Atherosclerosis: X 1 (2019) 100002

Contents lists available at ScienceDirect

Atherosclerosis: X

journal homepage: www.journals.elsevier.com/atherosclerosis-x

Review article

Pharmaceutical strategies for reducing LDL-C and risk of cardiovascular disease

Alberico L. Catapano[a,*], Lale Tokgözoğlu[b], Alberto Mello e Silva[c], Eric Bruckert[d,**]

[a] Department of Pharmacological and Biomolecular Sciences, University of Milan, Via Balzaretti, 9 20133, Milan, Italy
[b] Department of Cardiology, Hacettepe University, Ankara, Turkey
[c] Hospital Egas Moniz, Centro Hospitalar de Lisboa Ocidental, Serviço de Medicina I, Rua da Junqueira 126, 1349-019, Lisbon, Portugal
[d] Hopital Pitié Salpêtrière et Université Paris Sorbonne, 83 Boulevard de l'hôpital, 75013, Paris, France

HIGHLIGHTS

- LDL-C-lowering is the key strategy to prevent cardiovascular (CV) disease.
- Statins are essential to achieve LDL-C level reduction.
- Alternative strategies to achieve LDL-C goal are available.
- Combination therapies can increase efficacy and reduce adverse events.
- PCSK9 inhibition significantly reduce LDL-C levels and CV outcomes.

ARTICLE INFO

Keywords:
Low-density lipoprotein cholesterol
Statins
Statin potency
Combination therapy
PCSK9 inhibition therapy

ABSTRACT

A key strategy in preventing cardiovascular (CV) disease is the reduction of low-density lipoprotein cholesterol (LDL-C). Statins are a crucial therapy for achieving LDL-C reductions, with the highest tolerated dose often prescribed, especially for patients who are at the greatest risk of CV disease. However, statin intolerance, heterogeneous responses to statins and non-adherence make alternative therapies necessary in some cases. Statins can be combined with a multitude of therapies with synergistic mechanisms of action to effectively manage lipid profiles, while improving safety and tolerability profiles. Addition of a cholesterol absorption inhibitor, bile acid sequestrant or fibrate to statin therapy leads to greater numbers of patients achieving and maintaining LDL-C goals. Furthermore, combination therapies can alter the plasma profiles of other molecules involved in hypercholesterolaemia, including triglycerides and high-density lipoprotein cholesterol. An additional strategy is proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition therapy, for use in patients who are statin intolerant, patients with heterozygous or homozygous familial hypercholesterolaemia, and patients at very high CV risk, as a potential means for achieving large LDL-C reductions and maintaining LDL-C goals. Clinical trials have demonstrated that PCSK9 inhibition therapy is not only effective but can also be combined with statin therapy to ensure greater reductions in LDL-C. Current, ongoing studies are investigating the efficacy of novel therapies, including selective peroxisome proliferator-activated receptor (PPAR) alpha modulators, PCSK9-specific ribonucleic acid (RNA) interference and anti-inflammatory therapies.

1. Introduction

Lowering levels of low-density lipoprotein cholesterol (LDL-C) is a key strategy in preventing cardiovascular (CV) disease (CVD) [1,2]. When lifestyle interventions prove ineffective in lowering LDL-C levels, a variety of pharmaceutical therapies can be considered. While statins are most often prescribed as a primary treatment, other therapies that may be considered include cholesterol absorption inhibitors, bile acid sequestrants and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitory monoclonal antibodies [1]. These monotherapies are

* Corresponding author. Department of Pharmacological and Biomolecular Sciences, University of Milan and IRCCS Multimedica, Via Balzaretti, 9 - 20133 Milan, Italy.
** Corresponding author.
E-mail addresses: alberico.catapano@unimi.it (A.L. Catapano), laletok@gmail.com (L. Tokgözoğlu), amelloesilva@gmail.com (A. Mello e Silva), eric.bruckert@aphp.fr (E. Bruckert).

https://doi.org/10.1016/j.athx.2019.100002
Received 22 February 2019; Accepted 26 February 2019
Available online 01 April 2019

generally efficacious and well tolerated but may be associated with low compliancy rates, heterogeneous efficacy and the occurrence of adverse events [3]. Monotherapy is often adequate in achieving LDL-C goals, although patients with very high LDL-C or at very high risk of CVD may require additional treatment, and in these situations, combination therapy is often recommended [1]. This overview will discuss monotherapies and combination therapies further.

