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The HDL paradox: what does it mean and how to manage low serum HDL cholesterol level?

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INTRODUCTION

It has been long known from population studies that low serum high-density lipoprotein cholesterol level (HDL-C) is a risk factor for cardiovascular disease (CVD) and high HDL-C level is associated with a decreased risk. This relation has been recently confirmed in a metaanalysis of 68 studies involving more than 300,000 subjects [1]. In addition, it has been shown in another metaanalysis of 8 large studies that even in patients on statin therapy in whom a very low level of low-density lipoprotein cholesterol level (LDL-C) has been achieved, strong negative relations exist between HDL-C and apolipoprotein (apo) A-I levels and the risk of major CV events [2].

However, not all studies gave such clear results. In a recent study, HDL-C level was a predictor of CV deaths in subjects without coronary artery disease (CAD) but had no such predictive value in subjects with CAD [3]. Similar findings were reported in a study showing that HDL-C level did not predict major CV events in patients after coronary artery bypass grafting [4].

Some studies indicated that in patients receiving intensive lipid-lowering therapy who reached low target LDL-C levels, HDL-C level was not a risk factor or showed a weak association with the risk. In the recently reported SMART study in patients with CVD who received no lipid-lowering therapy or were on usual doses of lipid-lowering drugs, low HDL-C level was associated with an increased risk but no such association was seen in patients receiving intensive therapy [5]. Similar results were reported in the JUPITER study in which a large rosuvastatin dose of 20 mg per day was used in healthy subjects [6, 7]. Also in the PROVE IT TIMI 22 study, HDL-C level had no predictive value in patients with an acute coronary syndrome (ACS) receiving intensive atorvastatin therapy (80 mg/day) [8], and in the TNT study in patients with stable CAD randomised to 80 mg of atorvastatin daily the association between HDL-C level and the risk was weaker compared to the control group (atorvastatin 10 mg/day) [9]. In contrast to the above studies showing that intensive statin therapy abolished the relation between HDL-C level and the risk, the recently reported COURAGE study in patients with stable CAD who were optimally treated to a target LDL-C level of 60–85 mg/dL with lipid-lowering drugs (statin ± ezetimibe, extended-release niacin, or fibrate) showed the risk to be associated with HDL-C level [10].

A preventive effect of HDL-C level on the risk observed in prospective epidemiological studies has been the rationale for search for drugs that would increase levels of this lipid. However, clinical trials of such drugs in patients receiving statins were unsuccessful as no addition risk reduction could be seen. Such results were obtained in studies with nicotinic acid (NA) [11, 12] and first drugs from the class of cholesteryl ester transfer protein (CETP) inhibitors [13, 14]. These results support the concept of dysfunctional HDL. According to this concept, the anti-atherosclerotic effect via various mechanisms is exerted by HDL particles themselves and not the transported cholesterol. This is also supported by clinical observations of patients in whom CAD develops despite high HDL-C level. Probably HDL in these patients do not exert their antiatherogenic effects.

As summarised in this introduction, the similarity between HDL-C and LDL-C levels in regard to their relation to CVD risk, albeit obviously directed in opposite directions (atherogenic and antiatherogenic effect), is limited to population studies, as statin trials indicate that LDL-C level reduction indeed results in a proportional reduction in risk [15], while increasing HDL-C level has no such effect.

The role of HDL in atherogenesis has resurfaced in the literature and in our opinion it is interesting enough to deserve a review. Regarding this issue, lipidology is now at the crossroads.

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HDL METABOLISM

The current knowledge on the metabolism and functions of HDL has been summarised in a number of recent publications [16–20].

HDLs are a very heterogeneous lipoprotein fraction. HDL particles differ by size, composition, physicochemical properties and also their physiologic function. HDL contain large amounts of surface apolipoproteins (mostly apo A-I), variable amounts of cholesterol and phospholipids, small amounts of triglycerides and various enzymes. Mature HDL have a spherical shape and consist of a hydrophobic core (cholesterol esters, triglycerides) and a cap that contains free cholesterol, phospholipids, apolipoproteins and enzymes including paraoxonase 1 (PON-1), lecithin-cholesterol acyltransferase (LCAT) and CETP.

