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# High density lipoprotein and cardiovascular diseases

Theodosios D Filippatos, Moses S Elisaf

Theodosios D Filippatos, Moses S Elisaf, Department of Internal Medicine, School of Medicine, University of Ioannina, 45110 Ioannina, Greece
Author contributions: Filippatos TD wrote the commentary article; Elisaf MS edited and supervised the commentary article.
Correspondence to: Moses S Elisaf, MD, FRSH, FASA, FISA, Professor, Department of Internal Medicine, School of Medicine, University of Ioannina, Staurou Niarchou Avenue, 45110 Ioannina, Greece. egepi@cc.uoi.gr
Telephone: +30-265-1007509 Fax: +30-265-1007016
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## Abstract

Several epidemiological studies have clearly shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) represent a cardiovascular disease (CVD) risk factor. However, it is unclear if there is a causal association between HDL-C concentration and CVD. A recent study published in the Lancet, which performed two Mendelian randomization analyses, showed that increased HDL-C levels were not associated with a decreased risk of myocardial infarction. These findings, together with the termination of the niacin-based AIM-HIGH trial and the discontinuation of cholesteryl ester transfer protein inhibitor dalcetrapib, challenge the concept that raising of plasma HDL-C will uniformly translate into reductions in CVD risk. HDL particles exhibit several anti-atherosclerotic properties, such as anti-inflammatory and anti-oxidative activities and cellular cholesterol efflux activity. Furthermore, HDL particles are very heterogeneous in terms of size, structure, composition and metabolism. HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. More research is needed to assess the association of the structure of HDL particle with its functionality and metabolism.



**Key words:** High density lipoprotein; Functionality; Structure; Cardiovascular risk; Niacin; Cholesteryl ester transfer protein inhibitors

**Core tip:** Epidemiological studies have shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) represent a cardiovascular disease (CVD) risk factor. However, recent studies challenge the concept that an increase of plasma HDL-C will uniformly translate into a reduction in CVD risk. Certain patients with atherosclerosis may have "dysfunctional" HDL despite normal HDL-C levels. Furthermore, HDL-C levels are influenced by dietary patterns, drugs or concomitant diseases. The association of the structure of HDL particle with its functionality and metabolism has not been fully clarified. More research is needed to assess the association of HDL functionality with CVD risk.

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## COMMENTARY ARTICLE

Several epidemiological studies have clearly shown that low plasma levels of high density lipoprotein cholesterol (HDL-C) represent a cardiovascular disease (CVD) risk factor[1-5]. Furthermore, some large randomized clinical trials have provided evidence of a clinical benefit of drugs increasing HDL-C, such as fibrates, in patients with combined low HDL-C and high triglyceride levels[6-12]. However, whether there is a causal association between HDL-C concentration and CVD is unclear.

A recent study published in the *Lancet* performed two mendelian randomisation analyses, testing a single nucleotide polymorphism (SNP) in the endothelial lipase gene (LIPG Asn396Ser) in 20 studies (20913 myocardial infarction cases, 95407 controls) and a genetic score con-

sisting of 14 common SNPs that exclusively associate with HDL-C (12482 cases of myocardial infarction and 41331 controls)[13]. Carriers of the LIPG 396Ser allele (2.6% frequency) had significantly higher HDL-C levels (0.14 mmol/L higher, $P < 0.001$) but similar levels of other lipid and non-lipid CVD risk factors compared with non-carriers. This difference in HDL-C is expected to decrease the risk of myocardial infarction by 13% (OR = 0.87, 95%CI: 0.84-0.91). However, the LIPG 396Ser allele was not associated with a reduced risk of myocardial infarction (OR = 0.99, 95%CI: 0.88-1.11, $P = 0.85$). Furthermore, whereas it is expected from observational epidemiology that an increase of 1 SD in HDL-C will be associated with a 38% reduced risk of myocardial infarction (OR = 0.62, 95%CI: 0.58-0.66), an 1 SD increase in HDL-C due to genetic score was not associated with a reduced risk of myocardial infarction (OR = 0.93, 95%CI: 0.68-1.26, $P = 0.63$)[13]. These results became more intriguing when a genetic score of 13 common SNPs exclusively associated with low density lipoprotein cholesterol (LDL-C), used as a positive control, was associated with myocardial infarction risk in concordance with observational epidemiology[13].

