE Collaboration. Int J Cardiol. 2013;170(1):30–5. doi:10.1016/j.ijcard.2013.10.007 [published Online First: Epub Date].
33. Soliman EZ, Mendis S, Dissanayake WP, et al. A Polypill for primary prevention of cardiovascular disease: a feasibility study of the World Health Organization. Trials. 2011;12:3. 1745-6215-12-3 [pii]. doi:10.1186/1745-6215-12-3 [published Online First: Epub Date]‖.
34. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry: fixed dose combinations, co-packaged drug products, and single-entity versions of previously approved antiretrovirals for the treatment of HIV. Rockville: Food and Drug Administration; 2006.
35. Smith R, McCready T, Yusuf S. Combination therapy to prevent cardiovascular disease: slow progress. JAMA. 2013;309(15):1595–6. doi:10.1001/jama.2013.3180. 1671770 [pii] [published Online First: Epub Date].
36. Ebrahim S, Beswick A, Burke M, et al. Multiple risk factor interventions for primary prevention of coronary heart disease. Cochrane Database Syst Rev. 2006;(4). http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001561/frame.html. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001561.pub2/abstract.
37. Wald DS, Morris JK, Wald NJ. Randomized Polypill crossover trial in people aged 50 and over. PLoS One. 2012;7(7), e41297. doi:10.1371/journal.pone.0041297 [published Online First: Epub Date].

38. Wald DS, Law N. Polypill Prevention Programme. Secondary Polypill Prevention Programme. 2013. http://www.polypill.com.
39. Kmietowicz Z. Polypill inventor puts product online after failing to get backing from industry. BMJ. 2013;346:f3991. doi:10.1136/bmj.f3991 [published Online First: Epub Date].

Chapter 15
Drug Evaluation: The Combination of Fenofibrate and Simvastatin for the Treatment of Dyslipidemia: When and for Whom?

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Background and Introduction

Fibrates are the most commonly used fibric acid derivative with several benefits on lipids (reduce total cholesterol, low-density lipoprotein cholesterol [LDL-C], apolipoprotein B [apoB], triglyceride [TG] and TG-rich lipoprotein [very low-density lipoprotein cholesterol - VLDL]), but also non-lipid parameters such as inflammatory markers (C-reactive protein [CRP], intrleukin-6 [IL-6]), plasma platelet-activating factor, and parameters of oxidative stress and the thrombotic/fibrinolytic system [7, 31]. Also, an increase in high-density lipoprotein cholesterol (HDL-C) is observed, that is more pronounced in subjects with higher fasting TG levels. A study performed in patients with type 2 diabetes mellitus (T2DM) showed that fenofibrate causes a 40 % reduction in the rate of progression of coronary artery disease compared with placebo [40]. Several recent studies suggest that fibrates, particularly fenofibrate, may lead to paradoxical reductions in HDL-C levels in certain patient populations, such as those with T2DM, that can be influenced by elevated or reduced pre-treatment HDL-C levels, as well as by co-administration of a statin with other medications [6]. However, there is wide variability in the literature regarding this issue and such paradoxical HDL-C reductions may be at least in part due to the natural variability in HDL-C changes over time, differences in measurement techniques and/or the absence of a placebo group in those studies [12]. Finally, the potential role of fibrates in reducing cardiovascular (CV) risk in diabetic patients remains suboptimally defined after the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, but this trial also provided some information on the potential of fibrates to be combined with statins [41].

The statin-mediated benefit of cardiovascular disease (CVD) risk reduction is well established, but residual CVD risk remains, especially in T2DM patients with high TG and low HDL-C [1]. Both simvastatin and fenofibrate are commonly used as lipid lowering agents with distinct mechanisms of action, and both drugs also exert favorable effects on different lipid subparticles [1, 21, 29, 31, 42]. Especially in the case of combined hyperlipidemia (increased total cholesterol and atherogenic dyslipidemia - high TG, small, dense LDL particles, and low HDL-C), combination drug therapy increases the likelihood of successful management. While statins are effective in decreasing LDL-C, fibrates are potentially beneficial for atherogenic dyslipidemia [43], thus their co-administration could improve the overall lipoprotein profile in such patients and may reduce the residual CVD risk during statin therapy [5, 31]. In addition, the effects of these two drugs on different HDL-related biomarkers in dyslipidemic patients with low HDL-C have been compared indicating that combination therapy improves these indices [15]. In subjects at high CV risk, the co-administration of a statin and fibrate led to greater risk reductions compared with monotherapy with either drug, and this is more effective in a subgroup of subjects with high TG and low HDL [7]. However, some data exists regarding the effects of such combination on CVD outcomes in diabetic patients [1, 5, 22, 31]. Clinical evidence supports the combined use of simvastatin and fenofibrate either given simultaneously or at staggered intervals, but simultaneous dosing has

advantages in terms of patient compliance for drug intake, a fixed dose combination [45], as well as its clinically relevant pharmacokinetic interaction at steady state and good tolerability [5]. Finally, the available evidence indicates that concomitant administration of a single dose of either atorvastatin or simvastatin has no significant effect on the pharmacokinetics of a single dose of Insoluble Drug Delivery®-MicroParticleIDD-P fenofibrate [35].

On the other hand, some data indicates that the combination of fibrates and statins increases the risk of myopathy and rhabdomyolysis, that together with the lack of proven clinical benefit made it difficult to be recommended [11]. This heightened risk is particularly relevant with gemfibrozil, a fibrate that can reduce the disposal of statins because of its ability to inhibit multiple glucuronosyltransferases [36]. However, fenofibrate is substantially safer and poses much less risk for muscle related adverse events [20]. Especially before the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study had been performed, physicians were aware of potential side effects when prescribing simvastatin/fenofibrate combination, but a careful selection and monitoring of patients, including their education on risk and potential adverse effects, especially in elderly population, is warranted [19]. In the context that this combination therapy causes concern about safety in clinical practice, ABT-335 (fenofibric acid, Trilipix®) has been designed to overcome the drawbacks of older fibrates (particularly in terms of pharmacokinetic properties) and several studies have been conducted in order to evaluate it both as monotherapy and in combination with different statins (atorvastatin, rosuvastatin and simvastatin) in patients with mixed dyslipidemia for up to 2 years. Overall, ABT-335 seems to be a safe and effective option in the management of dyslipidemia as previously reviewed [31].

The Combination in Different Clinical Patterns of Dyslipidemia

The effects of fenofibrate (160 mg/day) and simvastatin (40 mg/day) were compared in 52 dyslipidemic patients with low HDL-C [15]. This study demonstrated that simvastatin decreased plasma LDL-C and apoB levels, but did not change plasma HDL-C levels and HDL-related biomarkers, except for a small, significant increase in scavenger receptor class B type I (SR-BI) mediated cholesterol efflux. On the other hand, fenofibrate did not affect plasma LDL-C levels but lowered TG, and raised HDL-C, with patients in the lowest range of HDL-C having the maximal benefit. The HDL-C increase was associated with a shift of HDL from large to small particles, and from LpA-I to LpA-I:A-II, which might explain the increase in the plasma capacity to promote ABCA1-mediated efflux with no changes in SR-BI efflux [15]. It has been suggested that fenofibrate therapy can be considered in statin-treated patients with dyslipidemia who do not tolerate niacin as a second-line agent or if their HDL-C remained <40 mg/dl and TG was >150 mg/dl [11]. Recently, this combination resulted in improvements in TG, LDL- and HDL-C levels in

Chinese patients with atherogenic dyslipidemia and CVD [33]. Some evidence suggests that niacin therapy offsets the increase in proprotein convertase subtilisin-like/kexin type 9 (PCSK9) levels noted with statin therapy and a portion of the LDL-C reduction seen with niacin therapy may be due to this reduction in PCSK9 [23].

The ACCORD study showed that simvastatin/fenofibrate combination therapy does not significantly reduce the rate of CVD events compared with simvastatin/placebo combination in patients with T2DM. A possible benefit in a pre-specified post hoc analysis in the subgroup of subjects with high TG and low HDL-C levels suggests a nominally significant benefit [16]. Furthermore, in the same study the simvastatin/fenofibrate combination reduced the rate of progression of retinopathy compared with statin/placebo administration. In a subgroup of the subjects from the ACCORD study attempting to clarify the effects of this combination on postprandial TG, it was shown that simvastatin plus fenofibrate lowered postprandial TG similarly in all participants compared with simvastatin plus placebo. However, levels of atherogenic apoB48 particles were decreased only in subjects with increased fasting levels of TG [37]. Recently, the evidence supporting the use of statin/fibrate combination in patients with T2DM and atherogenic mixed dyslipidemia has been reviewed [1], indicating this combination is an effective treatment approach for these patients. In another study of T2DM patients, the fenofibrate/pravastatin (160/40 mg) fixed combination was well tolerated and associated with significantly greater changes from baseline in non-HDL-C, TG, and HDL-C concentrations when compared with simvastatin (20 mg) monotherapy [14]. In a randomized, double-blind study, 196 participants with recently diagnosed and previously untreated T2DM and mixed dyslipidemia were included, complying throughout the study with lifestyle intervention, treated with metformin and also receiving simvastatin (40 mg), fenofibrate (200 mg), simvastatin plus fenofibrate, or placebo for 90 days [24]. The effect of simvastatin and fenofibrate treatment on the secretory function of human monocytes and lymphocytes and on systemic inflammation were assessed as well as whether their co-administration is superior to any single treatment. The results showed that these two drugs have a similar effect on the investigated measures [24]. Furthermore, it was shown in 20 T2DM subjects with dyslipidemia, that simvastatin and fenofibrate impact the severity of oxidative stress [39]. While fenofibrate decreased malondialdehyde, a marker of oxidative stress, without any effects on the measured parameters of the antioxidant defense system, simvastatin decreased plasma malondialdehyde and the reduced form of glutathione, and increased serum ascorbic acid, serum N-acetyl-hglucosaminidase activity, and plasma plasminogen activator inhibitor (PAI-1) concentrations. The combination therapy of simvastatin (20 mg) and fenofibrate (160 mg) has favorable effects on lipid subparticles in the Diabetes and Combined Lipid Therapy Regimen (DIACOR) study. This study included 300 diabetic patients with mixed dyslipidemia (having more than 2 of the following lipid parameters: LDL-C >100 mg/dl, TG >200 mg/dl, and HDL-C <40 mg/dl), and without history of coronary heart disease (CHD). Combination therapy was superior to either fenofibrate or simvastatin monotherapy in lowering the prevalence of LDL-C pattern B and VLDL-C and these changes were greater in those patients with baseline TG >170 mg/dl. Also,

combination therapy exerted the greatest change in HDL profile increasing HDL-3 with also a potential effect on lipoprotein (a) [28]. The DIACOR study showed that the combination therapy was no more effective compared with either monotherapy on impacting markers of inflammation, but each therapy lowered high-sensitivity CRP (hsCRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2), and anti-inflammatory effects were most pronounced in individuals with increased baseline levels of inflammatory markers [32].