Compared to other lipoproteins, HDL have small size and easily penetrate through the vascular endothelium to the intima. Precursors of mature HDL are lipid-free apo A-I particles which then transform into lipid-poor discoid pre-β_1-HDL. By binding to the ABCA1 transporter, pre-β_1-HDL acquire phospholipids and non-esterified cholesterol from the surface of various cells including macrophages. LCAT present in these lipoproteins catalyses cholesterol esterification on their surface. Cholesterol esters then migrate to the core, leaving lipoprotein surface free to accept free cholesterol. This process results in formation of larger HDL_3 particles which also accept free cholesterol from cells. Cholesterol esterification by the action of LCAT takes place also in HDL_3. As a result of these two processes, HDL_3 particles are transformed into even larger HDL_2 particles. Thus, HDL maturation from pre-β_1-HDL through HDL_3 to HDL_2 is mediated by LCAT. The ABCA1 transporter plays a key role in cholesterol removal from cells to pre-β_1--HDL and in a lesser extent to HDL_3, while other transporter, ABCG1, and the SRBI receptor, which are present on the cell surface, facilitate cholesterol transport to more mature HDL particles. The SRBI scavenging receptor on hepatocytes removes cholesterol from HDL_2 and regenerates pre-β_1 HDL and HDL_3 from HDL_2. As can be thus seen, the main role of HDL is to remove excess cholesterol from cells (reverse cholesterol transport) but it is a very dynamic lipid fraction which undergoes constant transformations.

HDL maturation or transformation of small into larger HDL particles is a prerequisite for normal reverse cholesterol transport. It has been suggested that impairment of this process leads to an increased CVD risk.

In addition to the above described direct transport of excess cholesterol by HDL from peripheral cells to the liver, these lipoproteins also participate in indirect cholesterol transport by exchanging cholesterol for triglycerides with apo B-containing lipoproteins. This process is mediated by CETP, and cholesterol contained in LDL is transferred to the liver by binding of these lipoproteins with the LDL receptor.

ANTIATHEROGENIC EFFECT OF HDL

Normally functioning HDL receive excess cholesterol from macrophages in the arterial wall (direct reverse transport) and transport it to the liver or exchange it with apo B-containing lipoproteins. Direct reverse cholesterol transport is considered the main mechanism of antiatherogenic effect of HDL.

Recently, a study has been published that supports a major role of antiatherogenic effect of HDL via reverse cholesterol transport. Khera et al. [21] reported that the ability of HDL to accept cholesterol from cultured macrophages showed a negative association with coronary events regardless of HDL-C level. The authors found that the coronary event risk decreased by 30% for each increase of the ability to remove cholesterol from macrophages by 1 standard deviation. In addition, a significant negative correlation was found between the ability of HDL to accept cholesterol from macrophages ex vivo and the carotid artery intima–media thickness, even when adjusted for HDL-C level. Recently, Khera and Rader [22] summarised the current knowledge on complex links between cholesterol removal from macrophages by HDL and atherogenesis in an editorial article published in a prestigious journal devoted to research on atherosclerosis.

Evidence of the role of HDL in reverse cholesterol transport were also provided by the studies on the use of HDL infusion to treat atherosclerosis, summarised in a recent review paper by Kingwell and Chapman [23]. Intravenous HDL infusions remove cholesterol from atherosclerotic plaques and reduce their macrophage content which may have an effect on plaque stabilisation and/or regression. As reported by the authors, rapid cholesterol removal from plaques by HDL may occur via multiple mechanisms of cholesterol clearance from cells. The main mechanism is transfer through the ABCA1 transporter to pre-β-HDL and in a smaller extent to HDL_3. SRBI and ABCG1 may also promote cholesterol influx to mature, cholesterol-rich, spherical HDL particles. ABCA1-mediated removal is particularly important due to the fact that expression of the transporter in plaques is large and some HDL infusion therapies increase the number of pre-β-HDL particles which accept cholesterol via ABCA1 [23].

The antiatherogenic effect of HDL is not limited to reverse cholesterol transport. Below we will briefly summarise these other mechanisms as recently reviewed by Soran et al. [24], Lüscher et al. [20] and Rosenson et al. [18] who published extensive reviews on this topic.