Additionally, the termination of the cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib was recently announced. Dalcetrapib, in contrast with torcetrapib, was not associated with non-lipid adverse effects[14]. In the dal-VESSEL trial, dalcetrapib reduced CETP activity and increased HDL-C levels without affecting nitric oxide-dependent endothelial function, blood pressure, or markers of inflammation and oxidative stress[15]. Furthermore, co-administration of dalcetrapib with pravastatin resulted in decreased CETP activity, increased HDL-C, apolipoprotein (apo) A-Ⅰ and A-Ⅱ levels and increased CETP mass. A relative increase in large HDL and LDL subfractions, combined with adenosine triphosphate (ATP)-binding cassette A1- and scavenger receptor type BI-mediated cholesterol efflux increase were also observed[16]. These effects seemed promising, but recently Roche announced that, following the results of the second interim analysis of the dalcetrapib dal-OUTCOMES Phase Ⅲ trial (aimed to evaluate the efficacy and safety profile of dalcetrapib when added to existing standard of care in patients with stable coronary heart disease following an acute coronary syndrome), the independent Data and Safety Monitoring Board recommended stopping the trial due to a lack of clinically meaningful efficacy[17].

Furthermore, the results of two large studies of niacin were recently added to these disappointing results. In AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial there was no incremental clinical benefit from the addition of niacin to statin therapy during a 36 mo follow-up period, despite significant improvements in HDL-C and triglyceride levels[18]. More specifically, 3314 patients with atherosclerotic CVD and LDL-C levels < 70 mg/dL (1.81 mmol/L), were randomly assigned to extended-release niacin (1500-2000 mg/d) or placebo. All patients received simvastatin (40-80 mg/d) plus ezetimibe (10 mg/d), if needed, to maintain an LDL-C level of 40-80 mg/dL (1.03-2.07 mmol/L). The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy. At 2 years, niacin therapy had significantly increased the median HDL-C level from 35 mg/dL (0.91 mmol/L) to 42 mg/dL (1.08 mmol/L) and decreased triglyceride level from 164 mg/dL (1.85 mmol/L) to 122 mg/dL (1.38 mmol/L) and LDL-C concentration from 74 mg/dL (1.91 mmol/L) to 62 mg/dL (1.60 mmol/L). However, the primary end point did not differ significantly between niacin (282 patients, 16.4%) and placebo (274 patients, 16.2%) groups (HR = 1.02; 95%CI: 0.87-1.21; $P = 0.79$)[18]. In the HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) study, the combination of niacin and laropiprant in addition to statin therapy did not significantly reduce the risk of major vascular events in patients with well-controlled LDL-C levels[19,20]. More specifically, the primary end point (the combination of coronary death, nonfatal myocardial infarction, stroke, or coronary revascularization) occurred in 13.7% of patients in the control arm and 13.2% of patients in the niacin/laropiprant arm (RR = 0.96, 95%CI: 0.90-1.03, $P = 0.29$)[20].

These data challenge the concept that an increase of plasma HDL-C will uniformly translate into a reduction in CVD risk. HDL-C may simply be a marker of CVD risk, or, alternatively, may represent a biomarker of adverse metabolic processes, as for example of insulin resistance and inflammation.

Some investigators proposed that the failure of dalcetrapib and niacin is related to the only moderate elevation of HDL-C and we have to wait until more potent HDL-increasing drugs to be tested. This thought is based on findings from previous trials. A meta-analysis of 23 trials showed that the sum of percent reduction in LDL-C plus the percent increase in HDL-C predicts CVD benefits much more effectively than either lipoprotein component[21]. Hence, in populations that have already low LDL-C we need potent HDL-elevating drugs to produce significant increases in HDL-C in order to show clinical benefit.

