Brief Report

Lipoproteins and Cardiovascular Disease: An Update on the Clinical Significance of Atherogenic Small, Dense LDL and New Therapeutical Options

Ali A. Rizvi [1,2], Anca Pantea Stoian [3] , Andrej Janez [4] and Manfredi Rizzo [2,3,5,*]

1   Department of Medicine, University of Central Florida College of Medicine, Orlando, FL 32827, USA; ali.rizvi@ucf.edu
2   Division of Endocrinology, Diabetes and Metabolism University of South Carolina School of Medicine Columbia, Columbia, SC 29209, USA
3   Department of Diabetes, Nutrition and Metabolic Diseases, Carol Davila University of Medicine, 050474 Bucharest, Romania; ancastoian@yahoo.com
4   Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Centre Ljubljana, Faculty of Medicine, University of Ljubljana, 1000 Ljubljana, Slovenia; andrej.janez@kclj.si
5   Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (Promise), University of Palermo, 90133 Palermo, Italy
*   Correspondence: manfredi.rizzo@unipa.it

Abstract: Dyslipidemia is a potent risk factor for the genesis and progression of cardiovascular disease (CVD), and both the concentration and type of low-density lipoproteins (LDL) augment this association. The small, dense LDL (sdLDL) subfraction is the subtype which is most strongly predictive of atherosclerosis and cardiovascular events. In addition to the traditionally available lipid-lowering treatment options, certain novel therapies have been shown to favorably impact sdLDL, among them the antidiabetic class of agents known as glucagon-like peptide 1 receptor agonists (GLP1-RAs). These drugs seem to alter the pathophysiologic mechanisms responsible for the formation and accumulation of atherogenic lipoprotein particles, thus potentially reducing cardiovascular outcomes. They represent a uniquely targeted therapeutic approach to reduce cardiometabolic risk and warrant further study for their beneficial nonglycemic actions.

Keywords: small; dense LDL; prevention; cardiovascular risk; therapy; diabetes; GLP1

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death globally, causing an estimated 18 million deaths each year [1], and hyperlipidemia is a major risk factor for the development and progression of atherosclerotic CVD [1]. Low-density lipoprotein (LDL)-cholesterol has been identified as a key target for management and prevention of CVD [2]. Clinical interest has focused recently on a common human atherogenic lipoprotein phenotype characterized by a moderate increase in plasma triglycerides, a decrease in high density lipoprotein (HDL) cholesterol and the prevalence of small dense LDL (sdLDL) subspecies [3].

Despite adherence to current standard treatment guidelines, many patients with atherogenic dyslipidemia display a high residual risk of atherosclerotic cardiovascular events [4]. The atherogenic process is also due to the increased number of apolipoprotein B (apoB)-containing particles characterized by elevated non-HDL-C levels. LDL cholesterol-to-apo B ratio is a potential indicator of LDL particle size and plasma atherogenicity in type 2 diabetes (T2DM) as well as a potential indicator of increased cardiovascular risk in these patients. [5]. The emerging role of the retinol-binding protein 4 (RBP4) in the metabolism of sdLDL is also being increasingly recognized, since changes in RBP4 levels are associated with those in the apolipoprotein B-containing lipoproteins during dietary

and drug treatment [6,7]. The current brief report is designed to provide an update on recent knowledge gained in this field.

2. Atherogenicity of Small, Dense LDL

Up to seven distinct LDL subspecies have been historically identified by nondenaturing gradient gel electrophoresis and ultracentrifugation based on density, size, charge, and the lipid and apoprotein content [8]. Ethnicity and genetics seem to be associated with LDL heterogeneity [9–11]. Smaller LDL particles have a greater propensity for uptake by arterial tissue than larger subspecies [8], suggesting greater transendothelial transport. Small, dense LDL also has decreased receptor mediated uptake, increased proteoglycan binding, and more susceptibility to oxidation [8,12]. The latter has been linked to a number of factors that are peculiar to sdLDL, such as altered properties of the surface lipid layer associated with reduced content of free cholesterol, diminished antioxidant content, and increased content of polyunsaturated fatty acids [12].