2. The importance of potency in statin monotherapy

The joint European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) 2016 guidelines dictate that the greatest LDL-C reductions lead to the greatest reductions in CVD risk, with the highest potency statins proving the most effective at decreasing LDL-C levels [1,4]. Statin potency differs according to the type of statin and the dose used. Equal doses of atorvastatin and rosuvastatin lead to the greatest reductions in LDL-C compared with those of other statins, such as fluvastatin [5,6]. Atorvastatin and rosuvastatin are both recommended for use in patients with the highest CVD risk [4]. In pairwise dose-to-dose comparisons with atorvastatin, rosuvastatin leads to a significantly greater decrease in LDL-C ($p = 0.001$) and an increase in high-density lipoprotein cholesterol (HDL-C) ($p = 0.001$) [7], while changes in triglyceride (TG) levels are similar (with the exception of 10 mg atorvastatin *vs* 10 mg rosuvastatin, $p < 0.001$) [8]. Contrary to LDL-C, high levels of HDL-C may provide protection against CVD, while high TG levels are considered a direct cause of CVD [1].

The greatest reductions in the occurrence of CVD can be achieved by decreasing LDL-C in patients who have the greatest CVD risk (Table 1) [9]. High-potency statins should be used in patients with the greatest CVD risk [4]. Furthermore, prolonged statin therapy leads to the greatest reduction of CVD risk [9]. However, prolonged use of high-potency statins may not be possible for every patient. Response to statins is heterogeneous [3], and elevated dosage of high-potency statins may increase the likelihood of statin intolerance and statin-related adverse events, including myalgia [1]. In these patients, the highest tolerable dose or an alternative dosing schedule may be considered [1]. Alternative therapies can also be employed to achieve and maintain a desired LDL-C goal.

Great variation in the level of LDL-C reduction achieved exists between individuals on the same fixed-dose statin regimen [3]. Consequently, prescribed doses can vary across a 64-fold range, with great variation between individual statins [10]. Another source of heterogeneity in response to statin therapy is the patient demographic. Small but significant differences in LDL-C reduction have been reported in female patients compared with male patients treated with atorvastatin ($p < 0.05$) and rosuvastatin ($p = 0.02$) monotherapies [11,12]. Differences in rosuvastatin efficacy have also been observed between different ethnic populations [13].

3. Alternative strategies to achieve LDL-C goal

Many patients with a high CVD risk or very high LDL-C levels are not able to achieve LDL-C goals through statins alone. Additionally, a number of patients are either statin intolerant, or unable to tolerate high doses of statins [1]. The EURIKA study found that only 41.2% of patients from 12 European countries achieved target total cholesterol and LDL-C goals when treated with lipid-lowering drugs [14]. Although full adherence is associated with a reduced rate of CV-related morbidity and mortality, non-adherence is commonplace [15].

For patients who are unable to achieve LDL-C goal, the two main recommended strategies are to: 1) increase statin dose to the maximum tolerated, or 2) use a combination of therapies after statin monotherapies have been unsuccessful [1].

Table 1
Reduction in major vascular events as determined by LDL-C reduction and 5-year risk of major vascular event. Adapted from Collins et al. (2016) [9]

Major vascular events avoided, per 10,000 patients treated for 5 years		5-year risk of major vascular event, %			
		5–9	10–19	20–29	≥30
LDL-C reduction achieved with statin treatment, mmol/L	**1.00**	170	370	540	730
	1.50	250	540	800	1130
	2.00	310	680	1010	1440

LDL-C: low-density lipoprotein cholesterol.

3.1. Intensive statin therapy

By using uptitrated doses of high-potency statins, lower LDL-C goals can be achieved compared with standard doses of lower-potency statins, decreasing the occurrence of major CV events [16,17]. However, due to the heterogeneity in individual response to intensive statin therapy, > 40% of patients still do not achieve an LDL-C goal of < 70 mg/dl, with non-adherence a major factor due to dose-related adverse events and patient-related issues [3].

3.2. Combination therapy

The ESC/EAS 2016 guidelines recommend that “If the [LDL-C] goal is not reached [with statin monotherapy], statin combination with a cholesterol absorption inhibitor should be considered” [1]. Combination therapy can increase efficacy and reduce the occurrence of adverse events [18]. Multiple combination therapies have been developed for the improvement of lipid profiles (Fig. 1).