HDL exert antiinflammatory, anticoagulant, and antioxidative effects. A potential antiinflammatory effect of HDL may be largely dependent on PON-1, a HDL-related antioxidant enzyme. Antioxidant HDL properties mediated by PON-1 contribute to reduction of oxidative stress and inflammation. HDL reduce production of inflammatory cytokines by macrophages and endothelial expression of adhesion molecules (ICAM-1 i VCAM-1) which facilitate penetration of monocytes and neutrophils into the arterial wall.

The anticoagulant effect of HDL is related to a reduced expression of tissue factor on endothelial cells and inhibition of platelet activation. In vitro studies showed that HDL reduce platelet aggregation induced by collagen, thrombin, and adenosine diposphate. These lipoproteins may also inhibit thrombus formation by maintaining the integrity of endothelial cells. In addition, HDL stimulate prostacyclin synthesis.

Stimulation of nitric oxide (NO) synthesis and expression of an antiapoptotic Bel-xL protein should also be mentioned among the antiatherogenic effects of HDL.

Evidence is available from in vitro studies that HDL protect LDL from oxidation. Lipid peroxides may be transferred from LDL to HDL to be metabolised in the latter. The ability of HDL to reduce accumulation of lipid peroxides is associated mostly with apo A-I and PON-1 activity.

HDL also play a role in glucose homeostasis. Low HDL-C level may increase the risk of the development of type 2 diabetes. Low levels of this lipid fraction are associated with insulin resistance. Genetic defects leading to low HDL-C level are associated with impaired insulin secretion and increased resistance to insulin. An infusion of reconstituted HDL (rHDL) reduced blood glucose level in patients with type 2 diabetes. These data are inconsistent with the observed reduction of insulin sensitivity and increased risk of type 2 diabetes in patients treated with niacin which increases HDL-C level, and the increased risk of diabetes despite moderate increase in HDL-C level among those treated with statins.

ATHEROGENIC EFFECTS OF HDL

The effect of HDL on the vascular wall in patients with various inflammatory diseases is different from that in healthy subjects. Thus, a term of dysfunctional HDL has been created. As noted by Zheng and Aikawa [16], HDL become dysfunctional after exposure to the inflammatory milieu and in some chronic diseases. It becomes increasingly clear that both the number and the quality of HDL particles are of importance. On one hand, loss or modification of HDL proteins (e.g., apo A-I) and enzymes (e.g., PON-1) decreases their ability to accept cholesterol and exert an antiinflammatory effect, and on the other hand, enrichment in proinflammatory and prothrombotic proteins (e.g., apolipoprotein CIII, lipoprotein-associated phospholipase A2, and serum amyloid A) contributes to HDL dysfunction. HDL structure and composition undergo changes in conditions of inflammation and oxidative stress.

The current knowledge on HDL dysfunction has been recently briefly summarised by Lüscher et al. [20] and discussed in more detail by Serban et al. [25]. It should be noted, however, that our knowledge on dysfunctional HDL is still fragmentary. In general, reverse cholesterol transport becomes impaired, as are the antiinflammatory, antioxidant, and anticoagulant properties of HDL. A loss of these antiatherogenic functions has been indicated by in vitro studies.

The cause of reverse cholesterol transport impairment is oxidative modification of apo A-I by reactive oxygen species, mediated by myeloperoxidase produced in macrophages. Oxidatively modified apo A-I is no longer able to bind to the ABCA1 transporter on macrophages and accept cholesterol. In inflammation, the ability of HDL to accept cholesterol from macrophages becomes largely impaired also due to replacement of apo A-I with serum amyloid A, which is an acute phase protein.

The loss of antioxidative HDL properties is related to oxidation of apo A-I, impaired removal of lipid peroxides from LDL, and with reduced PON-1 activity (oxidation, glycation) and reduced NO synthesis. A proinflammatory effect of dysfunctional HDL is indicated by reduced inhibition of induction of adhesion molecules in the endothelium and increased release of proinflammatory cytokins which are responsible for monocyte recruitment to the arterial wall, which ultimately leads to macrophage accumulation. In addition, dysfunctional HDL show a reduced ability to induce an antiapoptotic protein. Their procoagulant effect may be attributed to reduced inhibition of platelet activity, expression of tissue factor, and impairment of fibrinolysis by increased expression of plasminogen activator inhibitor-1 (Fig. 1).