The predominance of sdLDL is associated with a significant increased risk of coronary artery disease. This association was demonstrated several years ago in case control studies of subjects with myocardial infarction [13–15], and confirmed in studies performed on patients with angiographically documented coronary disease [16]. Prospective studies of the relation of LDL size with the development of coronary artery disease have been carried out, including the first pioneer nested case-control analysis in the Physician's Health Study [17], the population-based Stanford Five Cities Project [18], and the Quebec Cardiovascular Study [19]. These studies clearly showed that reduced LDL size was a significant univariate predictor of coronary disease. These findings were later confirmed in many subsequent studies, and critically reviewed by the European panel of experts' discussions on LDL subclasses [20]. It seems the all the metabolic changes associated with the production of sdLDL collectively contribute to cardiometabolic risk, and increased number of atherogenic LDL particles must be present for disease risk to be evident.

3. The Clinical Significance of Small, Dense LDL

All the above-mentioned characteristics make sdLDL particles highly atherogenic and closely linked to the early stages of subclinical atherosclerosis and endothelial dysfunction, thus enhancing the risk of cardiovascular events [21]. Predominance of sdLDL particles is associated with increased risk of coronary artery disease, as demonstrated in case control studies, large epidemiological studies, clinical intervention trials, and angiographic studies [22]. Therefore, sdLDL is recognized as an emerging risk factor for CVD [23] since it is a major lipid alteration seen in patients with coronary artery disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes, the metabolic syndrome and other categories of patients at high CV risk [24–28] (Figure 1).

The evidence for sdLDL as a crucial factor for the development and progression of atherosclerosis stems from the observation that the initial discernible accumulation of lipids in the arterial (the so-called "fatty streak") consists of the accumulation of foam cells which have a high sdLDL content [29]. Because of reduced affinity to LDL receptor, sdLDL tends to circulate for a longer period in the blood stream. In addition, due to their distinctive physico-chemical composition, these LDL particles have greater arterial uptake and retention. They are able to penetrate into the vascular intima and are quickly transformed into oxidized LDL because of high susceptibility to oxidation [8,20]. An increased carotid artery intima-media thickness (IMT) is considered one of the best surrogate markers of early "subclinical" atherosclerosis, and has been shown to correlate significantly with the presence of coronary heart disease and to predict coronary events [30]. Studies have demonstrated sdLDL is independently associated with carotid IMT [31].
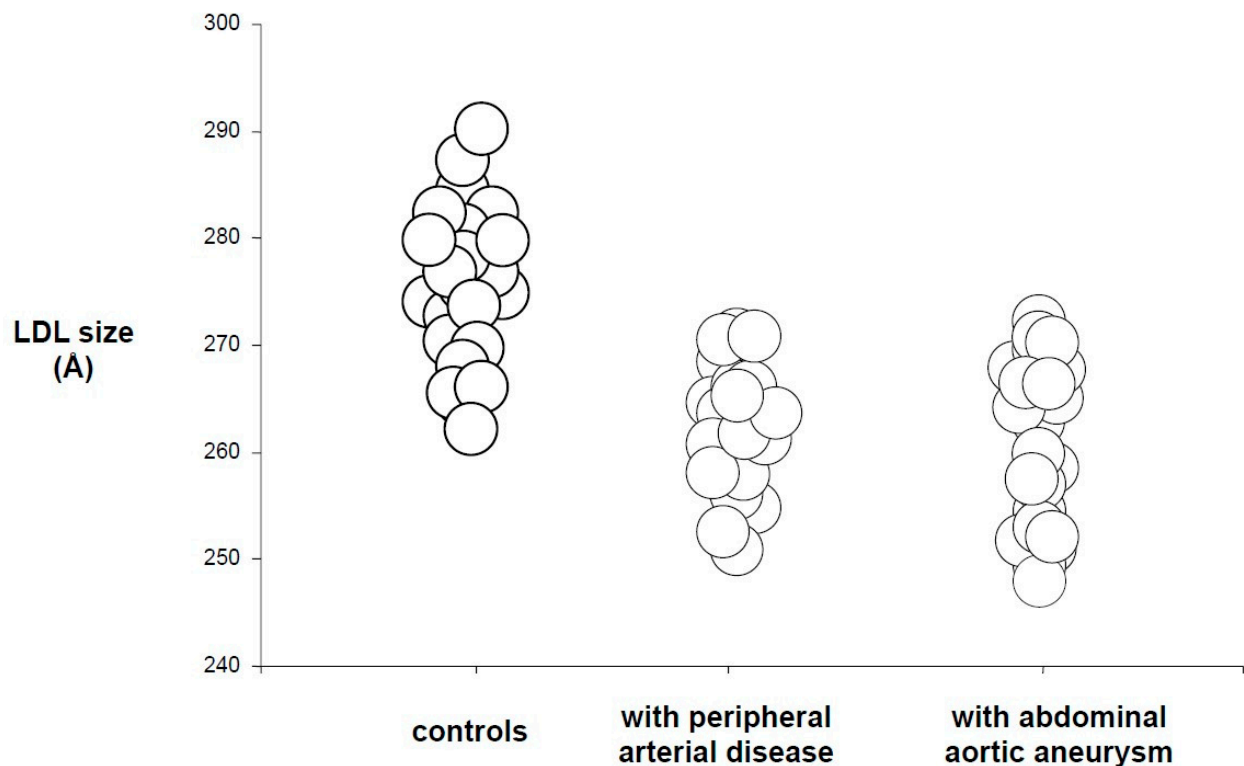
Figure 1. LDL size in patients with peripheral arterial disease, abdominal aortic aneurysm and controls (adapted from [23,24]).