Moreover, differences between levels of LDL-C and HDL-C and their corresponding particle number measures were observed in many trials. This may be of clinical importance since recent studies have shown that CVD risk in patients with discordance between cholesterol and particle measures of LDL and HDL may be associated more with particle measures[22,23]. For example, the significant CVD event reduction in the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) could not be fully explained by the 6% increase in HDL-C with gemfibrozil[6,8]. When HDL subpopulations (characterized by 2-dimensional gel electrophoresis) were determined in subjects who were treated with gemfibrozil ($n = 754$) or placebo ($n = 741$), it was shown that gemfibrozil-mediated improvement in CVD risk might not be reflected

by changes in blood lipids and HDL subpopulations[24]. In contrast, when nuclear magnetic resonance (NMR) spectroscopy was used to quantify levels of LDL and HDL particle subclasses and mean particle sizes during treatment with gemfibrozil (364 men) or placebo (697 age-matched controls), it was shown that gemfibrozil increased LDL size and lowered numbers of LDL particles (-5%), whereas it increased the numbers of HDL particles (+10%) and small HDL subclass particles (+21%). In fact, the concentrations of these LDL and HDL particles achieved with gemfibrozil were independent predictors of new CHD events [total LDL particles: OR = 1.28 (95%CI: 1.12-1.47), total HDL particles: OR 0.71 (95%CI: 0.61-0.81)], whereas mean LDL and HDL particle sizes were not associated with CHD events[25]. Additionally, a nested case-control study within the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk cohort showed that both HDL size and HDL particle concentration were independently associated with coronary artery disease (CAD), but only HDL particle concentration was independently associated with CAD risk after adjustment for apoB and triglyceride levels [adjusted OR = 0.50 (95%CI: 0.37-0.66)][26]. These findings suggest that increasing HDL-C without increasing HDL particle number may influence the clinical outcome. The results of AIM-HIGH could be partly explained by these observations[27]. Niacin, similarly to CETP inhibitors, alters the composition of HDL, making the particle larger. However, whereas it significantly decreases the mean number of small HDL particles and increases the mean number of large HDL particles, niacin does not significantly alter the total number of NMR-determined HDL particles[28]. If these effects played significant role in the negative clinical outcomes of AIM-HIGH remains to be established.

HDL particles exhibit several anti-atherosclerotic properties, such as anti-inflammatory and anti-oxidative activities and cellular cholesterol efflux activity[29-32]. In this setting it is important that certain patients with atherosclerosis may have "dysfunctional" HDL despite normal HDL-C levels[33-35]. Furthermore, HDL-C levels are influenced by many factors, such as dietary patterns, drugs or concomitant diseases[36-42]. The heterogeneity in functionality should be taken into account when assessing the association of HDL with CVD risk[43]. HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. However, we do not know which of the HDL functions is more strongly associated with CVD in order to use it in clinical trials. Furthermore, there are several methods assessing different aspects of HDL functionality and many of them are complex and not part of routine bioassays[44]. More research is needed to assess the association of HDL functionality with CVD risk and to simplify its determination.

Additionally, HDL particles are very heterogeneous in terms of size, structure, composition and metabolism[45]. These characteristics may play divergent roles and result in different clinical outcomes[46-48]. Hence, the association of the structure of HDL particle with its functionality and metabolism should be clarified and accordingly used in the clinical setting.

The role of HDL in CVD may be clarified by the Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trial which includes 30000 patients and is currently testing whether the CETP inhibitor anacetrapib (which markedly increases HDL-C along with a lowering of LDL-C) on top of statin therapy will reduce the incidence of major coronary events (coronary mortality, myocardial infarction, and coronary revascularization) in patients with a history of CVD[49]. This phase Ⅲ study is expected to be completed by 2017. It should be mentioned that niacin and other HDL-increasing drugs, such as anacetrapib, also exhibit beneficial effects on atherogenic lipoproteins, such as LDL or lipoprotein a, so the results of on-going trials will not definitely answer the HDL hypothesis. In this setting, the results of on-going trials with drugs increasing apolipoprotein A- I [50,51] may help to clarify the role of HDL in CVD.