Fenofibric acid plus low- or moderate-dose statin combination therapy in patients with mixed dyslipidemia (HDL-C <40 mg/dl for men, and HDL-C <50 mg/dl for women, TG ≥150 mg/dl and LDL-C ≥130 mg/dl) improved some components of metabolic syndrome, mainly TG and HDL-C, compared with statin monotherapy, including the percent of patients meeting diagnostic criteria for metabolic syndrome compared with either agent alone [4]. In another study including patients with mixed dyslipidemia, combination therapy (ABT-335 [135 mg] + simvastatin [20 mg or 40 mg]) provided more effective control of multiple lipid parameters than either monotherapy, with a safety profile similar to both monotherapies [30]. Furthermore, a post hoc analysis of 92 patients with mixed dyslipidemia showed that the addition of fenofibric acid to moderate-dose statin, in patients whose LDL-C was optimal but TG remained >200 mg/dl, led to additional improvements in non-HDL-C, apoB, HDL-C, and TG and resulted in greater proportions of patients achieving optimal levels of all these parameters, including LDL-C [2]. From a genetic point of view, Ma et al. [27] showed that patients with mixed dyslipidemia treated with combination therapy including fenofibric acid and a statin may experience less apoB reduction and CV risk reduction compared with statin monotherapy, if they are homozygous for the minor allele of single-nucleotide polymorphisms in both the *ANGPTL3* and *RXRA* genes. However, these results remain to be confirmed in other studies. Finally, co-administration of ezetimibe/simvastatin (10/20 mg) and fenofibrate (160 mg) effectively improves the lipid and lipoprotein profile of patients with mixed hyperlipidemia [13].

The effects of statins and fibrates on the secretory function of T-lymphocytes was investigated in individuals with primary type II dyslipidemia. In this study, 63 patients with type IIa dyslipidemia were randomized to fluvastatin (40 mg daily; $n=33$) or simvastatin (20 mg daily; $n=30$), while 68 type IIb dyslipidemic individuals were treated with micronized ciprofibrate (100 mg daily; $n=34$) or micronized fenofibrate (200 mg daily; $n=34$). Compared with healthy subjects ($n=59$), both type IIa and IIb dyslipidemic participants exhibited higher baseline release of interferon-γ and interleukin-2 (IL-2). Fluvastatin, simvastatin and, to a less extent, ciprofibrate and fenofibrate inhibited the release of both cytokines, but this effect did not correlate with their lipid-lowering potential. Both classes of drugs (statin and fibrate) also had a lipid-independent inhibitory effect on the secretory function of T-lymphocytes, but the action of statins was stronger than fibrates. Overall, a reduction in the release of cytokines by these two drug classes may contribute to their clinical effectiveness in treating atherosclerosis [34]. In this context, Krysiak et al. reported that fenofibrate inhibits lymphocyte secretory function and reduces low-grade inflammation in simvastatin-treated asymptomatic atherosclerotic patients (with common carotid intima-media

thickness ≥0.7 mm), a normal lipid profile (total plasma cholesterol <200 mg/dl, LDL-C <130 mg/dl, TG <150 mg/dl), and with impaired fasting glucose and glucose tolerance. These findings support the use of combination therapy with simvastatin and fenofibrate as a better treatment option compared with simvastatin monotherapy in patients at high CV risk and mixed dyslipidemia [25].

A multicenter, randomized, double-blind, active-controlled study (the Simvastatin plus Fenofibrate for Combined Hyperlipidemia [SAFARI] trial) was conducted in the United States to determine if co-administration of simvastatin (20 mg) plus fenofibrate (160 mg) is more effective in reducing elevated TG levels, thus improving the lipoprotein pattern, in individuals with combined hyperlipidemia (fasting TG levels >150 and <500 mg/dl, and LDL cholesterol >130 mg/dl; $n=411$) compared with simvastatin monotherapy (20 mg/day; $n=207$), and to evaluate its safety and tolerability [18]. The study lasted for 12 weeks following a 6-week diet and placebo run-in period and the combination therapy resulted in decreased median TG levels (43.0 % vs 20.1 %; $p<0.001$) and mean LDL-C (31.2 % vs 25.8 %; $p<0.001$), while HDL-C levels increased (18.6 % vs 9.7 %; $p<0.001$). Serious adverse events were not observed. Combination therapy also resulted in additional improvements in lipoprotein parameters and was well tolerated. Consequently, combination therapy was shown to be a beneficial therapeutic option for managing combined hyperlipidemia [18]. Guidelines recommend non-HDL-C as a secondary target for therapy after the LDL-C goals have been met in patients with hypertriglyceridemia, and non-HDL-C is viewed as a surrogate for apoB, an alternate end point of treatment [3, 42]. The subanalysis of the SAFARI trial assessed the associations of non-HDL-C and LDL-C with apoB levels in patients with combined hyperlipidemia. Each therapy significantly reduced LDL-C, TG, non-HDL-C and apoB levels and non-HDL-C/apoB ratio ($p<0.0004$). Such changes were seen regardless of the TG level, but the greatest reductions occurred with combination treatment. The baseline levels of non-HDL-C and LDL-C correlated highly with apoB and were stronger in the lower TG than in the higher TG tertiles; 12 weeks later these correlations increased with combination therapy. Such findings indicate that both non-HDL-C and apoB provide similar information in relation to treatment response in patients with combined hyperlipidemia and hypertriglyceridemia, supporting the recommended use of non-HDL-C as a secondary therapeutic target in these patients [17].

Given that some evidence indicates that combination therapy with statin plus fibrate bring a risk of myopathy, in a randomized double-blind study it was investigated whether statin or fibrate monotherapies are associated with greater clinical benefit in patients with combined hyperlipidemia, comparing the efficacy of these drugs on indices of endothelial function (flow-mediated dilation (FMD) of the brachial artery) and inflammatory markers (such as plasma hsCRP, IL-1β, soluble CD40, and CD40 ligand [sCD40L] levels), as surrogate indicators of future CHD [44]. Seventy patients with plasma TG levels between 200 and 500 mg/dl and total cholesterol levels of >200 mg/dl were randomly assigned to receive either simvastatin (20 mg/day) ($n=35$) or micronized fenofibrate (200 mg/day) ($n=35$) for 8 weeks. Simvastatin led to a greater reduction in total cholesterol and LDL-C, while the decrease in TG was greater in patients treated with fenofibrate. Both fenofibrate and simvastatin reduced

plasma levels of inflammatory markers independently of baseline clinical characteristics, and improved endothelium-dependent FMD but such changes correlated with baseline HDL-C levels. In detail, in individuals with a baseline HDL-C ≤40 mg/dl, only fenofibrate significantly improved the endothelium-dependent FMD, while in those with HDL-C >40 mg/dl, only treatment with simvastatin achieved significant improvement in FMD. However, this should be validated by additional studies [44].

The safety and efficacy of a combination of low-dose simvastatin and fenofibrate was examined in the treatment of combined hyperlipidemia, in a randomized, placebo-controlled trial with a crossover design, with three phases (double placebo, simvastatin 10 mg/day and placebo, and simvastatin 10 mg/day plus fenofibrate 200 mg/day); each phase lasted for 3 months [43]. Simvastatin reduced total cholesterol (by 27 %), non-HDL-C (by 30 %), apoB (by 31 %), VLDL plus intermediate-density lipoprotein (IDL)-C (by 37 %), VLDL plus IDL apoB (by 14 %), LDL-C (by 28 %), and LDL apoB (by 21 %). The addition of fenofibrate resulted in an additional reduction in VLDL plus IDL-C and VLDL plus IDL apoB (by 36 % and 32 %, respectively). Simvastatin alone caused a small increase in the ratio of large to small dense LDL, whereas the addition of fenofibrate to simvastatin therapy caused a marked increase in the ratio of large to small LDL species. Simvastatin alone induced a significant increase in HDL-C concentrations although small (6 %), but when fenofibrate was added, HDL-C increased more significantly (by 23 %). No significant side effects were observed. Hence, a combination of simvastatin (10 mg/day) and fenofibrate (200 mg/day) seems to be beneficial and safe for the treatment of atherogenic dyslipidemia in combined hyperlipidemia [43].

The benefits of fenofibrate/simvastatin combination therapy in different clinical dyslipidemic patterns are summarized on the Fig. 15.1.

Although some evidence suggests a possible heightened risk for myopathy and rhabdomyolysis [11], the combination of statin with fenofibrate is demonstrably safe, as shown in the FIELD study. However, the combination of gemfibrozil and a statin is associated with an increased risk (15-fold compared to fenofibrate) of myopathy [10, 20]. Additionally, a very recent meta-analysis [9] reported superior effects of the combination therapy compared to fibrate monotherapy, but there was an increased risk of kidney-related adverse events. Larger studies are requested to elucidate this issue, but in clinical practice physicians prescribing such co-administration should consider other potential factors known to raise the risk of myopathy (such as hypothyroidism, old age, and renal dysfunction) [26, 38].