4. Small, Dense LDL, Insulin Resistance and Diabetes

We are in the midst of an inexorable increase in the incidence of T2DM worldwide [32]. The atherogenic lipoprotein phenotype manifested by hypertriglyceridemia, low HDL-cholesterol concentrations and elevated levels of sdLDL particles [3] is predominant lipid abnormality in subjects with insulin resistance, T2DM and the metabolic syndrome [33]. The genesis of sdLDL is closely linked to the presence of hypertriglyceridaemia, and Berneis and Kaspar have proposed two different pathways for the formation of sdLDL, according to hepatic triglyceride availability [8]. The secretion of very-low density lipoproteins (VLDL) by the liver is followed by the action of specific enzymes, first by lipoprotein lipase, with the production of remnant particles, intermediate density lipoproteins or larger LDL, and then by hepatic lipase, with the production of LDL subspecies with smaller size and higher density [8]. Another enzyme, the cholesteryl ester transfer protein (CETP), which usually collects triglycerides from VLDL or chylomicrons in exchange of cholesteryl esters from HDL, is able to transfer triglycerides to LDL, that are further processed by hepatic lipase into sdLDL [8]. Small, dense LDL are typically formed in states of hypertriglyceridaemia [8], and treatment of the latter, including that originating secondarily from suboptimally controlled diabetes, is often appropriate management of an individual with high levels of sdLDL [20]. An association of LDL particle size with the cluster of risk factors that characterize the insulin resistance syndrome has been demonstrated [34], and there is strong evidence that the smaller denser LDL particles can be added to the group of cardiometabolic alterations described as the metabolic syndrome [35].

It follows that the risk factor profile of subjects with a predominance of sdLDL is similar to that observed in states of insulin resistance, T2DM or the metabolic syndrome. It also seems that some adipokines, such as resistin, are closely associated with LDL heterogeneity [36]. A pioneer nested case control study of 204 elderly men and women from Finland clearly demonstrated that subjects with elevated levels of sdLDL had the greatest risk for developing T2DM over a 3.5-year follow-up period, independently of age, gender, glucose tolerance and body mass index [37]. Of interest, in this study a

significant decrease in the risk of T2DM was associated with a very slight increase in LDL diameter [37], providing the basis for an effective cardiometabolic prevention by targeting atherogenic LDL particles. This link between atherogenic profile, insulin resistance and T2DM is explained by the effects of insulin and triglycerides on VLDL production and secretion, hepatic lipase activity and the resulting remodeling of triglyceride-enriched LDL particles to denser and more atherogenic LDL subspecies [20].

5. Managing Small, Dense LDL to Reduce Cardiometabolic Risk

The clinical significance of sdLDL has gained increasing interest for current-day management of cardiometabolic risk. and the question has been raised whether cardiometabolic treatments may favorably impact particle atherogenecity. Beyond the known effects of traditional lipid-lowering and oral glucose-lowering drugs [38,39], novel antidiabetic therapies with cardiovascular benefit may also reduce sdLDL concentrations [40]. The latter include three main categories of innovative drugs: (a) dipeptidyl peptidase 4 inhibitors (DPP-4i); (b) glucagon like peptide 1 receptor agonists (GLP-1RAs) and (c) sodium-glucose co-transporter-2 inhibitors (SGLT-2i). Cardiovascular safety has been shown with the use of DPP-4i, while GLP-1RAs and SGLT-2i have shown significant cardiovascular benefit. The last two classes of drugs are recommended as first-line antidiabetic therapies in high-risk individuals by current international guidelines [41].