Overall, based on the current evidence, it is unclear if there is a causal association between HDL-C concentration and CVD. HDL particles are very heterogeneous in terms of size, structure, composition and metabolism and exhibit several anti-atherosclerotic properties. The conflicting results of epidemiological and interventional studies may be attributed to the fact that HDL functionality may be associated more strongly with CVD risk than the traditional HDL-C levels. More research is needed to assess the association of CVD risk with HDL functionality and metabolism.

## REFERENCES


1 **Gordon T**, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am J Med* 1977; **62**: 707-714 [PMID: 193398]

2 **Jafri H**, Alsheikh-Ali AA, Karas RH. Meta-analysis: statin therapy does not alter the association between low levels of high-density lipoprotein cholesterol and increased cardiovascular risk. *Ann Intern Med* 2010; **153**: 800-808 [PMID: 21173414 DOI: 10.1059/0003-4819-153-12-201012210-00006]

3 **Arsenault BJ**, Barter P, DeMicco DA, Bao W, Preston GM, LaRosa JC, Grundy SM, Deedwania P, Greten H, Wenger NK, Shepherd J, Waters DD, Kastelein JJ. Prediction of cardiovascular events in statin-treated stable coronary patients by lipid and nonlipid biomarkers. *J Am Coll Cardiol* 2011; **57**: 63-69 [PMID: 21185503 DOI: 10.1016/j.jacc.2010.06.052]

4 **Assmann G**, Schulte H, von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis* 1996; **124** Suppl: S11-S20 [PMID: 8831911 DOI: 10.1016/0021-9150(96)05852-2]

5 **Di Angelantonio E**, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009; **302**: 1993-2000 [PMID: 19903920 DOI: 10.1001/jama.2009.1619]

6 **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**: 410-418 [PMID: 10438259 DOI: 10.1056/NEJM199908053410604]

7 **Frick MH**, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V. 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**: 1237-1245 [PMID: 3313041 DOI: 10.1056/NEJM198711123172001]

8 **Robins SJ**, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, McNamara JR, Kashyap ML, Hershman JM, Wexler LF, Rubins HB. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. *JAMA* 2001; **285**: 1585-1591 [PMID: 11268266 DOI: 10.1001/jama.285.12.1585]

9 **Tonelli M**, Collins D, Robins S, Bloomfield H, Curhan GC. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int* 2004; **66**: 1123-1130 [PMID: 15327407 DOI: 10.1111/j.1523-1755.2004.00862.x]

10 **Filippatos TD**, Elisaf MS. Fenofibrate plus simvastatin (fixed-dose combination) for the treatment of dyslipidaemia. *Expert Opin Pharmacother* 2011; **12**: 1945-1958 [PMID: 21736529 DOI: 10.1517/14656566.2011.593509]

11 **Ginsberg HN**, Elam MB, Lovato LC, Crouse JR, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**: 1563-1574 [PMID: 20228404 DOI: 10.1056/NEJMoa1001282]

12 **Filippatos T**, Milionis HJ. Treatment of hyperlipidaemia with fenofibrate and related fibrates. *Expert Opin Investig Drugs* 2008; **17**: 1599-1614 [PMID: 18808320 DOI: 10.1517/13543784.17.10.1599]

13 **Voight BF**, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012; **380**: 572-580 [PMID: 22607825 DOI: 10.1016/S0140-6736(12)60312-2]

14 **Shinkai H**. Cholesteryl ester transfer-protein modulator and inhibitors and their potential for the treatment of cardiovascular diseases. *Vasc Health Risk Manag* 2012; **8**: 323-331 [PMID: 22661899 DOI: 10.2147/VHRM.S25238]