Potential Pleiotropic Effects of Fenofibrate/Simvastatin Combination Therapy

Results of a preclinical study demonstrated that fenofibrate (50 mg/kg) and simvastatin (37.5 mg/kg) may exert neuroprotective and pleiotropic effects in experimental models of traumatic brain injury (TBI), because this combination therapy synergistically enhanced peroxisome proliferator-activated receptor (PPAR-α) activation,

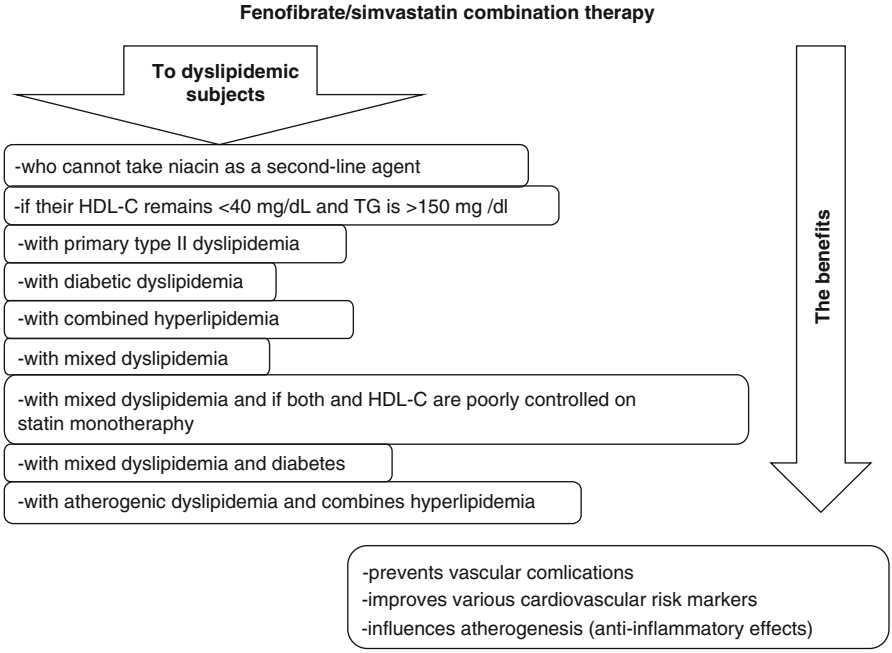

Fig. 15.1 The benefits of fenofibrate/simvastatin combination therapy in different clinical dyslipidemic patterns

suggesting a prolonged and neuroprotective and antiedematous effects, decreasing the volume of post-traumatic brain lesions, compared with each drug alone that further may have an important therapeutic significance for the treatment of TBI [8].

Importantly, as it has been reviewed above, fenofibrate/simvastatin combination therapy can lead to decreased overall CV risk in patients with atherogenic lipid disorders, including those with T2DM, but patient tolerance and safety should be carefully monitored.

Conclusions

On the basis of currently available data, the co-administration of fenofibrate plus simvastatin may be recommended in the case of: (1) dyslipidemic patients who cannot take niacin (it is important to note that niacin is not available on the market in several countries) as a second-line agent if their HDL-C is <40 mg/dl and TG are >150 mg/dl; (2) mixed dyslipidemia if both TG and HDL-C are poorly controlled on statin monotherapy (except for gemfibrozil which has unacceptable risk of myopathy when used in combination with a statin); (3) mixed dyslipidemic patients who also have T2DM where combination therapy may have beneficial effects on

several CV risk markers and prevent vascular complications, and, (4) patients with combined hyperlipidemia. The use of combination therapy is recommended either given simultaneously or at staggered intervals. The influence of genetic factors on apoB response to fibrate/statin therapy remains to be evaluated in further studies. However, a choice for such treatment should be individualized and supported by clinical data, based on patient tolerability and safety, and then, most importantly, carefully monitored.

Declaration of Interest

DN has participated in clinical trials sponsored by AstraZeneca and Novo Nordisk. NK has given talks, attended conferences and participated in studies sponsored by Amgen, AstraZeneca, MSD, Novartis and Novo Nordisk. PPT has given talks, attended conferences and participated in studies sponsored by Aegerion, Amarin, Amgen, GSK, Kowa, Merck, Novartis, and Sanofi-Regeneron. MB none. KAW none. KAR has given talks sponsored by AstraZeneca and Pfizer and received educational grant by Pfizer. MR has given lectures, received honoraria or research support, and participated in conferences, advisory boards and clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Bromatech, Chiesi Farmaceutici, Kowa, MSD Merck Sharp & Dohme, Novartis, Novo Nordisk, Rikrea and Servier. DPM has given talks, attended conferences and participated in studies sponsored by Merck, Sharp & Dohme, AstraZeneca and Genzyme.

References

1. Agouridis AP, Rizos CV, Elisaf MS, Filippatos TD. Does combination therapy with statins and fibrates prevent cardiovascular disease in diabetic patients with atherogenic mixed dyslipidemia? Rev Diabet Stud. 2013;10(2–3):171–90. doi:10.1900/RDS.2013.10.171.
2. Ballantyne CM, Jones PH, Kelly MT, Setze CM, Lele A, Thakker KM, Stolzenbach JC. Long-term efficacy of adding fenofibric acid to moderate-dose statin therapy in patients with persistent elevated triglycerides. Cardiovasc Drugs Ther (Sponsored by the International Society of Cardiovascular Pharmacotherapy). 2011;25(1):59–67. doi:10.1007/s10557-011-6280-1.
3. Barylski M, Toth PP, Nikolic D, Banach M, Rizzo M, Montalto G. Emerging therapies for raising high-density lipoprotein cholesterol (HDL-C) and augmenting HDL particle functionality. Best Pract Res Clin Endocrinol Metab. 2014;28(3):453–61. doi:10.1016/j.beem.2013.11.001.
4. Bays HE, Roth EM, McKenney JM, Kelly MT, Thakker KM, Setze CM, Obermeyer K, Sleep DJ. The effects of fenofibric acid alone and with statins on the prevalence of metabolic syndrome and its diagnostic components in patients with mixed dyslipidemia. Diabetes Care. 2010;33(9):2113–6. doi:10.2337/dc10-0357.
5. Bergman AJ, Murphy G, Burke J, Zhao JJ, Valesky R, Liu L, Lasseter KC, He W, Prueksaritanont T, Qiu Y, Hartford A, Vega JM, Paolini JF. Simvastatin does not have a clinically significant pharmacokinetic interaction with fenofibrate in humans. J Clin Pharmacol. 2004;44(9):1054–62. doi:10.1177/0091270004268044.

6. Brousseau ME, Schaefer EJ, Wolfe ML, Bloedon LT, Digenio AG, Clark RW, Mancuso JP, Rader DJ. Effects of an inhibitor of cholesteryl ester transfer protein on HDL cholesterol. N Engl J Med. 2004;350(15):1505–15. doi:10.1056/NEJMoa031766.
7. Chang CN, How CH, Tavintharan S. Beyond low-density lipoprotein cholesterol: why, who and when. Singapore Med J. 2012;53(9):566–8. quiz 569.
8. Chen XR, Besson VC, Beziaud T, Plotkine M, Marchand-Leroux C. Combination therapy with fenofibrate, a peroxisome proliferator-activated receptor alpha agonist, and simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, on experimental traumatic brain injury. J Pharmacol Exp Ther. 2008;326(3):966–74. doi:10.1124/jpet.108.140368.
9. Choi HD, Shin WG, Lee JY, Kang BC. Safety and efficacy of fibrate-statin combination therapy compared to fibrate monotherapy in patients with dyslipidemia: a meta-analysis. Vascul Pharmacol. 2014;65–66:23–30. doi:10.1016/j.vph.2014.11.002.
10. Davidson MH. Statin/fibrate combination in patients with metabolic syndrome or diabetes: evaluating the risks of pharmacokinetic drug interactions. Expert Opin Drug Saf. 2006;5(1):145–56. doi:10.1517/14740338.5.1.145.
11. Dujovne CA, Williams CD, Ito MK. What combination therapy with a statin, if any, would you recommend? Curr Atheroscler Rep. 2011;13(1):12–22. doi:10.1007/s11883-010-0150-3.
12. Farnier M, Dong Q, Shah A, Johnson-Levonas AO, Brudi P. Low incidence of paradoxical reductions in HDL-C levels in dyslipidemic patients treated with fenofibrate alone or in combination with ezetimibe or ezetimibe/simvastatin. Lipids Health Dis. 2011;10:212. doi:10.1186/1476-511X-10-212.
13. Farnier M, Roth E, Gil-Extremera B, Mendez GF, Macdonell G, Hamlin C, Perevozskaya I, Davies MJ, Kush D, Mitchel YB, Ezetimibe/Simvastatin + Fenofibrate Study G. Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia. Am Heart J. 2007;153(2):335e331–338. doi:10.1016/j.ahj.2006.10.031.
14. Farnier M, Steinmetz A, Retterstol K, Csaszar A. Fixed-dose combination fenofibrate/pravastatin 160/40 mg versus simvastatin 20 mg monotherapy in adults with type 2 diabetes and mixed hyperlipidemia uncontrolled with simvastatin 20 mg: a double-blind, randomized comparative study. Clin Ther. 2011;33(1):1–12. doi:10.1016/j.clinthera.2011.02.006.
15. Franceschini G, Calabresi L, Colombo C, Favari E, Bernini F, Sirtori CR. Effects of fenofibrate and simvastatin on HDL-related biomarkers in low-HDL patients. Atherosclerosis. 2007;195(2):385–91. doi:10.1016/j.atherosclerosis.2006.10.017.
16. Ginsberg HN, Elam MB, Lovato LC, Crouse 3rd JR, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff Jr DC, Cushman WC, Simons-Morton DG, Byington RP, Accord Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563–74. doi:10.1056/NEJMoa1001282.
17. Grundy SM, Vega GL, Tomassini JE, Tershakovec AM. Correlation of non-high-density lipoprotein cholesterol and low-density lipoprotein cholesterol with apolipoprotein B during simvastatin + fenofibrate therapy in patients with combined hyperlipidemia (a subanalysis of the SAFARI trial). Am J Cardiol. 2009;104(4):548–53. doi:10.1016/j.amjcard.2009.04.018.
18. Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE, Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol. 2005;95(4):462–8. doi:10.1016/j.amjcard.2004.10.012.
19. Jacob SS, Jacob S, Williams C, Deeg MA. Simvastatin, fenofibrate, and rhabdomyolysis. Diabetes Care. 2005;28(5):1258.
20. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. Am J Cardiol. 2005;95(1):120–2. doi:10.1016/j.amjcard.2004.08.076.
21. Katsiki N, Nikolic D, Montalto G, Banach M, Mikhailidis DP, Rizzo M. The role of fibrate treatment in dyslipidemia: an overview. Curr Pharm Des. 2013;19(17):3124–31.
22. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M, investigators Fs. Effects of long-term fenofibrate therapy on cardiovascular