Of interest, glucagon-like peptide 1 receptor agonists (GLP1-RAs) have shown favorable effects on lipids. They reduce lipoprotein and chylomicron production, as well as postprandial triglycerides, in patients with T2DM [42]. In addition, preclinical studies in mice models with T2DM have shown that certain GLP1-RAs, such as liraglutide, have lipid-lowering effects due to their action on hepatic liposynthesis, with a consequent reduction in triglycerides levels [43]. Both fasting and postprandial triglycerides levels seem to be modulated by liraglutide [44,45]. Of important clinical relevance is that metabolism of triglycerides in T2DM has a primary role in cardiovascular risk; indeed, longitudinal studies have shown that plasma triglycerides represent independent predictors of cardiovascular mortality in T2DM patients [46]. As discussed above, triglyceride-rich lipoproteins are the precursors of sdLDL and, therefore, of great clinical significance in patients with various cardiometabolic disorders [23]. Liraglutide has been shown to reduce such atherogenic lipoproteins [47,48].

In a randomized, double-blind, placebo-controlled, cross-over trial, the combination of liraglutide and metformin reduced both total LDL subfractions and sdLDL in patients with stable coronary artery disease and newly diagnosed T2DM [47]. These findings were confirmed in a real-world setting when the vascular benefit of liraglutide in patients with T2DM was associated with reductions in sdLDL, independent of glycemic control and body weight reduction [49]. This evidence points to a direct role of liraglutide in atherosclerosis formation and progression, supporting the postulated anti-atheroscletotic role of this agent [29]. Emerging clinical data appear to confirm the pioneering findings from preclinical studies that showed a reduction of intracoronary plaque and a decrease in myocardial infarct size with the use of liraglutide [49,50].

In summary, the direct action of GLP1-RAs on sdLDL, as exemplified by liraglutide, is most likely due to their modulation of the pathophysiological alterations responsible for the proatherogenic activity of lipoprotein subfractions [51]. Of note, it may represent one of the key mechanisms by which GLP1-RAs are able to reduce cardiovascular events and mortality [29,52].

6. Conclusions

It is becoming increasingly evident that sdLDL is both a strong predictor of coronary artery disease severity as well as a treatment target for the prevention of future CV events. It appears to confer an additional amount of risk stratification beyond that obtained from the well-recognized lipid-based parameters such as total and LDL cholesterol values. In addition, elevated sdLDL levels seem to be a consistent lipid abnormality in subjects with

insulin resistance, T2DM and the metabolic syndrome. These data reinforce the importance of both the quantity and the quality of LDL for effective management of cardiometabolic risk. Finally, the newer classes of antidiabetic agents such as GLP1-RAs exert favorable effects on sdLDL through mechanisms that are only partially understood at this point. By contrast, contradictory findings on the lowering effect of sdLDL have been shown with the use of CETP inhibitors. Evacetrapib, as monotherapy or with statins, significantly reduced the concentrations of atherogenic apoB-containing particles, including sdLDL [53], while opposite to that, anacetrapib produced significant reductions in total LDL particles and all LDL subfractions, except for increases in the smallest, most dense subspecies [54,55]. This field is ripe for further elucidation and progress in order to streamline future therapeutic options and translate them into clinical benefits.