These briefly summarised mechanisms of proatherogenic action of dysfunctional HDL are closely related to each other and difficult to analyse separately.

Dysfunctional HDL may be present in CAD, diabetes, obesity, chronic kidney disease, sleep apnoea, autoimmune diseases (lupus erythematosus, rheumatoid arthritis, scleroderma), and in smokers [25].

Of final note, oxidated (dysfunctional) apo A-I amounting to 29% of the total apo A-I has been recently identified in human atherosclerotic plaques [26].

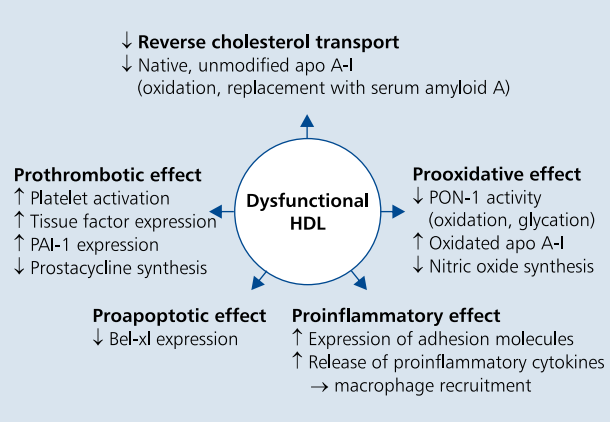

Figure 1. Proatherogenic effects of dysfunctional high density lipoprotein (HDL); apo A-I — apolipoprotein A-I; PON-1 — paraoxonase-1; PAI-1 — plasminogen activator inhibitor 1; Bel-xl — endothelial protein Bel-xl

INCREASING HDL LEVELS IN CLINICAL TRIALS

Until recently, no studies evaluated the effect of increasing HDL-C levels on the CV event risk. For many years, the only available drug increasing HDL-C level was crystalline NA which was poorly tolerated by patients. Later, new preparations of extended-release NA and extended-release NA combined with laropiprant were developed to reduce side effects. These newer forms of NA as well as a novel class of potent drugs increasing HDL-C level, CETP inhibitors, have been evaluated in clinical trials for some years now. Inhibition of CETP prevents cholesterol transfer from HDL to very-low-density lipoproteins (VLDL) and LDL. As a result, an increase in the serum level of large, lipid-rich HDL_2 is mostly seen. In addition, drugs of this class increase apo A-I level and reduce its catabolism, leading to its longer persistence in the circulation [27]. CETP inhibitors also reduce LDL-C level by inhibiting indirect reverse cholesterol transfer from HDL to LDL. These drugs also increase VLDL apo B clearance.

As already mentioned, however, clinical studies on newer NA preparations [11, 12] and two CETP inhibitors, torcetrapib and dalcetrapib [13, 14], did not show a reduction in CV events in patients receiving intensive statin therapy which may indicate that no causal relation exists between cholesterol content of HDL and CVD. Clinical trials continue with two other CETP inhibitors, i.e. anacetrapib (REVEAL study) and evacetrapib (ACCELERATE study) which also potently reduce LDL-C level and perhaps will induce CV risk reduction by this mechanism.

INFUSION THERAPY

Currently, clinical studies are underway to evaluate novel methods of treating atherosclerosis, mostly in the coronary arteries, by intravenous infusions of HDL preparations. This therapy is intended to induce rapid reduction of the lipid content of vulnerable plaques, resulting in their stabilisation and regression. Such atherosclerotic plaques contain up to 40% of lipids [28], and their cholesterol ester level is positively correlated with macrophage accumulation and negatively correlated with fibrous cap thickness [29]. Recently Kingwell and Chapman [23] and Hafiane and Geneset [30] evaluated the therapeutic utility of intravenous HDL infusions.