events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366(9500):1849–61. doi:10.1016/S0140-6736(05)67667-2.
23. Khera AV, Qamar A, Reilly MP, Dunbar RL, Rader DJ. Effects of niacin, statin, and fenofibrate on circulating proprotein convertase subtilisin/kexin type 9 levels in patients with dyslipidemia. Am J Cardiol. 2015;115(2):178–82. doi:10.1016/j.amjcard.2014.10.018.
24. Krysiak R, Gdula-Dymek A, Okopien B. Effect of simvastatin and fenofibrate on cytokine release and systemic inflammation in type 2 diabetes mellitus with mixed dyslipidemia. Am J Cardiol. 2011;107(7):1010–8. doi:10.1016/j.amjcard.2010.11.023. e1011.
25. Krysiak R, Gdula-Dymek A, Okopien B. The effect of fenofibrate on lymphocyte release of proinflammatory cytokines and systemic inflammation in simvastatin-treated patients with atherosclerosis and early glucose metabolism disturbances. Basic Clin Pharmacol Toxicol. 2013;112(3):198–202. doi:10.1111/bcpt.12003.
26. Kursat S, Alici T, Colak HB. A case of rhabdomyolysis induced acute renal failure secondary to statin-fibrate-derivative combination and occult hypothyroidism. Clin Nephrol. 2005;64(5):391–3.
27. Ma L, Ballantyne CM, Belmont JW, Keinan A, Brautbar A. Interaction between SNPs in the RXRA and near ANGPTL3 gene region inhibits apoB reduction after statin-fenofibric acid therapy in individuals with mixed dyslipidemia. J Lipid Res. 2012;53(11):2425–8. doi:10.1194/jlr.M028829.
28. May HT, Anderson JL, Pearson RR, Jensen JR, Horne BD, Lavasani F, Yannicelli HD, Muhlestein JB. Comparison of effects of simvastatin alone versus fenofibrate alone versus simvastatin plus fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study). Am J Cardiol. 2008;101(4):486–9. doi:10.1016/j.amjcard.2007.09.095.
29. Mikhailidis DP, Elisaf M, Rizzo M, Berneis K, Griffin B, Zambon A, Athyros V, de Graaf J, Marz W, Parhofer KG, Rini GB, Spinas GA, Tomkin GH, Tselepis AD, Wierzbicki AS, Winkler K, Florentin M, Liberopoulos E. "European panel on low density lipoprotein (LDL) subclasses": a statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses. Curr Vasc Pharmacol. 2011;9(5):533–71.
30. Mohiuddin SM, Pepine CJ, Kelly MT, Buttler SM, Setze CM, Sleep DJ, Stolzenbach JC. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3, randomized, controlled study. Am Heart J. 2009;157(1):195–203. doi:10.1016/j.ahj.2008.08.027.
31. Moutzouri E, Kei A, Elisaf MS, Milionis HJ. Management of dyslipidemias with fibrates, alone and in combination with statins: role of delayed-release fenofibric acid. Vasc Health Risk Manag. 2010;6:525–39.
32. Muhlestein JB, May HT, Jensen JR, Horne BD, Lanman RB, Lavasani F, Wolfert RL, Pearson RR, Yannicelli HD, Anderson JL. The reduction of inflammatory biomarkers by statin, fibrate, and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. J Am Coll Cardiol. 2006;48(2):396–401. doi:10.1016/j.jacc.2006.05.009.
33. NCT01462877. A study to evaluate fenofibrate combination with statin in Chinese patients with Dyslipidemia. https://clinicaltrials.gov/ct2/show/study/NCT01462877?term=fenofibrate+for+dyslipidemia&rank=10
34. Okopien B, Krysiak R, Kowalski J, Madej A, Belowski D, Zielinski M, Labuzek K, Herman ZS. The effect of statins and fibrates on interferon-gamma and interleukin-2 release in patients with primary type II dyslipidemia. Atherosclerosis. 2004;176(2):327–35. doi:10.1016/j.atherosclerosis.2004.05.009.
35. Penn R, Williams 3rd RX, Guha-Ray DK, Sawyers WG, Braun SL, Rains KT. An open-label, crossover study of the pharmacokinetics of Insoluble Drug Delivery-MicroParticle fenofibrate in combination with atorvastatin, simvastatin, and extended-release niacin in healthy volunteers. Clin Ther. 2006;28(1):45–54. doi:10.1016/j.clinthera.2005.12.004.
36. Prueksaritanont T, Zhao JJ, Ma B, Roadcap BA, Tang C, Qiu Y, Liu L, Lin JH, Pearson PG, Baillie TA. Mechanistic studies on metabolic interactions between gemfibrozil and statins. J Pharmacol Exp Ther. 2002;301(3):1042–51.

37. Reyes-Soffer G, Ngai CI, Lovato L, Karmally W, Ramakrishnan R, Holleran S, Ginsberg HN. Effect of combination therapy with fenofibrate and simvastatin on postprandial lipemia in the ACCORD lipid trial. Diabetes Care. 2013;36(2):422–8. doi:10.2337/dc11-2556.
38. Satarasinghe RL, Ramesh R, Riyaaz AA, Gunarathne PA, de Silva AP. Hypothyroidism is a predisposing factor for fenofibrate-induced rhabdomyolysis–patient report and literature review. Drug Metabol Drug Interact. 2007;22(4):279–83.
39. Skrha J, Stulc T, Hilgertova J, Weiserova H, Kvasnicka J, Ceska R. Effect of simvastatin and fenofibrate on endothelium in Type 2 diabetes. Eur J Pharmacol. 2004;493(1–3):183–9. doi:10.1016/j.ejphar.2004.04.025.
40. Steiner G. Treating lipid abnormalities in patients with type 2 diabetes mellitus. Am J Cardiol. 2001;88(12A):37N–40.
41. Tenenbaum A, Fisman EZ, Boyko V, Benderly M, Tanne D, Haim M, Matas Z, Motro M, Behar S. Attenuation of progression of insulin resistance in patients with coronary artery disease by bezafibrate. Arch Intern Med. 2006;166(7):737–41. doi:10.1001/archinte.166.7.737.
42. Toth PP, Barylski M, Nikolic D, Rizzo M, Montalto G, Banach M. Should low high-density lipoprotein cholesterol (HDL-C) be treated? Best Pract Res Clin Endocrinol Metab. 2014;28(3):353–68. doi:10.1016/j.beem.2013.11.002.
43. Vega GL, Ma PT, Cater NB, Filipchuk N, Meguro S, Garcia-Garcia AB, Grundy SM. Effects of adding fenofibrate (200 mg/day) to simvastatin (10 mg/day) in patients with combined hyperlipidemia and metabolic syndrome. Am J Cardiol. 2003;91(8):956–60.
44. Wang TD, Chen WJ, Lin JW, Cheng CC, Chen MF, Lee YT. Efficacy of fenofibrate and simvastatin on endothelial function and inflammatory markers in patients with combined hyperlipidemia: relations with baseline lipid profiles. Atherosclerosis. 2003;170(2):315–23.
45. Winsemius A, Ansquer JC, Olbrich M, van Amsterdam P, Aubonnet P, Beckmann K, Driessen S, van Assche H, Piskol G, Lehnick D, Mihara K. Pharmacokinetic interaction between simvastatin and fenofibrate with staggered and simultaneous dosing: does it matter? J Clin Pharmacol. 2014;54(9):1038–47. doi:10.1002/jcph.291.

Chapter 16
Drug Evaluation: Olmesartan Medoxomil + Rosuvastatin for the Treatment of Dyslipidemia and Concomitant Risk Factors: A Chance for Better Compliance?

Joanna Gozdzikiewicz-Lapinska and Jolanta Malyszko

Despite the progress in prevention, cardiovascular disease (CVD) remains the main cause of death in developed countries [1, 2]. Among the established, most common, and well-controlled by pharmacotherapy risk factors of CVD remain high blood pressure and cholesterol abnormalities: increased serum concentration of low-density lipoprotein - cholesterol (LDL) and low levels of high-density lipoprotein – cholesterol (HDL). Commonly used drugs for the treatment of hypertension and dyslipidemia are angiotensin receptor blockers (ARBs) and HMGCoA reductase inhibitors (statins) respectively. Recent years' trials emphasize the potential pleiotropic actions of these groups of drugs, beyond its conventional indications.

Worth of greater interest are well-known olmesartan medoxomil and rosuvastatin.

Olmesartan Medoxomil

The rennin–angiotensin–aldosteron system (RAAS) is a target for drugs used in the treatment of hypertension. ARBs inhibit the RAAS by competitive binding to the type 1 receptor for angiotensin II, which blocks the enzyme actions: vasoconstriction, increased aldosteron secretion and sympathetic activation, salt and fluid retention.

Olmesartan, as other ARBs, is a potent angiotensin II type – 1 receptor (AT1 receptor) antagonist, without any effect on angiotensin II type – 2 receptor [3]. Its affinity for the AT1 receptor is greater than that of losartan and similar to that of candesartan [4]. Olmesartan esterification with the medoxomil moiety increases bioavailability of the drug [5]. The mean plasma half-life of olmesartan during

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chronic treatment is 10–15 h. The drug is excreted mainly in feces, with about 10–16 % excreted in the urine (briefly revised in [6]). Dosage adjustment for patients with renal or hepatic impairment as well as for elderly is not indicated; however, some manufacturers of the drug recommend lower initial dose [6].

Efficacy and tolerability of olmesartan (5–80 mg/day) in the treatment of hypertension in different populations of patients was examined in placebo-controlled trials as well as in the studies comparing it with different other classes of antihypertensives (among others amlodypine, hydrochlorotiazyd, atenolol, captopril) [7–12]. The researchers proved the efficacy of monotherapy as well as combined therapy of olmesartan with calcium channel blocker or diuretic in the treatment of mild to moderate hypertension, masked hypertension, or white coat hypertension. They also showed no more adverse effects of olmesartan as compared to placebo or amlodypine/calcium channel blocker alone, but slightly higher incidence of adverse effects was observed in the elderly population treated with olmesartan and diuretic [7–12]. Other conclusions of these studies were as follow: (1) higher possibility to achieve goal blood pressure with olmesartan than with other hypertensives, (2) olmesartan plus calcium channel blocker could be more effective in reducing risk of stroke than olmesartan plus diuretic in the elderly, (3) higher doses of olmesartan or addition of hydrochlorotiazyd to olmesartan therapy are equally effective and safe for patients who didn't respond to monotherapy with olmesartan alone [7–12].