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References

1. Cardiovascular Diseases. Available online: https://www.who.int/health-topics/cardiovascular-diseases (accessed on 18 September 2021).
2. Visseren, F.L.J.; Mach, F.; Smulders, Y.M.; Carballo, D.; Koskinas, K.C.; Bäck, M.; Benetos, A.; Biffi, A.; Boavida, J.M.; Capodanno, D.; et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur. Heart J.* **2021**, *42*, 3227–3337. [CrossRef] [PubMed]
3. Rizzo, M.; Berneis, K. Lipid Triad or Atherogenic Lipoprotein Phenotype: A Role in Cardiovascular Prevention? *J. Atheroscler. Thromb.* **2005**, *12*, 237–239. [CrossRef] [PubMed]
4. Garcia-Rios, A.; Nikolic, D.; Perez-Martinez, P.; Lopez-Miranda, J.; Rizzo, M.; Hoogeveen, R.C. LDL and HDL subfractions, dysfunctional HDL: Treatment options. *Curr. Pharm. Des.* **2014**, *20*, 6249–6255. [CrossRef]
5. Viktorinova, A.; Malickova, D.; Svitekova, K.; Choudhury, S.; Krizko, M. Low-density lipoprotein cholesterol-to-apolipoprotein B ratio as a potential indicator of LDL particle size and plasma atherogenicity in type 2 diabetes. *Diabetes Res. Clin. Pract.* **2021**, *176*, 108858. [CrossRef]
6. Christou, G.A.; Tellis, C.C.; Elisaf, M.S.; Tselepis, A.D.; Kiortsis, D.N. The changes in plasma retinol-binding protein 4 levels are associated with those of the apolipoprotein B-containing lipoproteins during dietary and drug treatment. *Angiology* **2012**, *63*, 67–75. [CrossRef]
7. Usui, S.; Ichimura, M.; Ikeda, S.; Okamoto, M. Association between serum retinol-binding protein 4 and small dense low-density lipoprotein cholesterol levels in young adult women. *Clin. Chim. Acta* **2009**, *399*, 45–48. [CrossRef]
8. Berneis, K.K.; Krauss, R.M. Metabolic origins and clinical significance of LDL heterogeneity. *J. Lipid Res.* **2002**, *43*, 1363–1379. [CrossRef] [PubMed]
9. Goedecke, J.H.; Utzschneider, K.; Kahn, S.E.; Faulenbach, M.V.; Rizzo, M.; Berneis, K.; Spinas, G.A.; Dave, J.; Levitt, N.S.; Lambert, E.; et al. Ethnic differences in serum lipoproteins and their determinants in South African women. *Metabolism* **2010**, *59*, 1341–1350. [CrossRef] [PubMed]
10. Bayram, F.; Kocer, D.; Gundogan, K.; Kaya, A.; Demir, O.; Coskun, R.; Sabuncu, T.; Karaman, A.; Cesur, M.; Rizzo, M.; et al. Prevalence of dyslipidemia and associated risk factors in Turkish adults. *J. Clin. Lipidol.* **2014**, *8*, 206–216. [CrossRef]
11. Bossé, Y.; Pérusse, L.; Vohl, M.C. Genetics of LDL particle heterogeneity: From genetic epidemiology to DNA-based variations. *J. Lipid. Res.* **2004**, *45*, 1008–1026. [CrossRef] [PubMed]
12. de Graaf, J.; Hak-Lemmers, H.L.; Hectors, M.P.; Demacker, P.N.; Hendriks, J.C.; Stalenhoef, A.F. Enhanced susceptibility to in vitro oxidation of the dense low density lipoprotein subfraction in healthy subjects. *Arterioscler. Thromb.* **1991**, *11*, 298–306. [CrossRef]
13. Campos, H.; Genest, J.J., Jr.; Blijlevens, E.; McNamara, J.R.; Jenner, J.L.; Ordovas, J.M.; Wilson, P.W.; Schaefer, E.J. Low density lipoprotein particle size and coronary artery disease. *Arterioscler. Thromb.* **1992**, *12*, 187–195. [CrossRef] [PubMed]
14. Austin, M.A.; Breslow, J.L.; Hennekens, C.H.; Buring, J.E.; Willett, W.C.; Krauss, R.M. Low-density lipoprotein subclass patterns and risk of myocardial infarction. *JAMA* **1988**, *260*, 1917–1921. [CrossRef] [PubMed]

15. Griffin, B.A.; Freeman, D.J.; Tait, G.W.; Thomson, J.; Caslake, M.J.; Packard, C.J.; Shepherd, J. Role of plasma triglyceride in the regulation of plasma low density lipoprotein (LDL) subfractions: Relative contribution of small, dense LDL to coronary heart disease risk. *Atherosclerosis* **1994**, *106*, 241–253. [CrossRef]

16. Coresh, J.; Kwiterovich, P.J.; Smith, H.; Bachorik, P. Association of plasma trigglyceride concentration and LDL diameter density, and chemical composition with premature coronary artery disease in men and woman. *J. Lipid. Res.* **1993**, *34*, 1687–1697. [CrossRef]

17. Stampfer, M.J.; Krauss, R.M.; Ma, J.; Blanche, P.J.; Holl, L.G.; Sacks, F.M.; Hennekens, C.H. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA* **1996**, *276*, 882–888. [CrossRef] [PubMed]

18. Gardner, C.D.; Fortmann, S.P.; Krauss, R.M. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA* **1996**, *276*, 875–881. [CrossRef] [PubMed]

19. Lamarche, B.; St-Pierre, A.C.; Ruel, I.L.; Cantin, B.; Dagenais, G.R.; Després, J.P. A prospective, population-based study of low density lipoprotein particle size as a risk factor for ischemic heart disease in men. *Can. J. Cardiol.* **2001**, *17*, 859–865.