15 **Lüscher TF**, Taddei S, Kaski JC, Jukema JW, Kallend D, Münzel T, Kastelein JJ, Deanfield JE. 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**: 857-865 [PMID: 22345126 DOI: 10.1093/eurheartj/ehs019]

16 **Ballantyne CM**, Miller M, Niesor EJ, Burgess T, Kallend D, Stein EA. Effect of dalcetrapib plus pravastatin on lipoprotein metabolism and high-density lipoprotein composition and function in dyslipidemic patients: results of a phase IIb dose-ranging study. *Am Heart J* 2012; **163**: 515-521, 521. e1-e3 [PMID: 22424025 DOI: 10.1016/j.ahj.2011.11.017]

17 Available from: URL: http: //www.roche.com/med-cor-2012-05-07-e.pdf

18 **Boden WE**, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; **365**: 2255-2267 [PMID: 22085343 DOI: 10.1056/NEJMoa1107579]

19 Available from: URL: http: //clinicaltrials.gov/ct2/show/NCT00461630

20 Available from: URL: http: //www.mercknewsroom.com/press-release/research-and-development-news/results-hps2-thrive-study-tredaptive-extended-release-ni

21 **Brown BG**, Stukovsky KH, Zhao XQ. Simultaneous low-density lipoprotein-C lowering and high-density lipoprotein-C elevation for optimum cardiovascular disease prevention with various drug classes, and their combinations: a meta-analysis of 23 randomized lipid trials. *Curr Opin Lipidol* 2006; **17**: 631-636 [PMID: 17095907 DOI: 10.1097/MOL.0b013e32800ff750]

22 **Cromwell WC**, Otvos JD, Keyes MJ, Pencina MJ, Sullivan L, Vasan RS, Wilson PW, D'Agostino RB. LDL Particle Number and Risk of Future Cardiovascular Disease in the Framingham Offspring Study - Implications for LDL Management. *J Clin Lipidol* 2007; **1**: 583-592 [PMID: 19657464 DOI: 10.1016/j.jacl.2007.10.001]

23 **Parish S**, Offer A, Clarke R, Hopewell JC, Hill MR, Otvos JD, Armitage J, Collins R. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study. *Circulation* 2012; **125**: 2469-2478 [PMID: 22539783 DOI: 10.1161/CIRCULATIONAHA.111.073684]

24 **Asztalos BF**, Collins D, Horvath KV, Bloomfield HE, Robins SJ, Schaefer EJ. 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**: 77-83 [PMID: 18078862 DOI: 10.1016/j.metabol.2007.08.009]

25 **Otvos JD**, Collins D, Freedman DS, Shalaurova I, Schaefer EJ, McNamara JR, Bloomfield HE, Robins SJ. Low-density lipoprotein and high-density lipoprotein particle subclasses predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. *Circulation* 2006; **113**: 1556-1563 [PMID: 16534013 DOI: 10.1161/CIRCULATIONAHA.105.565135]

26 **El Harchaoui K**, Arsenault BJ, Franssen R, Després J-P, Hovingh GK, Stroes ESG, Otvos JD, Wareham NJ, Kastelein JJP, Khaw K-T, Boekholdt SM. High-Density Lipoprotein Particle Size and Concentration and Coronary Risk. *Annals of Internal Medicine* 2009; **150**: 84-93 [DOI: 10.1059/0003-4819-150-2-200901200-00006]

27 **Otvos JD**. The surprising AIM-HIGH results are not surprising when viewed through a particle lens. *J Clin Lipidol* 2011; **5**: 368-370 [PMID: 21981836 DOI: 10.1016/j.jacl.2011.06.012]

28 **Jafri H**, Alsheikh-Ali AA, Mooney P, Kimmelstiel CD, Karas RH, Kuvin JT. Extended-release niacin reduces LDL

particle number without changing total LDL cholesterol in patients with stable CAD. *J Clin Lipidol* 2009; **3**: 45-50 [PMID: 21291788 DOI: 10.1016/j.jacl.2008.12.003]