Efficacy of olmesartan was also compared with other ARBs and summarized in a meta-analysis of 22 randomized controlled trials [13]. The study showed better efficacy of olmesartan in systolic blood pressure (SBP) reduction as compared to losartan or valsartan, and also better efficacy in diastolic blood pressure (DBP) reduction than losartan; when compared with valsartan, olmesartan was equally effective in DBP reduction [13]. No difference in the total number of adverse events was described while comparing olmesartan with losartan and valsartan [13].

Recent years' trials point on a link between hypertension and vascular inflammation/atherosclerosis, where the key player is angiotensin II (Ang II) [14].

Ang II proinflammatory actions are (1) in human endothelial and smooth muscle cells as well as in monocytes, increases the expression of different proinflammatory cytokines and adhesion molecules, such as interleukin 6 (Il-6), interleukin 1 beta (Il-1β), tumor necrosis factor alpha (TNFα), nuclear factor kappa B (NF-kappaB), monocyte chemoattractant protein 1 (MCP-1), and vascular cell adhesion molecule (VCAM); (2) induces recruitment of inflammatory cells; (3) induces production of superoxide anions and activates NADH/NADPH signaling – increases the oxidative stress and decreases nitric oxide bioavailability; (4) induces cell hypertrophy and activates fibrosis [14–19].

Olmesartan medoxomil as a long-acting antagonist of AT1 receptor is able to improve endothelial dysfunction/atherosclerosis in animal models and human studies.

Olmesartan's influence on oxidative stress mediators was shown in rat studies. After treatment of methotrexate-induced mucositis model in Wistar rats with olmesartan (5 mg/kg/day), reductions in mucosal inflammatory infiltrations, ulcerations, and hemorrhagic areas were observed as well as decrease in concentra-

tions of proinflammatory cytokines Il-1β and TNFα [20]. Moreover, authors noticed an increase in anti-inflammatory cytokine interleukin 10 (Il-10) concentration [20]. In a rat model of high-salt diet-induced glomerular and tubulointerstitial kidney injury, treatment with olmesartan (10 mg/kg/day) as well as with olmesartan and calcium channel blocker (CCB) caused a significant regression of morphological changes [21]. It was explained by the reductions in expression of other proinflammatory cytokines: MCP-1 and tumor growth factor β (TGF-β). Also, decrease in NADPH oxidase activity and NADPH oxidase-dependent superoxide production was observed [21]. Similar decrease in NADPH oxidase activity was noticed in olmesartan-treated rats with a stroke model (permanent middle cerebral artery occlusion) [22]. Significantly better functional scores and reduced infarct sizes were confirmed in a group of rats treated with olmesartan (10 mg/kg/day) 7 days before and 14 days after infarct, but also in the group only pretreated with this ARB or treated after infarct induction [22]. In a previous study, the antioxidative properties of olmesartan measured as the decrease in superoxide production and NADPH oxidase activity were confirmed for the lower dose of ARB – 3 mg/kg/day – in apolipoprotein E knockout mice [23].

Amelioration of oxidative stress in the endothelium improves its function. In spontaneously hypertensive rats treated with olmesartan (5 mg/kg/day) for 4 weeks and subsequently divided into 5 groups – increased dose of olmesartan (10 mg/kg/day) or addition of azelnidipine or temocapril or atenolol or hydrochlorothiazide, endothelial function, assessed by evaluating dilatory response to acetylcholine, was significantly improved compared to the control group [24]. Beneficial effects of olmesartan were probably connected with the upregulation or inhibition of the disruption of endothelial nitric oxide synthase (eNOS) [25, 26]. Antiatherogenic effects of olmesartan administration are further confirmed also by amelioration of atherosclerotic areas in the thoracic aorta, perivascular fibrosis, and medial thickness of the coronary arteries in diabetic apolipoprotein E-deficient mice treated with the combination of this ARB and CCB [26].

Olmesartan's effects on interstitial matrix were also evaluated. In spontaneously hypertensive rats treated with high (15 mg/kg/day) or low (1 mg/kg/day) dose of olmesartan, left ventricular weight–to–body weight ratio (RLVM) was measured, and cardiac, aortic, and glomerular interstitial collagen content was evaluated [27]. Both high and low dose of olmesartan normalized, increased in control group rats, collagen content in hart, kidneys and aorta. The significantly increased RLVM in untreated rats was decreased in high-dose olmesartan-treated group [27]. In addition, reduction in expression of matrix metalloproteinases 2 and 9 could also contribute to antifibrotic effects of this ARB [20]. Attenuation of cardiac hypertrophy, remodeling, and improved cardiac diastolic function by olmesartan might be also a result of the influence of olmesartan on other molecular pathways: activation of delta-like ligand 4/Notch 1 pathway or calcineurin pathway [28, 29].

Olmesartan's observed renoprotective effects in animal models (based on improvement in urinary protein excretion and histological kidney injury/fibrosis) might be augmented by the increased expression of klotho mRNA in olmesartan + alfadiol-treated chronic renal failure rats [21, 30].

Not only in study animals but also in hypertensive patients, olmesartan medoxomil therapy results in improvements in endothelial function. In a double-blinded, placebo-controlled study (EUTOPIA), authors showed that 12 weeks of olmesartan therapy (20 mg/day), in contrast to placebo, significantly reduced serum concentration of high-sensitivity C reactive protein (hsCRP), TNF-α, IL-6, and MCP-1 [31]. The effect was observed already after 6 weeks of treatment, and further augmented during the next 12 weeks of therapy [31].

Amelioration of the endothelial function was documented by other authors who investigated arterial dilation after treatment with this ARB. In a Japanese study, 26 patients with essential hypertension, previously untreated, were assigned to the treatment either with olmesartan (20 mg/day; dose was doubled in case of not reaching desirable blood pressure or halved in case of too low blood pressure) or amlodypine for 12 weeks [32]. The protocol resulted in significant increase in the corrected myocardial blood flow and decrease in the change of coronary vascular resistance in the olmesartan group; effects were not observed in amlodypine-treated patients. What more, serum superoxide dismutase (SOD) concentration increased in the olmesartan group during the treatment period, but not in the amlodypine group, and could at least partially explain ameliorated myocardial blood flow [32]. Improved endothelial function evaluated by flow-mediated dilation (FMD) of brachial artery was also found in a 12 week trial of olmesartan vs amlodypine therapy [33].

Other studies concentrated on vascular hypertrophy and remodeling. Hypertensive, nondiabetic patients after a 4 week washout period were randomized to olmesartan (20–40 mg/day) or atenolol (50–100 mg/day) plus additional hypotensive drugs if needed (hydrochlorothiazide, amlodypine, hydralazine) [34]. At baseline and after a year of treatment upon biopsies, subcutaneous gluteal resistance arteries were examined to evaluate remodeling. In the control group, the wall-to-lumen ratio was 11 %. After the treatment period, the wall-to-lumen ratio in the olmesartan-treated group significantly decreased from 14.9 to 11.1 %. No significant change was observed in the atenolol group [34]. In the MORE study, in patients with hypertension and increased cardiovascular risk with carotid wall thickening (measured by means of ultrasound), olmesartan's or atenolol's influence on common carotid intima-media thickness (IMT) and atherosclerotic plaque volume was investigated [35]. After 2 years of treatment, olmesartan and atenolol produced similar significant reductions in IMT. However, only olmesartan reduced the volume of large atherosclerotic plaques [35].

In diabetic patients, olmesartan treatment was shown to be associated not only with delayed onset of microalbuminuria (early predictor of diabetic nephropathy and cardiovascular disease) but also delayed development of left ventricular remodeling [36, 37]. The latter effect was assessed during a randomized trial; signs of left ventricular hypertrophy were evaluated based on a 12-lead ECG at baseline and after 2 years of treatment with olmesartan or placebo (non-RAAS-influencing antihypertensive drugs were allowed) [36].

Rosuvastatin

HMGCoA reductase inhibitors are nowadays commonly used agents for lowering cholesterol concentration and thus preventing cardiovascular events. Competitive inhibition of HMGCoA reductase results in decreased hepatic cholesterol synthesis and apolipoprotein B-containing lipoproteins, increase in hepatic low-density lipoprotein (LDL) receptor expression, and enhanced LDL cholesterol uptake from plasma.

Rosuvastatin is one of the most recently available synthetic statins. It is rapidly absorbed after oral administration (briefly revised in [38]). Half-life of rosuvastatin is 19 h, which results in similar pharmacokinetics of the drug irrespective of the morning or evening dosing [39]. The drug is about 88 % reversibly bound to plasma proteins, mainly to albumin; it is eliminated in 90 % as unchanged drug with feces and remaining 10 % with the urine [38, 39]. In consequence, rosuvastatin administration is contraindicated in patients with active liver disease and unexplained transaminase elevations, and dosage adjustment is needed for patients with eGFR <30 ml/min/1.73 m^2 – 5–10 mg/day. However, in end-stage kidney disease patients on continuous ambulatory peritoneal dialysis, pharmacokinetics of 10 mg/day of rosuvastatin was similar as in healthy volunteers [40]. Similar observations were made in a small study of 10 mg of rosuvastatin in 11 hemodialysis patients, suggesting that no dose adjustment is needed for these patients [41].

Rosuvastatin shows higher efficacy in modifying atherogenic lipid profile in patients with hypercholesterolemia than other statins. In several meta-analyses and clinical trials, rosuvastatin was not only more efficacious in decreasing LDL cholesterol and increasing HDL cholesterol when compared to simvastatin, fluvastatin, lovastatin, or pravastatin but also in comparison to atorvastatin [42–44]. Rosuvastatin decreased LDL cholesterol levels better at the same dose of atorvastatin and 1:2 dose ratio; no significant difference in lipid profile goals was observed at 4 times higher atorvastatin doses [43]. What more, the same results were observed for different patient age-groups, and the incidence of adverse effects was the same for all the statins compared [42–44]. Rosuvastatin was also better than simvastatin in attaining LDL goals after switching patients from atorvastatin therapy – authors concluded it might be the drug of choice for lipid-lowering therapy in patients who failed to achieve cholesterol goals during atorvastatin treatment [45].