20. Mikhailidis, D.P.; Elisaf, M.; Rizzo, M.; Berneis, K.; Griffin, B.; Zambon, A.; Athyros, V.; de Graaf, J.; März, W.; Parhofer, K.G.; et al. "European panel on low density lipoprotein (LDL) subclasses": A statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses. *Curr. Vasc. Pharmacol.* **2011**, *9*, 533–571. [CrossRef] [PubMed]

21. Corrado, E.; Rizzo, M.; Coppola, G.; Muratori, I.; Carella, M.; Novo, S. Endothelial dysfunction and carotid lesions are strong predictors of clinical events in patients with early stages of atherosclerosis: A 24-month follow-up study. *Coron. Artery Dis.* **2008**, *19*, 139–144. [CrossRef]

22. Chaudhary, R.; Mathew, D.; Bliden, K.; Tantry, U.S.; Sharma, T.; Gesheff, M.G.; Franzese, C.; Pandya, S.; Toth, P.P.; Gurbel, P.A. Low-density lipoprotein 4: A novel predictor of coronary artery disease severity. *Curr. Med. Res. Opin.* **2017**, *33*, 1979–1984. [CrossRef]

23. Rizzo, M.; Berneis, K. Who needs to care about small, dense low-density lipoproteins? *Int. J. Clin. Pract.* **2007**, *61*, 1949–1956. [CrossRef] [PubMed]

24. Superko, H.R. Beyond LDL Cholesterol Reduction. *Circulation* **1996**, *94*, 2351–2354. [CrossRef] [PubMed]

25. Rizzo, M.; Pernice, V.; Frasheri, A.; Berneis, K. Atherogenic lipoprotein phenotype and LDL size and subclasses in patients with peripheral arterial disease. *Atherosclerosis* **2008**, *197*, 237–241. [CrossRef]

26. Rizzo, M.; Krayenbühl, P.A.; Pernice, V.; Frasheri, A.; Battista Rini, G.; Berneis, K. LDL size and subclasses in patients with abdominal aortic aneurysm. *Int. J. Cardiol.* **2009**, *134*, 406–408. [CrossRef] [PubMed]

27. Rizzo, M.; Berneis, K.; Altinova, A.E.; Toruner, F.B.; Akturk, M.; Ayvaz, G.; Rini, G.B.; Spinas, G.A.; Arslan, M. Atherogenic lipoprotein phenotype and LDL size and subclasses in women with gestational diabetes. *Diabet Med.* **2008**, *25*, 1406–1411. [CrossRef]

28. Rizzo, M.; Spinas, G.A.; Cesur, M.; Ozbalkan, Z.; Rini, G.B.; Berneis, K. Atherogenic lipoprotein phenotype and LDL size and subclasses in drug-naïve patients with early rheumatoid arthritis. *Atherosclerosis* **2009**, *207*, 502–506. [CrossRef]

29. Rizzo, M.; Nikolic, D.; Patti, A.M.; Mannina, C.; Montalto, G.; McAdams, B.S.; Rizvi, A.A.; Cosentino, F. GLP-1 receptor agonists and reduction of cardiometabolic risk: Potential underlying mechanisms. *Biochim. Biophys. Acta Mol. Basis Dis.* **2018**, *1864*, 2814–2821. [CrossRef]

30. Salonen, J.T.; Salonen, R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation* **1993**, *87*, II56–II65.

31. Skoglund-Andersson, C.; Tang, R.; Bond, M.G.; de Faire, U.; Hamsten, A.; Karpe, F. LDL Particle Size Distribution Is Associated With Carotid Intima-Media Thickness in Healthy 50-Year-Old Men. *Arter. Thromb. Vasc. Biol.* **1999**, *19*, 2422–2430. [CrossRef]

32. Diabetes. Available online: https://www.who.int/health-topics/diabetes (accessed on 18 September 2021).

33. Krauss, R.M. Lipids and Lipoproteins in Patients with Type 2 Diabetes. *Diabetes Care* **2004**, *27*, 1496–1504. [CrossRef]