29 **Podrez EA**. Anti-oxidant properties of high-density lipoprotein and atherosclerosis. *Clin Exp Pharmacol Physiol* 2010; **37**: 719-725 [PMID: 20374263 DOI: 10.1111/j.1440-1681.2010.05380.x]

30 **Andrews KL**, Moore XL, Chin-Dusting JP. Anti-atherogenic effects of high-density lipoprotein on nitric oxide synthesis in the endothelium. *Clin Exp Pharmacol Physiol* 2010; **37**: 736-742 [PMID: 20374256 DOI: 10.1111/j.1440-1681.2010.05387.x]

31 **Meurs I**, Van Eck M, Van Berkel TJ. High-density lipoprotein: key molecule in cholesterol efflux and the prevention of atherosclerosis. *Curr Pharm Des* 2010; **16**: 1445-1467 [PMID: 20199377 DOI: 10.2174/138161210791051022]

32 **Tabet F**, Rye KA. High-density lipoproteins, inflammation and oxidative stress. *Clin Sci* (Lond) 2009; **116**: 87-98 [PMID: 19076062 DOI: 10.1042/CS20080106]

33 **Ansell BJ**, Navab M, Hama S, Kamranpour N, Fonarow G, Hough G, Rahmani S, Mottahedeh R, Dave R, Reddy ST, Fogelman AM. Inflammatory/antiinflammatory properties of high-density lipoprotein distinguish patients from control subjects better than high-density lipoprotein cholesterol levels and are favorably affected by simvastatin treatment. *Circulation* 2003; **108**: 2751-2756 [PMID: 14638544 DOI: 10.1161/01.CIR.0000103624.14436.4B]

34 **Vazquez E**, Sethi AA, Freeman L, Zalos G, Chaudhry H, Haser E, Aicher BO, Aponte A, Gucek M, Kato GJ, Waclawiw MA, Remaley AT, Cannon RO. High-density lipoprotein cholesterol efflux, nitration of apolipoprotein A-I, and endothelial function in obese women. *Am J Cardiol* 2012; **109**: 527-532 [PMID: 22105786 DOI: 10.1016/j.amjcard.2011.10.008]

35 **Sorrentino SA**, Besler C, Rohrer L, Meyer M, Heinrich K, Bahlmann FH, Mueller M, Horváth T, Doerries C, Heinemann M, Flemmer S, Markowski A, Manes C, Bahr MJ, Haller H, von Eckardstein A, Drexler H, Landmesser U. Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. *Circulation* 2010; **121**: 110-122 [PMID: 20026785 DOI: 10.1161/CIRCULATIONAHA.108.836346]

36 **Siri-Tarino PW**. Effects of diet on high-density lipoprotein cholesterol. *Curr Atheroscler Rep* 2011; **13**: 453-460 [PMID: 21901431 DOI: 10.1007/s11883-011-0207-y]

37 **Gazi IF**, Apostolou FA, Liberopoulos EN, Filippatos TD, Tellis CC, Elisaf MS, Tselepis AD. Leptospirosis is associated with markedly increased triglycerides and small dense low-density lipoprotein and decreased high-density lipoprotein. *Lipids* 2011; **46**: 953-960 [PMID: 21688175 DOI: 10.1007/s11745-011-3580-y]

38 **Tsimihodimos V**, Gazi I, Filippatos T, Kostapanos M, Lagos K, Kostara C, Tellis CC, Elisaf M, Tselepis AD. Plasma triglyceride levels and body mass index values are the most important determinants of prebeta-1 HDL concentrations in patients with various types of primary dyslipidemia. *Atherosclerosis* 2010; **208**: 506-511 [PMID: 19682687 DOI: 10.1016/j.atherosclerosis.2009.07.038]

39 **Lagos KG**, Filippatos TD, Tsimihodimos V, Gazi IF, Rizos C, Tselepis AD, Mikhailidis DP, Elisaf MS. Alterations in the high density lipoprotein phenotype and HDL-associated enzymes in subjects with metabolic syndrome. *Lipids* 2009; **44**: 9-16 [PMID: 18956219 DOI: 10.1007/s11745-008-3251-9]