Rosuvastatin's efficacy in improving lipid profile and achieving target goals of cholesterol were also studied for so-called high-risk populations including patients with diabetes mellitus (DM) or metabolic syndrome, acute coronary syndrome (ACS) or chronic kidney disease (CKD) [38]. Additional effects of the drug were also observed: (1) rosuvastatin administration (2.5–10 mg/day for 24 weeks) reduced albuminuria, serum cystatin C levels in CKD patients regardless of presence or absence of DM; (2) rosuvastatin administration (2.5–20 mg/day for 24 weeks) decreased hsCRP and malondialdehyde-modified LDL (effect of oxidative stress) in diabetic nephropathy patients with eGFR >60 ml/min/1.73 m^2; (3) rosuvastatin

(5–20 mg/day for 24 months) induced lasting decrease in carotid plaque lipid content in lipid treatment subjects as assessed by magnetic resonance; (4) rosuvastatin treatment decreased the incidence of heart failure hospitalizations in heart failure patients over 60 years of age; (5) rosuvastatin treatment (10 mg/day for 1 year) significantly improved coronary flow reserve in hypertensive patients without coronary artery disease [46–50].

Rosuvastatin's influence on oxidative stress, independent of lipid-lowering properties, is also under investigation (briefly revised in [51]). This statin is able to ameliorate NADPH oxidase-mediated damage by reducing NADPH oxidase activity in rats and NADPH oxidase-dependent superoxide production in obese rats [52, 53]. Rosuvastatin also inhibits angiotensin II-mediated vascular impairment by decreasing NADPH oxidase-derived oxidant excess, stimulation of endogenous antioxidant mechanisms, and restoring NO availability [54].

In addition, rosuvastatin increases endothelial NO synthesis and attenuates myocardial necrosis (the effect of ischemia and reperfusion) in mice [55]. Inhibiting HMGCoA reductase increases NO bioavailability and improves endothelial function in congestive heart failure rats [56]. Finally, it also upregulates eNOS expression in mice protecting the animals from cerebral ischemia [57]. Rosuvastatin reduces also other prooxidative cytokines like Il-6 or TNFα [58]. The restoration of antioxidant defense is mediated by rosuvastatin-dependent improvement in SOD1 expression [59].

Combination Therapy: Olmesartan with Rosuvastatin – A Chance for Better Compliance

To effectively decrease cardiovascular adverse events in patients with multiple risk factors, it is required to act synergistically against all of them on different fields: change lifestyle to lose weight, change the dietary and exercise habits, and use the pharmacological measures. The doctor should notice that in hypertensive patients with other risk factors not only blood pressure goal achievement but also improved lipid profile or proper glycemia control significantly decreases cardiovascular risk [60]. Patients' adherence to the pharmacological therapy significantly decreases the risk of long-term adverse events including mortality [61]. However, treatment regimens for combined blood pressure, cholesterol, and glycemia control and antiplatelet therapy in high cardiovascular risk is often complicated and for the patients is the main reason for poor compliance [62]. Benefits of the use of single-pill combination therapy are not only good effects of free therapy but also better patient compliance [62].

Olmesartan medoxomil and rosuvastatin, thanks to its pleiotropic effects, besides blood pressure lowering and lipid lowering respectively, are very attractive for the prescribing doctor and for the patient as well. Lately, a fixed-dose combination tablet of these two drugs (rosuvastatin 20 mg/olmesartan 40 mg) was developed [63]. Pharmacokinetics of the fixed-dose combination tablet was equally effective as coadministration of each drug as a single pill [63].

References

1. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J. 2014;35(42):2950–9.
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, et al. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. Circulation. 2014;129(3):e28.
3. Johnston CI, Risvanis J. Preclinical pharmacology of angiotensin II receptor antagonists: update and outstanding issues. Am J Hypertens. 1997;10(12 Pt 2):306S–10.
4. Koike H, Sada T, Mizuno M. In vitro and in vivo pharmacology of olmesartan medoxomil, an angiotensin II type AT1 receptor antagonist. J Hypertens Suppl. 2001;19(1):S3–14.
5. Laeis P, Püchler K, Kirch W. The pharmacokinetic and metabolic profile of olmesartan medoxomil limits the risk of clinically relevant drug interaction. J Hypertens Suppl. 2001;19(1): S21–32.
6. Brunner HR. The new oral angiotensin II antagonist olmesartan medoxomil: a concise overview. J Hum Hypertens. 2002;16 Suppl 2:S13–6.
7. Neutel J, Elliott WJ, Izzo J, Chen CL, Masonson H. Antihypertensive efficacy of olmesartan medoxomil, a new angiotensin II receptor antagonist, as assessed by ambulatory blood pressure measurements. J Clin Hypertens (Greenwich). 2002;4(5):325–31.
8. Bolbrinker J, Huber M, Scholze J, et al. Pharmacokinetics and safety of olmesartan medoxomil in combination with either amlodipine or atenolol compared to respective monotherapies in healthy subjects. Fundam Clin Pharmacol. 2009;23(6):767–74.
9. Chrysant SG, Marbury TC, Robinson TD. Antihypertensive efficacy and safety of olmesartan medoxomil compared with amlodipine for mild-to-moderate hypertension. J Hum Hypertens. 2003;17(6):425–32.
10. Saruta T, Ogihara T, Saito I, et al. Comparison of olmesartan combined with a calcium channel blocker or a diuretic in elderly hypertensive patients (COLM Study): safety and tolerability. Hypertens Res. 2015;38(2):132–6.
11. Kario K, Saito I, Kushiro T, et al. Effects of olmesartan-based treatment on masked, white-coat, poorly controlled, and well-controlled hypertension: HONEST study. J Clin Hypertens (Greenwich). 2014;16(6):442–50.
12. Stumpe KO, Ludwig M. Antihypertensive efficacy of olmesartan compared with other antihypertensive drugs. J Hum Hypertens. 2002;16 Suppl 2:S24–8.
13. Wang L, Zhao JW, Liu B, et al. Antihypertensive effects of olmesartan compared with other angiotensin receptor blockers: a meta-analysis. Am J Cardiovasc Drugs. 2012;12(5): 335–44.
14. Durante A, Peretto G, Laricchia A, et al. Role of the renin-angiotensin-aldosterone system in the pathogenesis of atherosclerosis. Curr Pharm Des. 2012;18(7):981–1004.
15. Alvarez A, Cerdá-Nicolás M, Naim Abu Nabah Y, et al. Direct evidence of leukocyte adhesion in arterioles by angiotensin II. Blood. 2004;104(2):402–8.
16. Kranzhöfer R, Schmidt J, Pfeiffer CA, et al. Angiotensin induces inflammatory activation of human vascular smooth muscle cells. Arterioscler Thromb Vasc Biol. 1999;19(7):1623–9.
17. Tummala PE, Chen XL, Sundell CL, et al. Angiotensin II induces vascular cell adhesion molecule-1 expression in rat vasculature: a potential link between the renin-angiotensin system and atherosclerosis. Circulation. 1999;100(11):1223–9.
18. Chen XL, Tummala PE, Olbrych MT, et al. Angiotensin II induces monocyte chemoattractant protein-1 gene expression in rat vascular smooth muscle cells. Circ Res. 1998;83(9): 952–9.
19. Rajagopalan S, Kurz S, Münzel T, et al. Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J Clin Invest. 1996;97(8):1916–23.
20. de Araújo Jr RF, Reinaldo MP, Brito GA, et al. Olmesartan decreased levels of IL-1β and TNF-α, down-regulated MMP-2, MMP-9, COX-2, RANK/RANKL and up-regulated SOCs-1 in an intestinal mucositis model. PLoS One. 2014;9(12):e114923.

21. Rafiq K, Nishiyama A, Konishi Y, et al. Regression of glomerular and tubulointerstitial injuries by dietary salt reduction with combination therapy of angiotensin II receptor blocker and calcium channel blocker in Dahl salt-sensitive rats. PLoS One. 2014;9(9):e107853.
22. Gutiérrez-Fernández M, Fuentes B, Rodríguez-Frutos B, et al. Different protective and reparative effects of olmesartan in stroke according to time of administration and withdrawal. J Neurosci Res. 2014;93:806–14. doi:10.1002/jnr.23532.
23. Tsuda M, Iwai M, Li JM, et al. Inhibitory effects of AT1 receptor blocker, olmesartan, and estrogen on atherosclerosis via anti-oxidative stress. Hypertension. 2005;45(4):545–51.
24. Tomita N, Yamasaki K, Osako MK, et al. Combination therapy based on the angiotensin receptor blocker olmesartan for vascular protection in spontaneously hypertensive rats. Mol Med Rep. 2009;2(5):733–8.
25. Yamamoto E, Dong YF, Kataoka K, et al. Olmesartan prevents cardiovascular injury and hepatic steatosis in obesity and diabetes, accompanied by apoptosis signal regulating kinase-1 inhibition. Hypertension. 2008;52(3):573–80.
26. Noda K, Hosoya M, Nakajima S, et al. Anti-atherogenic effects of the combination therapy with olmesartan and azelnidipine in diabetic apolipoprotein E-deficient mice. Tohoku J Exp Med. 2012;228(4):305–15.
27. Porteri E, Rodella L, Rizzoni D, et al. Effects of olmesartan and enalapril at low or high doses on cardiac, renal and vascular interstitial matrix in spontaneously hypertensive rats. Blood Press. 2005;14(3):184–92.
28. You J, Wu J, Jiang G, et al. Olmesartan attenuates cardiac remodeling through DLL4/Notch1 pathway activation in pressure overload mice. J Cardiovasc Pharmacol. 2013;61(2):142–51.
29. Fu M, Zhou J, Xu J, et al. Olmesartan attenuates cardiac hypertrophy and improves cardiac diastolic function in spontaneously hypertensive rats through inhibition of calcineurin pathway. J Cardiovasc Pharmacol. 2014;63(3):218–26.
30. Fukui T, Munemura C, Maeta S, et al. The effects of olmesartan and alfacalcidol on renoprotection and klotho gene expression in 5/6 nephrectomized spontaneously hypertensive rats. Yonago Acta Med. 2011;54(3):49–58.
31. Fliser D, Buchholz K, Haller H. Antiinflammatory effects of angiotensin II subtype 1 receptor blockade in hypertensive patients with microinflammation. Circulation. 2004;110(9):1103–7.
32. Naya M, Tsukamoto T, Morita K, et al. Olmesartan, but not amlodipine, improves endothelium-dependent coronary dilation in hypertensive patients. J Am Coll Cardiol. 2007;50(12):1144–9.
33. Takiguchi S, Ayaori M, Uto-Kondo H, et al. Olmesartan improves endothelial function in hypertensive patients: link with extracellular superoxide dismutase. Hypertens Res. 2011;34(6):686–92.
34. Smith RD, Yokoyama H, Averill DB, et al. Reversal of vascular hypertrophy in hypertensive patients through blockade of angiotensin II receptors. J Am Soc Hypertens. 2008;2(3):165–72.
35. Stumpe KO, Agabiti-Rosei E, Zielinski T, et al. Carotid intima-media thickness and plaque volume changes following 2-year angiotensin II-receptor blockade. The Multicentre Olmesartan atherosclerosis Regression Evaluation (MORE) study. Ther Adv. Cardiovasc Dis. 2007;1(2):97–106.
36. Raff U, Ott C, Ruilope LM, et al. Prevention of electrocardiographic left ventricular remodeling by the angiotensin receptor blocker olmesartan in patients with type 2 diabetes. J Hypertens. 2014;32(11):2267–76.
37. Haller H, Ito S, Izzo Jr JL, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med. 2011;364(10):907–17.
38. Crouse 3rd JR. An evaluation of rosuvastatin: pharmacokinetics, clinical efficacy and tolerability. Expert Opin Drug Metab Toxicol. 2008;4(3):287–304.
39. Martin PD, Mitchell PD, Schneck DW. Pharmacodynamic effects and pharmacokinetics of a new HMG-CoA reductase inhibitor, rosuvastatin, after morning or evening administration in healthy volunteers. Br J Clin Pharmacol. 2002;54(5):472–7.