34. Friedlander, Y.; Kidron, M.; Caslake, M.; Lamb, T.; McConnell, M.; Bar-On, H. Low density lipoprotein particle size and risk factors of insulin resistance syndrome. *Atherosclerosis* **2000**, *148*, 141–149. [CrossRef]

35. Reaven, G.M.; Chen, Y.-D.I. Role of insulin in regulation of lipoprotein metabolism in diabetes. *Diabetes Metab. Rev.* **1988**, *4*, 639–652. [CrossRef]

36. Abate, N.; Sallam, H.; Rizzo, M.; Nikolic, D.; Obradovic, M.; Bjelogrlic, P.; Isenovic, E. Resistin: An Inflammatory Cytokine. Role in Cardiovascular Diseases, Diabetes and the Metabolic Syndrome. *Curr. Pharm. Des.* **2014**, *20*, 4961–4969. [CrossRef]

37. Austin, M.A.; Mykkänen, L.; Kuusisto, J.; Edwards, K.L.; Nelson, C.; Haffner, S.M.; Pyörälä, K.; Laakso, M. Prospective Study of Small LDLs as a Risk Factor for Non–Insulin Dependent Diabetes Mellitus in Elderly Men and Women. *Circulation* **1995**, *92*, 1770–1778. [CrossRef]

38. Chapman, M.J.; Orsoni, A.; Tan, R.; Mellett, N.A.; Nguyen, A.; Robillard, P.; Giral, P.; Thérond, P.; Meikle, P.J. LDL subclass lipidomics in atherogenic dyslipidemia: Effect of statin therapy on bioactive lipids and dense LDL. *J. Lipid Res.* **2020**, *61*, 911–932. [CrossRef] [PubMed]

39. Berneis, K.; Rizzo, M.; Stettler, C.; Chappuis, B.; Braun, M.; Diem, P.; Christ, E.R. Comparative effects of rosiglitazone and pioglitazone on fasting and postprandial low-density lipoprotein size and subclasses in patients with Type 2 diabetes. *Expert Opin. Pharmacother.* **2008**, *9*, 343–349. [CrossRef]

40. Brunell, S.; Toth, P.; Ramirez, G.; Cobble, M.; Chilton, R.; Chiquette, E. Treatment with exenatide once weekly or twice daily for 30 weeks is associated with changes in several cardiovascular risk markers. *Vasc. Health Risk Manag.* **2012**, *8*, 621–629. [CrossRef]

41. Maranta, F.; Cianfanelli, L.; Rizzo, M.; Cianflone, D. Filling the gap between Guidelines and Real World in the cardiovascular approach to the diabetic patients: The need for a call to action. *Int. J. Cardiol.* **2021**, *329*, 205–207. [CrossRef] [PubMed]

42. Taskinen, M.; Björnson, E.; Matikainen, N.; Söderlund, S.; Pietiläinen, K.H.; Ainola, M.; Hakkarainen, A.; Lundbom, N.; Fuchs, J.; Thorsell, A.; et al. Effects of liraglutide on the metabolism of triglyceride-rich lipoproteins in type 2 diabetes. *Diabetes Obes. Metab.* **2021**, *23*, 1191–1201. [CrossRef] [PubMed]

43. Cummings, B.P.; Stanhope, K.L.; Graham, J.; Baskin, D.G.; Griffen, S.C.; Nilsson, C.; Sams, A.; Knudsen, L.B.; Raun, K.; Havel, P.J. Chronic Administration of the Glucagon-Like Peptide-1 Analog, Liraglutide, Delays the Onset of Diabetes and Lowers Triglycerides in UCD-T2DM Rats. *Diabetes* **2010**, *59*, 2653–2661. [CrossRef] [PubMed]

44. Hermansen, K.; Bækdal, T.A.; Düring, M.; Pietraszek, A.; Mortensen, L.S.; Jørgensen, H.; Flint, A. Li-raglutide suppresses postprandial triglyceride and apolipoprotein B48 elevations after a fat-rich meal in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled, cross-over trial. *Diabetes Obes. Metab.* **2013**, *15*, 1040–1048. [CrossRef]

45. Matikainen, N.; Söderlund, S.; Björnson, E.; Pietiläinen, K.; Hakkarainen, A.; Lundbom, N.; Taskinen, M.-R.; Borén, J. Liraglutide treatment improves postprandial lipid metabolism and cardiometabolic risk factors in humans with adequately controlled type 2 diabetes: A single-centre randomized controlled study. *Diabetes Obes. Metab.* **2018**, *21*, 84–94. [CrossRef] [PubMed]