The currently tested rHDL preparation, designated CSL-111, contains human apo A-I isolated from the plasma and phosphatidylcholine from soybean, thus imitating native HDL. The result of the initial study (ERASE) using CSL-111 in 133 patients with an ACS was disappointing as no significant difference in reduction of plaque volume (evaluated using intravascular ultrasound) was seen between patients treated with 4 weekly CSL-111 infusions at 40 mg/kg and the placebo control group (–3.4% vs. –1.6%) [31]. In a clinical study of a single intravenous CSL-111 infusion in 29 patients with an ACS, no improvement of forearm artery vasodilator function was noted despite a mean increase in plasma HDL-C level by 64% and a decrease in LDL-C level by 23% [32]. However, in a study in 20 patients with peripheral arterial disease immediately after atherectomy, a single intravenous CSL-111 infusion at 80 mg/kg reduced plaque lipid content in the femoral artery by 62% compared to placebo [33]. In addition, a significant reduction of VCAM-1 and selectin P expression was noted. CSL-111 is being evaluated in phase II trials, and a new formula of CSL-111, designated CSL-112, is currently in phase I trials. CSL-112 is homologous with small particles, smaller than HDL_3. In rabbits and humans, it leads to formation of pre-β-HDL and more effectively removes cholesterol by the ABCA1 transporter than HDL_3. Although CSL-112 has not been shown to be more effective than CSL-111 at 40 mg/kg, it is better tolerated.

Another HDL preparation for intravenous administration is ETC-216, a preparation of recombinant apo A-I Milano combined with phosphatidylcholine. The idea of its therapeutic use originated from observations of patients with the apo A-I Milano mutation who do not develop premature atherosclerosis despite low HDL-C level (< 15 mg/dL), increased triglycerides and normal or elevated LDL-C level [34–36]. The only functional difference compared to normal HDL is a better ability of apo AI Milano to remove cholesterol through SRBI and ABCA1 [37, 38]. In 2003, a reduction in plaque volume by 4.2% after 5 intravenous infusions of ETC-216 at 45 mg/kg was shown in a small placebo-controlled study in patients with an ACS [39]. This observation showed the clinical utility of rHDL and prompted studies on other preparations. Of note, Pfizer ceased work on ETC-216 due to contamination during its production. A novel formula of ETC-216 is currently studied, designated MDCO-216. Another currently tested rHDL preparation is CER-001 (pre-β_1-like HDL). Studies are also underway on HDL mimetics which are synthetic peptides imitating apo A-I.

In summary, intravenous HDL infusions rapidly increase the number of HDL particles and by enhancing the ability to accept cholesterol, they may stabilise plaques during the first days after an ACS. A major role in cholesterol removal is played by ABCA1, as expression of this transporter in atherosclerotic plaques is particularly high, and some intravenous rHDL therapies mainly increase the number of pre-β_1-HDL which preferentially bind to ABCA-1.

It remains an open issue whether this form of therapy has an effect on the risk of CV events.

HOW TO MANAGE LOW HDL LEVEL?

As may be seen from the recent clinical studies [11–14], currently there is no justification for drug treatment of low HDL-C levels. We believe that the best approach has been summarised in the 2013 National Lipid Association consensus statement on HDL [40]. Below we recapitulate the most important recommendations from mentioned document in relation to this problem:

— HDL-C level is an important biomarker of the CV event risk and as such it is appropriately included into quantitative risk estimation models.
— Current evidence for therapy targeted at HDL-C level is insufficient. No evidence supports increasing HDL-C level to some arbitrarily set values (e.g. > 40 mg/dL in men and > 50 mg/dL in women).
— Currently available data do not support added benefits from using additional lipid-modifying drugs in patients with CVD in whom statin treatment results in optimal LDL-C and non-HDL-C levels.
— Combined therapy should be considered in patients who do not reach optimal LDL-C and non-HDL-C levels on statin treatment. The aim of such combined therapy is to lower LDL-C and non-HDL-C levels to risk-specific target levels.
— In patients with metabolic syndrome or insulin resistance, the best approach to raise HDL-C level is probably lifestyle modification (dietary modifications, body weight reduction, exercise, and smoking cessation) according to the National Cholesterol Education Program Adult Treatment Panel III guidelines.
— Clinical study results cannot be extrapolated to populations which have not been evaluated in these studies.

SUMMARY

The topic of this article is an important practical lipidologic issue, along with familial hypercholesterolaemia and severe hypertriglyceridaemia which have also been recently reviewed in the Polish literature [41, 42].