40 **Kostapanos MS**, Milionis HJ, Filippatos TD, Christogiannis LG, Bairaktari ET, Tselepis AD, Elisaf MS. Dose-dependent effect of rosuvastatin treatment on HDL-subfraction phenotype in patients with primary hyperlipidemia. *J Cardiovasc Pharmacol Ther* 2009; **14**: 5-13 [PMID: 19246334 DOI: 10.1177/1074248408331031]

41 **Nakou ES**, Filippatos TD, Kiortsis DN, Derdemezis CS, Tselepis AD, Mikhailidis DP, Elisaf MS. The effects of ezetimibe and orlistat, alone or in combination, on high-density lipoprotein (HDL) subclasses and HDL-associated enzyme activities in overweight and obese patients with hyperlipidaemia. *Expert Opin Pharmacother* 2008; **9**: 3151-3158 [PMID: 19040336 DOI: 10.1517/14656560802548430]

42 **Filippatos TD**, Liberopoulos EN, Kostapanos M, Gazi IF, Papavasiliou EC, Kiortsis DN, Tselepis AD, Elisaf MS. The effects of orlistat and fenofibrate, alone or in combination, on high-density lipoprotein subfractions and pre-beta1-HDL levels in obese patients with metabolic syndrome. *Diabetes Obes Metab* 2008; **10**: 476-483 [PMID: 17459096 DOI: 10.1111/j.1463-1326.2007.00733.x]

43 **Besler C**, Heinrich K, Riwanto M, Lüscher TF, Landmesser U. High-density lipoprotein-mediated anti-atherosclerotic and endothelial-protective effects: a potential novel therapeutic target in cardiovascular disease. *Curr Pharm Des* 2010; **16**: 1480-1493 [PMID: 20196740 DOI: 10.2174/138161210791051013]

44 **Navab M**, Reddy ST, Van Lenten BJ, Fogelman AM. HDL and cardiovascular disease: atherogenic and atheroprotective mechanisms. *Nat Rev Cardiol* 2011; **8**: 222-232 [PMID: 21304474 DOI: 10.1038/nrcardio.2010.222]

45 **Rye KA**, Bursill CA, Lambert G, Tabet F, Barter PJ. The metabolism and anti-atherogenic properties of HDL. *J Lipid Res* 2009; **50** Suppl: S195-S200 [PMID: 19033213 DOI: 10.1194/jlr.R800034-JLR200]

46 **Camont L**, Chapman MJ, Kontush A. Biological activities of HDL subpopulations and their relevance to cardiovascular disease. *Trends Mol Med* 2011; **17**: 594-603 [PMID: 21839683 DOI: 10.1016/j.molmed.2011.05.013]

47 **Asztalos BF**, Tani M, Schaefer EJ. Metabolic and functional relevance of HDL subspecies. *Curr Opin Lipidol* 2011; **22**: 176-185 [PMID: 21537175 DOI: 10.1097/MOL.0b013e3283468061]

48 **Lund-Katz S**, Phillips MC. High density lipoprotein structure-function and role in reverse cholesterol transport. *Subcell Biochem* 2010; **51**: 183-227 [PMID: 20213545 DOI: 10.1007/978-90-481-8622-8_7]

49 Available from: URL: http: //clinicaltrials.gov/ct2/show/NCT01252953

50 **Gordon SM**, Davidson WS. Apolipoprotein A-I mimetics and high-density lipoprotein function. *Curr Opin Endocrinol Diabetes Obes* 2012; **19**: 109-114 [PMID: 22278086 DOI: 10.1097/MED.0b013e32835056d4]

51 **Getz GS,** Wool GD, Reardon CA. Biological properties of apolipoprotein a-I mimetic peptides. *Curr Atheroscler Rep* 2010; **12**: 96-104 [PMID: 20425244 DOI: 10.1007/s11883-010-0097-4]

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