Statins are often combined with cholesterol absorption inhibitors, most commonly ezetimibe, due to their synergistic mechanisms of action [1]. The IMPROVE-IT trial found that the addition of ezetimibe to simvastatin led to a significant additional decrease in LDL-C levels of 24% compared with simvastatin alone ($p < 0.001$), and significantly lowered the risk of myocardial infarction (MI) ($p = 0.002$) and ischaemic stroke ($p = 0.008$) [19]. High-potency statins can also be combined with other therapies, as demonstrated by the EZ-PATH trial, where the addition of ezetimibe to atorvastatin led to a significant increase in the number of patients achieving an LDL-C goal of < 70 mg/dl compared with those receiving atorvastatin alone ($p < 0.001$) [20]. Significant improvements in coronary plaque regression have been observed with combined ezetimibe–atorvastatin therapy compared with atorvastatin alone ($p = 0.001$) [21]. Other combined therapies include combinations of statins and bile acid sequestrants, which have been shown to lead to a significant decrease in LDL-C of 17.5% compared with co-administration of simvastatin and placebo ($p < 0.001$) [22].

Alternative lipids and other CV-related molecules can be targeted in the management of lipid profiles. Fibrate monotherapy has been shown to decrease serum TG and increase HDL-C levels in patients with hypercholesterolaemia [23], and decrease levels of C-reactive protein [24]. In addition, combination therapy with fenofibrate–simvastatin decreased the rate of non-fatal MI, stroke or CV death by 31% in a subgroup of patients with type 2 diabetes with elevated TG and low HDL-C levels in the ACCORD Lipid trial [25]. Combined use of fibrates and statins, therefore, can be considered for use in patients with high LDL-C, low HDL-C and high TG levels [2].

Low rates of adherence can greatly affect the efficacy of therapy, leading to increased CV-related morbidity and mortality [26]. One solution is a combined treatment of multiple CV drugs, in the form of a fixed-dose ‘polypill’, in order to increase adherence in a cost-effective manner [1]. The UMPIRE trial showed that the use of a polypill containing simvastatin (alongside other molecules) significantly increased adherence (treatment effect = 1.33 [95% confidence interval 1.26, 1.41], $p < 0.001$) and significantly decreased LDL-C (treatment effect = −4.2 [95% confidence interval −6.6, −1.9], $p < 0.001$)

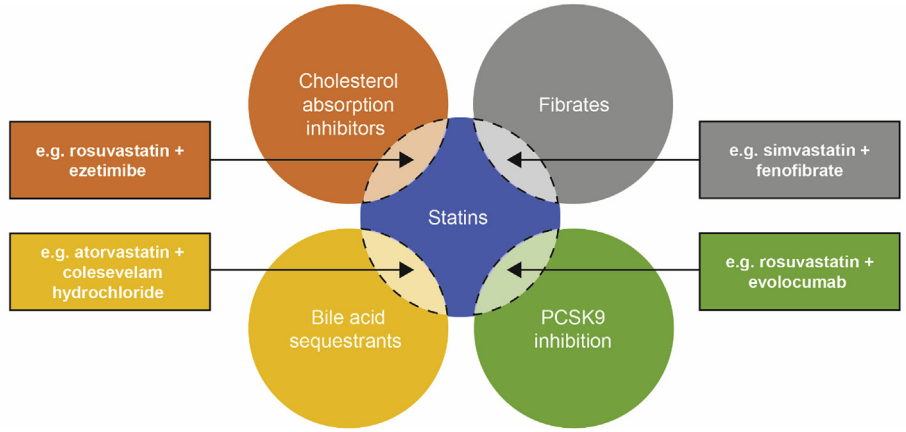

Fig. 1. Combination therapies for the management of LDL-C.
LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9.

compared with separate, concomitant treatments [27].

4. PCSK9, a new therapeutic target

Loss of function mutations within the PCSK9 gene are associated with reduced plasma LDL-C levels and large reductions in the risk of coronary heart disease [28]. Inhibition of PCSK9 represents a new therapeutic target to help achieve LDL-C goals in patients at high risk of CV events [29]. Meta-analysis on the efficacy of PCSK9 inhibition in patients with hypercholesterolaemia demonstrated a mean LDL-C level decrease from baseline of approximately 50%, and a decrease in MI event rate [30]. A separate meta-analysis demonstrated a reduced incidence of all-cause mortality, but found a higher rate of neurocognitive adverse events [31].