In this paper, we attempted to summarise current scientific evidence and views on the complex role of HDL in atherogenesis, as well as therapeutic recommendations in patients with low HDL-C level. In summary, it should be noted that the available evidence does not indicate that HDL are not antiatherogenic lipoproteins but rather directs our attention towards their functionality and dysfunctionality accompanying numerous pathologic conditions associated with inflammation. It may be hoped that effective methods to increase the number of functional HDL in the plasma will be developed in future studies, translating to a reduction in CV events and thus deserving a place in clinical practice guidelines.

Conflict of interest: *none declared*

References

1. The Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. JAMA, 2009; 302: 1993–2000.
2. Boekholdt SM, Arsenault BJ, Hovingh GK et al. Levels and changes of HDL cholesterol and apolipoprotein A-I in relation to risk of cardiovascular events among statin-treated patients. A meta-analysis. Circulation, 2013; 128: 1504–1512.
3. Silbernagel G, Schöttker, Appelbaum S et al. High-density lipoprotein cholesterol, coronary artery disease and cardiovascular mortality. Eur Heart J, 2013; 34: 3563–3571.
4. Angeloni E, Paneni F, Landmesser U et al. Lack of protective role of HDL-C in patients with coronary artery disease undergoing elective coronary artery bypass grafting. Eur Heart J, 2013; 34: 3557–3562.
5. Woestijne AP, van der Graaf Y, Liem AH et al. Low high-density lipoprotein cholesterol is not a risk factor for recurrent vascular event in patients with vascular disease on intensive lipid-lowering medication. J Am Coll Cardiol, 2013; 62: 1834–1841.
6. Ridker PM, Genset J, Boekholdt SM et al. HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial. Lancet, 2010; 376: 333–339.
7. Genset J. High-density lipoprotein and residual cardiovascular risk. J Am Coll Cardiol, 2013; 62: 1842–1844.
8. Ray KK, Cannon CP, Cairns R et al. Prognostic utility of apo B/AI, total cholesterol/HDL, non-HDL cholesterol, or CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. Arterioscler Thromb Vasc Biol, 2009; 29: 424–430.
9. Barter P, Gotto AM, La Rosa JC et al. For the Treating to New Targets Investigators. HDL cholesterol and cardiovascular events. N Engl J Med, 2007; 357: 1301–1310.
10. Acharjee S, Boden WE, Hartigan PM et al. Low levels of high-density lipoprotein cholesterol and increased risk of cardiovascular events in stable ischemic heart disease patients. A post-hoc analysis from the COURAGE Trial (Clinical Outcomes Utilizing Revascularization and Aggresive Drug Evaluation). J Am Coll Cardiol, 2013; 62: 1826–1833.
11. Boden WE, Probstfield JL, Anderson T et al. For the AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med, 2011; 365: 2255–2267.
12. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomised placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reason for stopping study treatment. Eur Heart J, 2013; 34: 1279–1291.
13. 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: 2109–2122.
14. Schwartz GG, Olsson AG, Abr M et al. Effects of dalcetrapib in patients with recent acute coronary syndrome. N Engl J Med, 2012; 367: 2089–2099.
15. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomized trials. Lancet, 2010; 376: 1670–1681.
16. Zheng C, Aikawa M. High-density lipoproteins: from function to therapy. J Am Coll Cardiol, 2012; 60: 2380–2383.
17. Schofield JD, France M, Ammori B et al. High-density lipoprotein cholesterol raising – does it matter ? Curr Opin Cardiol, 2013; 28: 464–474.
18. Rosenson RS, Brewer HB, Ansell B et al. Translation of high-density lipoprotein function into clinical practice. Current prospects and future challanges. Circulation, 2013; 128: 1256–1267.
19. Perez-Mendoz O, Pacheco HG, Martinez-Sanchez C, Franco M. HDL cholesterol in coronary artery disease risk: function or structure? Clin Chim Acta, 2014; 429: 111–122.
20. Luscher TF, Landmesser U, Eckardstein A, Fogelman AM. High-density lipoprotein. Vascular protective effects, dysfunction and potential as therapeutic target. Circ Res, 2014; 114: 171–182.