40. Bologa R, Levine D, Parker T, et al. Pharmacokinetics of rosuvastatin in patients with end-stage kidney disease undergoing peritoneal dialysis. Clin Nephrol. 2009;72(6):437–41.
41. Birmingham BK, Swan SK, Puchalski T, et al. Pharmacokinetic and pharmacodynamic profile of rosuvastatin in patients with end-stage renal disease on chronic haemodialysis. Clin Drug Investig. 2013;33(4):233–41.
42. Rader DJ, Davidson MH, Caplan RJ, et al. Lipid and apolipoprotein ratios: association with coronary artery disease and effects of rosuvastatin compared with atorvastatin, pravastatin, and simvastatin. Am J Cardiol. 2003;91(5A):20C–3.
43. Wlodarczyk J, Sullivan D, Smith M. Comparison of benefits and risks of rosuvastatin versus atorvastatin from a meta-analysis of head-to-head randomized controlled trials. Am J Cardiol. 2008;102(12):1654–62.
44. Harley CR, Gandhi S, Blasetto J, et al. Low-density lipoprotein cholesterol (LDL-C) levels and LDL-C goal attainment among elderly patients treated with rosuvastatin compared with other statins in routine clinical practice. Am J Geriatr Pharmacother. 2007;5(3):185–94.
45. Fox KM, Gandhi SK, Ohsfeldt RL, et al. Comparison of low-density lipoprotein cholesterol reduction after switching patients on other statins to rosuvastatin or simvastatin in a real-world clinical practice setting. Am J Manag Care. 2007;13 Suppl 10:S270–5.
46. Abe M, Maruyama N, Okada K, et al. Effects of lipid-lowering therapy with rosuvastatin on kidney function and oxidative stress in patients with diabetic nephropathy. J Atheroscler Thromb. 2011;18(11):1018–28.
47. Abe M, Maruyama N, Yoshida Y, et al. Efficacy analysis of the lipid-lowering and renoprotective effects of rosuvastatin in patients with chronic kidney disease. Endocr J. 2011;58(8):663–74.
48. Du R, Cai J, Zhao XQ, et al. Early decrease in carotid plaque lipid content as assessed by magnetic resonance imaging during treatment of rosuvastatin. BMC Cardiovasc Disord. 2014;14:83.
49. Rogers JK, Jhund PS, Perez AC, et al. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA Trial (Controlled Rosuvastatin Multinational Trial in Heart Failure). JACC Heart Fail. 2014;2(3):289–97.
50. Sun BJ, Hwang E, Jang JY, et al. Effect of rosuvastatin on coronary flow reserve in patients with systemic hypertension. Am J Cardiol. 2014;114(8):1234–7.
51. Mahalwar R, Khanna D. Pleiotropic antioxidant potential of rosuvastatin in preventing cardiovascular disorders. Eur J Pharmacol. 2013;711(1–3):57–62.
52. Sicard P, Acar N, Grégoire S, et al. Influence of rosuvastatin on the NAD(P)H oxidase activity in the retina and electroretinographic response of spontaneously hypertensive rats. Br J Pharmacol. 2007;151(7):979–86.
53. Erdös B, Snipes JA, Tulbert CD, et al. Rosuvastatin improves cerebrovascular function in Zucker obese rats by inhibiting NAD(P)H oxidase-dependent superoxide production. Am J Physiol Heart Circ Physiol. 2006;290(3):H1264–70.
54. Colucci R, Fornai M, Duranti E, et al. Rosuvastatin prevents angiotensin II-induced vascular changes by inhibition of NAD(P)H oxidase and COX-1. Br J Pharmacol. 2013;169(3):554–66.
55. Jones SP, Gibson MF, Rimmer 3rd DM, et al. Direct vascular and cardioprotective effects of rosuvastatin, a new HMG-CoA reductase inhibitor. J Am Coll Cardiol. 2002;40(6):1172–8.
56. Schäfer A, Fraccarollo D, Eigenthaler M, et al. Rosuvastatin reduces platelet activation in heart failure: role of NO bioavailability. Arterioscler Thromb Vasc Biol. 2005;25(5):1071–7.
57. Laufs U, Gertz K, Dirnagl U, et al. Rosuvastatin, a new HMG-CoA reductase inhibitor, upregulates endothelial nitric oxide synthase and protects from ischemic stroke in mice. Brain Res. 2002;942(1–2):23–30.
58. Gómez-García A, Martínez Torres G, Ortega-Pierres LE, et al. Rosuvastatin and metformin decrease inflammation and oxidative stress in patients with hypertension and dyslipidemia. Rev Esp Cardiol. 2007;60(12):1242–9.

59. Verreth W, De Keyzer D, Davey PC, et al. Rosuvastatin restores superoxide dismutase expression and inhibits accumulation of oxidized LDL in the aortic arch of obese dyslipidemic mice. Br J Pharmacol. 2007;151(3):347–55.
60. Teramoto T, Kawamori R, Miyazaki S, et al. Lipid and blood pressure control for the prevention of cardiovascular disease in hypertensive patients: a subanalysis of the OMEGA study. J Atheroscler Thromb. 2014;22:62–75.
61. Kumbhani DJ, Steg PG, Cannon CP, et al. Adherence to secondary prevention medications and four-year outcomes in outpatients with atherosclerosis. Am J Med. 2013;126(8):693–700.
62. Burnier M, Brown RE, Ong SH, et al. Issues in blood pressure control and the potential role of single-pill combination therapies. Int J Clin Pract. 2009;63(5):790–8.
63. Son H, Roh H, Lee D, et al. Pharmacokinetics of rosuvastatin/olmesartan fixed-dose combination: a single-dose, randomized, open-label, 2-period crossover study in healthy Korean subjects. Clin Ther. 2013;35(7):915–22.

Chapter 17
Conclusions and Take Home Message

Maciej Banach

Based on the data included in the chapters the following conclusions and take-home messages might be presented:

1. *Bile acid sequestrants* (*BAS*) *and statins*: the BAS have been shown to induce meaningful reductions in low-density lipoprotein cholesterol (LDL-C) and reduce risk of cardiovascular (CV) events; used either in monotherapy or in combination with other lipid lowering drugs have been shown to retard rates of atherosclerotic plaque progression and even induce plaque regression; in statin intolerant patients BAS may be combined with ezetimibe as needed; the BAS have a relatively favorable safety profile (however gastrointestinal adverse effects might be often present even at low doses, which limit their practical use), and their elimination is independent of hepatic and renal function [1];
2. *Fibrates and statins*: pharmacotherapy with fibrates should be considered in patients with the triglyceride (TG) level >2.3 mmol/L (200 mg/dL), in whom TG reduction could not be achieved through non-pharmacological treatment – exercise, weight reduction and diet; statins are the treatment of choice for moderate hypertriglyceridemia; fibrates should be recommended in the high risk group (including the one with diabetes), while in other patients the addition of fibrates to a statin should always be considered if statin monotherapy does not bring the satisfactory reduction in TG levels; hypertriglyceridemia-related acute pancreatitis is a clear indication for therapy with fibrates, as an adjunct to the right diet and omega fatty acids [2, 3];