Three monoclonal antibodies have been developed as therapies to lower LDL-C levels in patients with hypercholesterolaemia: bococizumab, alirocumab and evolocumab. Bococizumab, a humanised monoclonal antibody that inhibits PCSK9, demonstrated no benefit over placebo with respect to major adverse CV events in a randomised trial involving lower-risk patients (SPIRE-1), but did have a significant benefit in a parallel trial of higher-risk patients (SPIRE-2) [32], although the studies were terminated early after the sponsor discontinued development of bococizumab. The GAUSS-3 trial demonstrated a significantly greater reduction in mean LDL-C in patients intolerant to statins following treatment with evolocumab for 24 weeks compared with ezetimibe (52.8% and 16.7%, respectively; $p < 0.001$) [33]. The ODYSSEY ALTERNATIVE trial produced similar efficacy results in patients with statin intolerancy, with alirocumab leading to greater reductions in mean LDL-C compared with ezetimibe after 24 weeks compared with baseline (54.8% and 20.1%, respectively) [34].

The ODYSSEY FHI and FHII trials described similar efficacy levels in patients with heterozygous familial hypercholesterolaemia (FH) treated with alirocumab, leading to significant LDL-C reductions from baseline of 48.8% (FHI; $p < 0.0001$ *vs* placebo) and 48.7% (FHII; $p < 0.0001$ *vs* placebo) [35]. The TAUSSIG study in patients with homozygous FH showed that PCSK9 inhibition therapy lead to LDL-C reductions of 20.6% and 23.3% after 12 and 48 weeks, respectively, compared with baseline ($p < 0.0001$ for both timepoints) [36].

The first PCSK9 inhibition therapy clinical outcome study, the FOURIER trial, examined the efficacy of evolocumab in reducing the risk of CV events in high-risk patients. Evolocumab significantly reduced the composite risk of CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation by 15%, and specifically reduced the composite risk of CV death, MI and stroke by 20%, compared with placebo ($p < 0.001$ for both composite risks) (Fig. 2) [37].

The ESC/EAS 2016 guidelines recommend PCSK9 inhibition

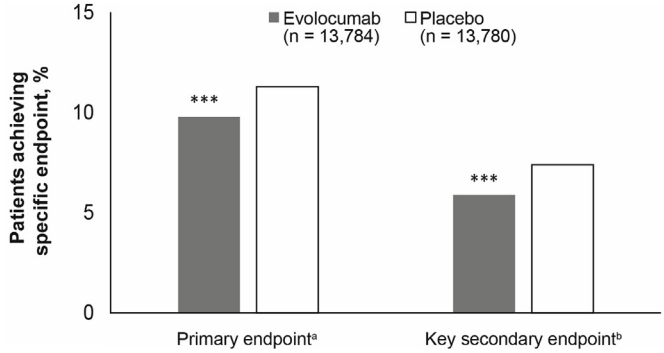

Fig. 2. The percentage of patients achieving the primary and key secondary endpoints from the FOURIER clinical trial. Data from Sabatine et al. (2017) [37].
***$p < 0.001$.
[a]The primary endpoint was the occurrence of major cardiovascular events, defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation.
[b]The key secondary endpoint was the composite of cardiovascular death, myocardial infarction or stroke.

therapy for use in patients who are statin intolerant, patients with heterozygous FH and homozygous FH, and patients at very high CV risk, as a potential means for achieving and maintaining LDL-C goals [1].

The ESC/EAS Task Force updated clinical guidance for the use of these novel agents and recommends consideration of PCSK9 inhibition therapy in very high-risk patients with atherosclerotic CVD and with FH without a prior clinical event, specifically in those not adequately controlled with maximally tolerated statin with or without ezetimibe therapy, or those who do not tolerate appropriate doses of at least three statins [29].