21. Khera AV, Cuchel M, de la Llera-Moya M et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med, 2011; 364: 127–135.
22. Khera AV, Rader DJ. Cholesterol efflux capacity. Full steam ahead or a bump on the road. Arterioscler Thromb Vasc Biol, 2013; 33: 1449–1451.
23. Kingwell BA, Chapman MJ. Future of high-density lipoprotein infusion therapies. Potential for clinical management of vascular disease. Circulation, 2013; 128: 1112–1121.
24. Soran H, Hama S, Yadav R, Durrington PN. HDL functionality. Curr Opin Lipidol, 2012; 23: 353–366.
25. Serban C, Muntean D, Mikhailidis DP et al. Dysfunctional HDL: the journey from savior to slayer. Clin Lipidol, 2014; 9: 49–59.
26. Huang Y, Didonato JA, Levison BS et al. An abudant dysfunctional apolipoprotein A in human atheroma. Nat Med, 2014, 2014; 20: 193–203.
27. Brousseau ME, Diffenderfer MR, Millar JS et al. Effects of cholesteryl ester transfer protein inhibition on high-density lipoprotein subspecies, apolipoprotein AI metabolism and fecal sterol excretion. Atheroscler Thromb Vasc Biol, 2005; 25: 1057–1064.
28. Davies MJ, Richardson PD, Woolf N et al. Risk of thrombosis in human atherosclerotic plaques : role of extracellular lipid, macrophage, and smooth muscle cell content. Br Heart J, 1993; 69: 377–381.
29. Felton CV, Crook D, Davies MJ, Oliver MF. Relation of plaque lipid composition and morphology to the stability of human aortic plaques. Arterioscler Thromb Vasc Biol, 1997; 17: 1337–1346.
30. Hafiane A, Genset J. HDL, atherosclerosis and emerging therapies. Cholesterol, 2013; http://dol.org/10.1155/2013/891403.
31. Tardif JC, Gregoire J, L'Allier PL et al. Effect of rHDL on Atherosclerosis-Safety and Efficacy (ERASE) Investigators. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. J Am Med Assoc, 2007; 297:1675–1682.
32. Chenevard R, Harlimann P, Spieker L et al. Reconstituted HDL in acute coronary syndromes. Cardiovasc Therapeutics, 2012; 30: e51–e57.
33. Shaw JA, Bobik A, Murphy RD et al. Infusion of reconstituted high-density lipoprotein leads to acute changes in human atherosclerotic plaque. Circ Res, 2008; 103: 1084–1091.
34. Calabresi L, Sirtori CR, Paoletti R, Franceschini G. Recombinant apolipoprotein A-I Milano for the treatment of cardiovascular diseases. Curr Atheroscler Rep, 2006; 8: 163–167.
35. Sirtori CR, Calabresi L, Franceschini G. Recombinant apolipoproteins for the treatment of vascular diseases. Atherosclerosis, 1999; 142: 29–40.
36. Chiesa G, Sirtori CR. Use of recombinant apolipoproteins in vascular diseases: the case of apo A-I. Curr Opin Investig Drugs, 2002; 3: 420–426.
37. Calabresi L, Canavesi M, Bernini F, Franceschini G. Cell cholesterol efflux to reconstituted high-density lipoproteins containing the apolipoprotein A-I Milano dimer. Biochemistry, 1999; 38: 1607–16314.
38. Favari E, Gomaraschi M, Zanotti I et al. A unique protease-sensitive high density lipoprotein particle containing the the apolipoprotein A-I (Milano) dimer effectively promates ATP-binding Cassette A-I mediated cell cholesterol efflux. J Biol Chem, 2007; 282: 5126–5132.
39. Nissen SE, Tsunoda Y, Tuzcu EM et al. Effect of recombinant Apo A-I Milano on coronary syndromes : a randomized controlled trial. JAMA, 2003; 290: 2292–2300.
40. Toth PP, Barter PJ, Rosenson RS. High-density lipoproteins: a consensus statement from the National Lipid Association. J Clin Lipidol, 2013; 7: 484–525.
41. Rynkiewicz A, Cybulska B, Banach M et al. Postępowanie w heterozygotycznej hipercholesterolemii rodzinnej. Stanowisko Forum Ekspertów Lipidowych. Kardiol Pol, 2013; 71: 102–111.
42. Cybulska B, Kłosiewicz-Latoszek L. Management of severe hypertriglyceridaemia. Kardiol Pol, 2013; 71: 1007–1012.