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3. *Ezetimibe and statins*: ezetimibe in monotherapy (e.g. in statin intolerant patients) or added to statin therapy reduces LDL-C level by additionally 20–25 %; the *IMProved Reduction of Outcomes*: *Vytorin Efficacy International Trial* (IMPROVE-IT) [4] with ezetimibe is the first proof of the concept that a non-statin LDL-lowering intervention further reduces CV risk to a similar extent as statin; however, even with ezetimibe on top of statin therapy unmet clinical need remains [5];
4. *Niacin and statins*: nicotinic acid (niacin) has been associated with increase in high density lipoprotein cholesterol (HDL-C) up to 30 % and reductions in LDL-C, total cholesterol (TC), TGs, small dense LDL particles, apolipoprotein B (apoB) and lipoprotein a [Lp(a)]; the addition of niacin to statins seems to improve the general lipid profile, however there has been no benefit in terms of CV prevention in the recent trials; an increase in serious adverse effects (AEs) was noted in the *Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events* (HPS2-THRIVE) trial [6] with niacin and laropiprant what further limits its practical use, and it was the reason that it is no longer on the market in many countries [7];
5. *Omega-3 fatty acids and statins*: omega-3 fatty acids (OM3 FAs) therapies added to optimal statin monotherapy is safe and well tolerated and reduces triglyceride-rich lipoproteins cholesterol (TRL-C)/non-HDL in subjects with hypertriglyceridemia; patients with elevated TGs may benefit from OM3 FAs supplementation as combination therapy to statins and lifestyle changes, especially those with TGs ≥500 mg/dL and perhaps, pending results of ongoing trials, those with TGs ≥200 and <500 mg/dL; additional roles for OM3 FAs lie in certain subgroups with specific familial dyslipidemias and those who do not tolerate statin therapy; the ongoing *STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia* (STRENGTH) and the *Reduction of Cardiovascular Events With EPA – Intervention Trial* (REDUCE-IT) are the first CV outcomes trials to appropriately target an elevated TG with a therapy that effectively lowers the atherogenic components of non-HDL that are not sufficiently managed by statin therapy alone [8];
6. *Cholesteryl ester transfer protein* (*CETP*) *inhibitors and statins*: despite an unfavorable history of clinical development with AEs of torcetrapib and no clinical benefit with dalcetrapib, the hope remains that potent CETP inhibitors (anacetrapib and evacetrapib) with favorable effects on both HDL and atherogenic lipoproteins, may prove to reduce CV events in ongoing clinical trials; the results of these trials will provide definitive information with regards to the efficacy and safety of this class in order to determine whether they will prove to be a useful adjunctive therapy in patients optimally treated with a statin [9];
7. *Mipomersen and statins*: mipomersen has complementary to statins mechanisms of action, as statins increase LDL catabolism and mipomersen inhibits apoB synthesis; the efficient dose-dependent reductions in plasma LDL-C concentrations achieved by mipomersen therapy is highly significant, however, the risk of hepatic steatosis and injection-site reactions continue to remain a concern that bear on the clinical use of this agent; despite the favorable effects of mipomersen on Lp(a), CV benefit of treating elevated Lp(a) remains untested;

new formulations of mipomersen that do not cause injection-site reactions are essential to increase the acceptability of this form of therapy by patients [10];

8. *Lomitapide and statins*: the use of lomitapide in association with statins help in further significant reduction of LDL-C levels and effectively prevent CVD, as well as to reduce the use of other drugs and interventions such as ezetimibe and LDL apheresis especially in patients with homozygous familial hypercholesterolemia (HoFH); lomitapide is a very effective perspective for patients with HoFH, along with other drugs, and despite very high costs of the therapy, it is a step forward and provides the patients with hope for a better life [11];
9. *Proprotein convertase subtilisin/kexin 9* (*PCSK9*) *inhibitors and statins*: the inhibition of PCSK9 is the most attractive new approach to reducing atherogenic lipoproteins (LDL-C, but also ApoB, TG and Lp(a)) and enhancing the efficacy of statins; phase II and III trials have shown that they are very effective and well tolerated [12]: PCSK9 inhibitors produce a 40–70 % reduction in the LDL-C level when combined with a statin, and even 56 % reduction in monotherapy (e.g. in statin intolerant patients) [13]; the available studies (the OSLER [14] and ODYSSEY LONG-TERM [15] trials) have also confirmed the efficacy of PCSK9 inhibitors on CV endpoints, however these studies were not designed for such analysis; therefore only the ongoing CV outcomes trials (FOURIER with evolocumab, ODYSSEY OUTCOMES with alirocumab and SPIRE with bococizumab [12]) will provide the necessary information on the efficacy of PCSK9 inhibitors in combination with a statin in reducing CVD events and on the long-term safety of this therapeutic approach for the treatment of patients with CVD or at risk for CVD not controlled by conventional lipid-lowering therapies [16];
10. *Other combinations with statins*: to treat residual dyslipidemias and patients with intolerance to currently available drugs the following lipid lowering therapies might be, among others, soon available: microsomal triglyceride transfer protein (MTP) inhibitors, thyromimetics, squalene synthase inhibitors and novel Lp(a) lowering therapies [17];
11. *Antihyrpentensives and statins*: while there have been substantial improvements over recent decades in the management of single risk factors including hypertension and dyslipidemia, control of composite risk factors, such as concomitant hypertension and dyslipidemia remains particularly low, even among those on medication; reduction of overall CVD risk, especially in patients with particular high CV risk populations (such as the elderly) decreases CVD events greater than single risk factor reduction; greater adherence (as well as compliance) is possible with fewer medications or a single pill to treat hypertension-dyslipidemia or overall CVD risk [18, 19];

According to Dr. Lafeber the polypill could be an important tool to help closing the existed treatment gaps among high-risk individuals, in whom the guidelines recommend concomitant treatment with aspirin, statin and antihypertensive drugs [20]. Recent data indicate that combination pills can produce sizeable risk factor reductions, with a significant reduction (even by 50 %) of predicted CV risk. Results from ongoing trials, that have been further assessing the effectiveness of polypills in

reducing cholesterol and blood pressure levels, effects on adherence to indicated medications and clinical outcomes, would provide clear evidence on the role of polypill-based treatment strategy on the long run [20]. The recent discussion has been whether polypill-based therapy might be equally effective as the application of each drug in monotherapy, especially that the preparations used in the polypills (what was usually based on available RCTs) might not be the best therapeutic option taking into account the efficacy and safety (e.g. moderate doses of simvastatin, atenolol, hydrochlorothiazide), and not for all patients with dyslipidemia and hypertension (mainly for low and moderate CV risk). Therefore further studies are still mandatory.

Taking into account the limited number of agents (some of them are not recommended, some other still not available) that might be used in the dyslipidemia combination therapy, there is a large interest of *so-called* nutraceuticals that might complement pharmaceutical therapies. Functional foods, dietary supplements and nutraceuticals exert their lipid-lowering benefits through complicated signals and mechanisms and interfere with various targets involved in the absorption and metabolism of lipids [21]. Soluble fiber, glucomannan, plant sterols and probiotics inhibit the absorption of cholesterol and biliary salts by the bowel; monacolins, polycosanols, garlic and bergamot inhibit HMG-CoA reductase, limiting the hepatic synthesis of cholesterol; berberine, soy proteins and green tea act as inducers of LDL cholesterol excretion [21, 22]. The available clinical trials have shown that these nutraceuticals have an additive effect to statins, allowing reducing the doses of statins without decrease the results in terms of effectiveness in reducing total and LDL-cholesterol and significantly limiting side effects [21]. The results of the studies carried out have been encouraging, but further well-designed, large clinical trials with long follow-up are required to better assess the potential and possible long-term side effects of nutraceuticals and their combination with statins. Besides well-designed confirmatory studies, we still also need more clinical research to clarify the potential role in therapy of some new interesting nutraceuticals with strong preclinical evidence of efficacy, such as guggulipid (*Commiphora mukul*) and curcumin (*Curcuma longa*) (and many others for which the available evidences are still very limited) [21, 23].

References

1. Toth PP, Nikolic D, Rizzo M, Rysz J, Banach M. Use of combination statin and bile acid sequestrant therapy to treat dyslipidemia. In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 1–10.
2. Chruściel P, Mikhailidis DP, Toth PP, Rysz J, Banach M. Statins and fibrates – should it be recommended? In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 11–24.
3. Nikolic D, Katsiki N, Toth PP, Banach M, Al-Waili K, Al-Rasadi K, Rizzo M, Mikhailidis DP. Drug Evaluation. The Combination of fenofibrate and simvastatin for the treatment of dyslipidemia: when and for whom? In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 179–90.

4. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015 Jun 3. [Epub ahead of print]; doi:10.1056/NEJMoa1410489.
5. Laufs U. Statins and ezetimibe – doubts or bright future? In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 25–36.
6. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014;371(3):203–12.
7. Agouridis AP, Mikhailidis DP. Statins and niacin – the end of residual risk therapy? In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 37–44.
8. Brandt EJ, Davidson MH. The role of omega-3 fatty acids in dyslipidemias. In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 45–64.
9. Nicholls SJ. Statins and CETP inhibitors – anacetrapib and evacetrapib – the last hope? In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 65–72.
10. Pang J, Chan DC, Watts GF. Statins and mipomersen – mechanisms of action and patient tolerability. In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 73–86.
11. Pirillo A, Catapano AL. Statins and lomitapide – a suitable response for homozygous familial hypercholesterolemia? In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 87–98.
12. Dragan S, Serban MC, Banach M. Proprotein convertase subtilisin/kexin 9 inhibitors: an emerging lipid-lowering therapy? J Cardiovasc Pharmacol Ther. 2015;20(2):157–68.
13. Banach M, Rizzo M, Toth PP, et al. Statin intolerance – an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci. 2015;11(1):1–23.
14. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA, Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372(16):1500–9.
15. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ, ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372(16):1489–99.
16. Farnier M. Statins and PCSK9 inhibitors: defining the correct patients. In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 99–118.
17. Kostner K. Other possible drug combinations for dyslipidaemia. In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 119–26.
18. Zhao Y, Wong ND. Combination of lipid lowering agents with antihypertensive drugs – a joint fight against the two most important risk factors? In: M Banach, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 153–64.
19. Gozdzikiewicz-Lapinska J, Malyszko J. Drug evaluation: olmesartan medoxomil + rosuvastatin for the treatment of dyslipidemia and concomitant risk factors: a chance for better compliance? In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 191–200.
20. Lafeber M. The cardiovascular polypill in the prevention of cardiovascular disease. In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 165–78.
21. Cicero AFG, Colletti A. Statins and nutraceuticals/functional food – could be they combined? In: Banach M, editor. Combination therapy in dyslipidaemia. 1st ed. Springer; 2015. pp. 127–42.
22. Serban C, Sahebkar A, Ursoniu S, Andrica F, Banach M. Effect of sour tea (Hibiscus sabdariffa L.) on arterial hypertension: a systematic review and meta-analysis of randomized controlled trials. J Hypertens. 2015;33(6):1119–27.
23. Sahebkar A, Serban MC, Ursoniu S, Banach M. Effect of curcuminoids on oxidative stress: a systematic review and meta-analysis of randomized controlled trials. J Funct Food. 2015. doi:10.1016/j.jff.2015.01.005.