5. Conclusion

The greatest reductions in LDL-C are most needed in patients at the highest risk of CVD [1]. Statin potency differs according to type of statin and dose [5,6], which can be strategically exploited in treating patients of varying CVD risk. However, the vast heterogeneity in patient statin responses and the possibility of developing statin intolerance often means that elevated statin monotherapy may not be optimal [3]. Combination therapy is recommended in patients not achieving LDL-C goal at the highest tolerated statin dose, and in patients who are statin intolerant [1,18]. Multiple combination therapies can be recommended, which may not only increase efficacy in lowering LDL-C

due to synergistic mechanisms of action (statin–ezetimibe combination therapy) but also reduce levels of other molecules involved in hypercholesterolaemia (statin–fibrate combinations in lowering TG) [1,2,19,23]. Following the observed decrease in CV events in patients with type 2 diabetes and low HDL-C and elevated TG levels (a pre-specified subgroup with atherogenic dyslipidaemia) with fenofibrate–simvastatin combination therapy in the ACCORD Lipid trial [25], the PROMINENT study (NCT03071692, https://clinicaltrials.gov) is currently evaluating a new selective peroxisome proliferator-activated receptor alpha modulator, pemafibrate, in addition to statin therapy. Additional benefits of combination therapy include increased adherence [27], which is a key strategy in increasing therapeutic efficacy [1].

PCSK9 inhibition therapy is capable of reducing LDL-C levels by 50% [30]. The ESC/EAS Task Force recommend consideration of PCSK9 inhibition therapy for very high-risk patients with atherosclerotic CVD or FH with inadequately controlled LDL-C levels [29]. Clinical data released after the authors' workshop provides further evidence regarding the efficacy of PCSK9 inhibition therapy. Alirocumab treatment has recently been shown in the ODYSSEY OUTCOMES trial to lead to a significant 15% decrease in major adverse cardiac events compared with placebo ($p = 0.0003$), after 48 months of treatment in patients who experienced an acute coronary syndrome within 1–12 months prior to randomisation. This was accompanied by significant reductions in all-cause mortality ($p = 0.026$), MI ($p = 0.006$), ischaemic stroke ($p = 0.01$), ischaemia-driven coronary revascularisation ($p = 0.02$) or unstable angina ($p = 0.02$) compared with placebo. Furthermore, LDL-C was reduced by 62.7% at 4 months and 54.7% at 48 months, compared with placebo [38]. The ORION-1 study has demonstrated that a single dose of inclisiran, a small interfering ribonucleic acid (RNA) that produces PCSK9-specific RNA silencing, produced a 27.9–41.9% reduction in LDL-C after 180 days, compared with baseline ($p < 0.001$ for all doses). ORION-1 showed inclisiran could reduce LDL-C safely but also maintain reductions consistently over time [39].

Therapies that decrease the risk of major CV events by mechanisms independent of LDL-C reduction present alternative therapeutic options, including anti-inflammatory therapies. Canakinumab, a monoclonal antibody targeting interleukin-1β, has recently been shown in the CANTOS trial to significantly reduce the rate of recurrent CV events and decrease the levels of C-reactive protein, compared with placebo ($p = 0.02$ and $p < 0.001$, respectively), in patients with previous MI and elevated C-reactive protein levels [40]. Low-dose methotrexate, a dihydrofolate inhibitor used as an anti-inflammatory agent, is currently being evaluated in lowering the risk of CV events in patients with diabetes and previous MI [41].

Conflicts of interest

ALC has received grants from Pfizer, Sanofi, Regeneron, Merck, Mediolanum, non-financial support from SigmaTau, Menarini, Kowa, Recordati, Eli Lilly, personal fees from Astrazeneca, Genzyme, Bayer, SigmaTau, Menarini, Kowa, Eli Lilly, Recordati, Pfizer, Sanofi, Mediolanum, Merck, Aegerion, Amgen, outside the submitted work.

LT has received personal fees from Amgen, Sanofi, Pfizer, NovoNordisk, MSD, Actelion, Recordati, Kowa, Abbott, Novartis, Mylan, outside the submitted work.

AMS has received honoraria or consultation fees from Amgen, AstraZeneca, Jaba-Recordati, Merck, Mylan, Novartis and Tecnimede, and has participated in sponsored speaker's bureau for Amgen, Merck, Mylan and Tecnimede.

EB has received personal fees from AstraZeneca, Amgen, MSD, Sanofi and Regeneron, Unilever, Danone, Lilly, Ionis-Pharmaceuticals, Akcea, Alexion Pharma, outside the submitted work.

Acknowledgements

Medical writing support was provided by Edward Johnson, PhD on behalf of Alpharmaxim Healthcare Communications.