46. Miselli, M.-A.; Nora, E.D.; Passaro, A.; Tomasi, F.; Zuliani, G. Plasma triglycerides predict ten-years all-cause mortality in outpatients with type 2 diabetes mellitus: A longitudinal observational study. *Cardiovasc. Diabetol.* **2014**, *13*, 135. [CrossRef]

47. Anholm, C.; Kumarathurai, P.; Haugaard, S.B.; Pedersen, L.R.; Samkani, A.; Walzem, R.L.; Nielsen, O.W.; Kristiansen, O.P.; Fenger, M.; Madsbad, S.; et al. Liraglutide in combination with metformin may improve the atherogenic lipid profile and decrease C-reactive protein level in statin treated obese patients with coronary artery disease and newly diagnosed type 2 diabetes: A randomized trial. *Atherosclerosis* **2019**, *288*, 60–66. [CrossRef]

48. Nikolic, D.; Giglio, R.V.; Rizvi, A.A.; Patti, A.M.; Montalto, G.; Maranta, F.; Cianflone, D.; Stoian, A.P.; Rizzo, M. Liraglutide Reduces Carotid Intima-Media Thickness by Reducing Small Dense Low-Density Lipoproteins in a Real-World Setting of Patients with Type 2 Diabetes: A Novel Anti-Atherogenic Effect. *Diabetes Ther.* **2021**, *12*, 261–274. [CrossRef]

49. Noyan-Ashraf, M.H.; Momen, M.A.; Ban, K.; Sadi, A.-M.; Zhou, Y.-Q.; Riazi, A.M.; Baggio, L.L.; Henkelman, R.M.; Husain, M.; Drucker, D.J. GLP-1R Agonist Liraglutide Activates Cytoprotective Pathways and Improves Outcomes After Experimental Myocardial Infarction in Mice. *Diabetes* **2009**, *58*, 975–983. [CrossRef]

50. Gaspari, T.; Welungoda, I.; Widdop, R.E.; Simpson, R.W.; Dear, A.E. The GLP-1 receptor agonist li-raglutide inhibits progression of vascular disease via effects on atherogenesis, plaque stability and endothelial function in an ApoE(-/-) mouse model. *Diabetes Vasc. Dis. Res.* **2013**, *10*, 353–360. [CrossRef]

51. Rizzo, M.; Rizvi, A.A.; Patti, A.M.; Nikolic, D.; Giglio, R.V.; Castellino, G.; Li Volti, G.; Caprio, M.; Montalto, G.; Provenzano, V.; et al. Liraglutide improves metabolic parameters and carotid intima-media thickness in diabetic patients with the metabolic syndrome: An 18-month prospective study. *Cardiovasc. Diabetol.* **2016**, *15*, 162. [CrossRef]

52. Nauck, M.A.; Quast, D.R.; Wefers, J.; Meier, J.J. GLP-1 receptor agonists in the treatment of type 2 diabetes—State-of-the-art. *Mol. Metab.* **2021**, *46*, 101102. [CrossRef] [PubMed]

53. Nicholls, S.J.; Ruotolo, G.; Brewer, H.B.; Wang, M.D.; Liu, L.; Willey, M.B.; Deeg, M.A.; Krueger, K.A.; Nissen, S.E. Evace-trapib alone or in combination with statins lowers lipoprotein(a) and total and small LDL particle concentrations in mildly hypercholesterolemic patients. *J. Clin. Lipidol.* **2016**, *10*, 519–527.e4. [CrossRef] [PubMed]

54. Krauss, R.M.; Pinto, C.A.; Liu, Y.; Johnson-Levonas, A.O.; Dansky, H.M. Changes in LDL particle concentrations after treatment with the cholesteryl ester transfer protein inhibitor anacetrapib alone or in combination with atorvastatin. *J. Clin. Lipidol.* **2015**, *9*, 93–102. [CrossRef] [PubMed]

55. Krauss, R.M.; Wojnooski, K.; Orr, J.; Geaney, J.C.; Pinto, C.A.; Liu, Y.; Wagner, J.A.; Luk, J.M.; Johnson-Levonas, A.O.; Anderson, M.S.; et al. Changes in lipoprotein subfraction concentration and composition in healthy individuals treated with the CETP inhibitor anacetrapib. *J. Lipid Res.* **2012**, *53*, 540–547. [CrossRef] [PubMed]