References

[1] A.L. Catapano, I. Graham, G. De Backer, O. Wiklund, M.J. Chapman, H. Drexel, et al., ESC/EAS guidelines for the management of dyslipidaemias, Eur. Heart J. 37 (2016) 2999–3058 2016.
[2] M.F. Piepoli, A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, et al., European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), Eur. Heart J. 37 (2016) 2315–2381 2016.
[3] S.M. Boekholdt, G.K. Hovingh, S. Mora, B.J. Arsenault, P. Amarenco, T.R. Pedersen, et al., Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials, J. Am. Coll. Cardiol. 64 (2014) 485–494.
[4] N.J. Stone, J.G. Robinson, A.H. Lichtenstein, C.N. Bairey Merz, C.B. Blum, R.H. Eckel, et al., 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 129 (2013) S1–S45 2014.
[5] M.R. Law, N.J. Wald, A.R. Rudnicka, Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis, BMJ 326 (2003) 1423.
[6] P.H. Jones, S. Kafonek, I. Laurora, D. Hunninghake, Comparative dose efficacy study of atorvastatin *versus* simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolaemia (the CURVES study), Am. J. Cardiol. 81 (1998) 582–587.
[7] P.H. Jones, M.H. Davidson, E.A. Stein, H.E. Bays, J.M. McKenney, E. Miller, et al., Comparison of the efficacy and safety of rosuvastatin *versus* atorvastatin, simvastatin, and pravastatin across doses (STELLAR* trial), Am. J. Cardiol. 92 (2003) 152–160.
[8] B.W. Karlson, M.K. Palmer, S.J. Nicholls, P. Lundman, P.J. Barter, A VOYAGER meta-analysis of the impact of statin therapy on low-density lipoprotein cholesterol and triglyceride levels in patients with hypertriglyceridemia, Am. J. Cardiol. 117 (2016) 1444–1448.
[9] R. Collins, C. Reith, J. Emberson, J. Armitage, C. Baigent, L. Blackwell, et al., Interpretation of the evidence for the efficacy and safety of statin therapy, Lancet 388 (2016) 2532–2561.
[10] S.B. Dimmitt, A. Moran, M. Scartozzi, H.G. Stampfer, J.B. Warren, Excessive range of statin dose in Western Australian primary care, Intern. Med. J. 45 (2015) 860–863.
[11] S.P. Adams, S.S. Sekhon, J.M. Wright, Lipid-lowering efficacy of rosuvastatin, Cochrane Database Syst. Rev. 11 (2014) CD010254.
[12] S.P. Adams, M. Tsang, J.M. Wright, Lipid-lowering efficacy of atorvastatin, Cochrane Database Syst. Rev. 3 (2015) CD008226.
[13] R. Naito, K. Miyauchi, H. Daida, Racial differences in the cholesterol-lowering effect of statin, J. Atheroscler. Thromb. 24 (2017) 19–25.
[14] J.R. Banegas, E. López-García, J. Dallongeville, E. Guallar, J.P. Halcox, C. Borghi, et al., Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: the EURIKA study, Eur. Heart J. 32 (2011) 2143–2152.
[15] S. Bansilal, J.M. Castellano, E. Garrido, H.G. Wei, A. Freeman, C. Spettell, et al., Assessing the impact of medication adherence on long-term cardiovascular outcomes, J. Am. Coll. Cardiol. 68 (2016) 789–801.
[16] C.P. Cannon, E. Braunwald, C.H. McCabe, D.J. Rader, J.L. Rouleau, R. Belder, et al., Intensive *versus* moderate lipid lowering with statins after acute coronary syndromes, N. Engl. J. Med. 350 (2004) 1495–1504.
[17] 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 376 (2010) 1670–1681.
[18] A.A. Taylor, J.L. Pool, Clinical pharmacology of antihypertensive therapy, Semin. Nephrol. 25 (2005) 215–226.
[19] C.P. Cannon, M.A. Blazing, R.P. Giugliano, A. McCagg, J.A. White, P. Theroux, et al., Ezetimibe added to statin therapy after acute coronary syndromes, N. Engl. J. Med. 372 (2015) 2387–2397.
[20] L.A. Leiter, H. Bays, S. Conard, S. Bird, J. Rubino, M.E. Hanson, 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. 102 (2008) 1495–1501.
[21] K. Tsujita, S. Sugiyama, H. Sumida, H. Shimomura, T. Yamashita, K. Yamanaga, et al., Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial, J. Am. Coll. Cardiol. 66 (2015) 495–507.
[22] H.E. Bays, M. Davidson, M.R. Jones, S.L. Abby, 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. 97 (2006) 1198–1205.
[23] C.H. Lee, P. Olson, R.M. Evans, Minireview: lipid metabolism, metabolic diseases,

and peroxisome proliferator-activated receptors, Endocrinology 144 (2003) 2201–2207.
[24] C. Duval, G. Chinetti, F. Trottein, J.-C. Fruchart, B. Staels, The role of PPARs in atherosclerosis, Trends Mol. Med. 8 (2002) 422–430.
[25] ACCORD Study Group, H.N. Ginsberg, M.B. Elam, L.C. Lovato, J.R. Crouse 3rd, L.A. Leiter, et al., Effects of combination lipid therapy in type 2 diabetes mellitus, N. Engl. J. Med. 362 (2010) 1563–1574.
[26] P. Maningat, B.R. Gordon, J.L. Breslow, How do we improve patient compliance and adherence to long-term statin therapy? Curr. Atheroscler. Rep. 15 (2013) 291.
[27] S. Thom, N. Poulter, J. Field, A. Patel, D. Prabhakaran, A. Stanton, 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, J. Am. Med. Assoc. 310 (2013) 918–929.
[28] J.C. Cohen, E. Boerwinkle, T.H. Mosley, H.H. Hobbs, Sequence variations in PCSK9, low LDL, and protection against coronary heart disease, N. Engl. J. Med. 354 (2006) 1264–1272.
[29] U. Landmesser, M.J. Chapman, J.K. Stock, P. Amarenco, J.J.F. Belch, J. Borén, et al., 2017 update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia, Eur. Heart J. 39 (14) (2018 Apr 7) 1131–1143 10.1093/eurheartj/ehx549:10.1093/eurheartj/ehx549.
[30] E.P. Navarese, M. Kolodziejczak, V. Schulze, P.A. Gurbel, U. Tantry, Y. Lin, et al., Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis, Ann. Intern. Med. 163 (2015) 40–51.
[31] M.J. Lipinski, U. Benedetto, R.O. Escarcega, G. Biondi-Zoccai, T. Lhermusier, N.C. Baker, et al., The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis, Eur. Heart J. 37 (2016) 536–545.
[32] P.M. Ridker, J. Revkin, P. Amarenco, R. Brunell, M. Curto, F. Civeira, et al., Cardiovascular efficacy and safety of bococizumab in high-risk patients, N. Engl. J. Med. 376 (2017) 1527–1539.
[33] S.E. Nissen, E. Stroes, R.E. Dent-Acosta, R.S. Rosenson, S.J. Lehman, N. Sattar, et al., Efficacy and tolerability of evolocumab *vs* ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial, J. Am. Med. Assoc. 315 (2016) 1580–1590.
[34] P.M. Moriarty, P.D. Thompson, C.P. Cannon, J.R. Guyton, J. Bergeron, F.J. Zieve, et al., Efficacy and safety of alirocumab *vs* ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial, J Clin Lipidol 9 (2015) 758–769.
[35] J.J. Kastelein, H.N. Ginsberg, G. Langslet, G.K. Hovingh, R. Ceska, R. Dufour, et al., ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia, Eur. Heart J. 36 (2015) 2996–3003.
[36] F.J. Raal, G.K. Hovingh, D. Blom, R.D. Santos, M. Harada-Shiba, E. Bruckert, et al., Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study, Lancet Diabetes Endocrinol 5 (2017) 280–290.
[37] M.S. Sabatine, R.P. Giugliano, A.C. Keech, N. Honarpour, S.D. Wiviott, S.A. Murphy, et al., Evolocumab and clinical outcomes in patients with cardiovascular disease, N. Engl. J. Med. 376 (2017) 1713–1722.
[38] G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, et al., Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome, N. Engl. J. Med. 379 (2018) 2097–2107.
[39] K.K. Ray, U. Landmesser, L.A. Leiter, D. Kallend, R. Dufour, M. Karakas, et al., Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol, N. Engl. J. Med. 376 (2017) 1430–1440.
[40] P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease, N. Engl. J. Med. 377 (2017) 1119–1131.
[41] R.A. Harrington, Targeting inflammation in coronary artery disease, N. Engl. J. Med. 377 (2017) 1197–1198.