Hyperalphalipoproteinemia and HDL

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Hyperalphalipoproteinemia (HALP) is a lipid disorder characterized by elevated plasma high-density lipoprotein cholesterol (HDL-C) levels above the 90th percentile of the distribution of HDL-C values in the general population. Secondary non-genetic factors such as drugs, pregnancy, alcohol intake, and liver diseases might induce HDL increases. Primary forms of HALP are caused by mutations in the genes coding for cholesteryl ester transfer protein (CETP), hepatic lipase (HL), apolipoprotein C-III (apo C-III), scavenger receptor class B type I (SR-BI) and endothelial lipase (EL).

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1. Introduction

The pathophysiology of other forms of HALP is not well characterized, and it is still unknown if the increased production or reduced catabolism of HDL are the cause of this lipid disorder [1]. Epidemiological studies have demonstrated a strong inverse relationship between low HDL-C levels and risk for developing atherosclerotic cardiovascular disease (ASCVD) [2][3]. Low plasma HDL-C levels strongly correlate with high CV risk, but genetically determined low HDL-C levels are not associated with an increased risk for ASCVD, suggesting that low HDL-C levels per se are not a cause of cardiovascular diseases [4][5]. Epidemiological studies have shown contradictory results on the relationship between high HDL levels and CV risk in subjects with primary HALP [6][7].

2. HDLs Physiology

HDLs are characterized by a heterogenous sub-population of lipoprotein particles, which undergo remodeling and transformation processes mediated by several plasma enzymes and transcription factors [8]. HDL particles are involved in the so-called “reverse cholesterol transport (RCT)”, a pivotal pathway involved in the return of excess cholesterol from peripheral tissues to the liver for excretion in the bile and eventually in the feces. Besides their major role in promoting cell cholesterol efflux and reverse cholesterol transport, HDLs may exert atheroprotective activity by preventing endothelial dysfunction [9], a key step in the development of atherosclerosis. Besides the antioxidative properties of apoA-I, the HDL accessory protein—paraoxonase 1 (PON1)—may exert an important role in determining the antioxidative capacity of HDL particles, and is implicated in reverse cholesterol transport and atheroprotective effects [10].

Although in this review we will mainly focus on the primary familial causes of HALP, it is worth mentioning that several conditions are known to be associated with elevated HDL-C levels. In users of combination oral

contraceptives, the rising effect of estrogen is partly counter-regulated by the presence of added progestin such levonorgestrel, which exerts an androgenic effect by decreasing the Apo-AI synthesis and increasing LPL activity [11]. The liver is one of the main sites for HDL catabolism [12], and in some chronic conditions, such as biliary cirrhosis, HDLs may accumulate in the bloodstream because of a defect in their catabolism giving rise to secondary HALP [12]. Several classes of commonly used drugs in clinical practice exert effects both on HDL levels and functions through various mechanisms.

3. Primary Causes of HALP

According to Japanese epidemiological data, 27.6% of Japanese subjects with HDL cholesterol 60 mg/dl, and 31.4–32.5% of those with HDL-cholesterol > 80 mg/dl are carriers of CETP gene mutations [13]. Moreover, in CETP-deficient subjects, HDL size correlates inversely with the CETP mass and activity, and HDLs are larger not only in normal subjects but also in patients with other forms of HALP [14]. On the other hand, males with considerably elevated HDL-C levels (>1.6 mmol/L), regardless of the CETP gene status, had a low frequency of cardiovascular disease (coronary heart disease)

Polymorphisms in the HL gene promoter act as modifiers of HDL-C levels, but the moderate increase in HDL induced by these polymorphisms cannot explain the high HDL levels observed in primary HALP.APO-CIII.Apolipoprotein CIII (Apo-CIII) is a small apolipoprotein synthesized mainly in the liver and regulates plasma TG homeostasis by inhibiting lipoprotein lipase (LPL) activity [15]. Apo-CIII plays an important role in HDL metabolism as well as in TG physiology. Loss of function of APO-CIII gene mutation carriers exhibits 39% lower plasma TG levels, 22% higher plasma HDL-C levels, 16% lower plasma LDL-C levels, and reduction in CVD risk [16][17]. Two novel loss-of-function mutations which affect the splice site of theAPOC3gene (c.13-2A > G and c.55+1G > A) have been identified and associated with plasma HDL-C levels above the 95th percentile and an atheroprotective lipid profile [18].

The scavenger receptor class B type I (SR-BI), encoded by the SCARB1 gene, is primarily expressed in the steroidogenic tissues and in the liver, where it acts as an important receptor for HDLs and controls selective uptake of the cholesterol esters by HDL [19]. SR-BI is involved in the bi-directional transfer of esterified cholesterol between cells and HDL [20]. SR-BI knock-out mice exhibited a twofold increase in HDL-C plasma levels, accelerated atherosclerosis, impairment of liver cholesterol transfer [21], and adrenal glucocorticoid-mediated stress response [22]. SCARB1 rare point mutations associated with a decreased SR-BI protein expression and function have been identified in subjects with high plasma HDL-C levels in humans [23][24][25].

Endothelial lipase (EL) is mostly involved in HDL phospholipid hydrolysis [26] through a mechanism independent from the dissociation of lipid-free/lipid-poor apoA-I [27]. EL is coded by the LIPG gene and it is expressed mainly in endothelial cells [26], but also in other several tissues including the liver, lungs, placenta, thyroid, kidney, and macrophages [26]. EL, together with hepatic lipase (HL), exerts a negative regulation in HDL metabolism and modulates the cholesterol efflux capacity (CEC) of serum and isolated HDL [28][29]. Carriers of loss-of-function

variants of EL have a reduced lipolytic activity [30] and a lipid phenotype characterized by an increase in HDL-C plasma levels with large HDL particles [27][28][31].

TaqIB is a silent base change affecting a nucleotide at position 277 on the first intron of the CETP gene and represents a common polymorphism associated to increased HDL cholesterol plasma levels and to a slight reduction in cardiovascular risk [32]. Another haplotype analysis demonstrated a correlation between the -2505 CETP variant and HDL metabolism and CV risk [33]. Beside the known candidate genes of primary HALP, other genes (such APOA1, LCAT, APOA4, APOE, PLTP and PON1) involved in HDL metabolism have been reported to modulate HDL-C plasma levels [34][35][36]. Although several genes have been discovered to be associated with HDL metabolism, to date, only a small percentage of this genetic variability can be explained and their effects on HDL phenotypes should be further investigated and probably related to environmental factors [37][38].

However, recent findings provided by Mendelian randomization studies support the hypothesis that some genetic mechanisms that raise plasma HDL cholesterol do not seem to lower risk of myocardial infarction [4][5]. These data may question the concept that HALP and/or the pharmacological raising of plasma HDL cholesterol will translate into atheroprotection and a reduction in risk of myocardial infarction [39]. For example, in statin clinical trials, ApoAI was inversely related to low CV risk, whereas HDL-C was not [40]. In summary, low HDL-C remains a significant factor for increased disease risk, whereas high HDL-C levels are not associated with cardioprotection, and this should prompt a re-evaluation of high HDL-C cutoffs in CVD risk calculations [41][42].

The concept that targeting HDL-C may be advantageous in terms of CV risk reduction has been taken into consideration for decades as an important treatment strategy. Niacin is a potent HDL-C-raising drug, seemingly an attractive approach to reduce cardiac events in patients with or at risk of atherosclerotic cardiovascular disease [43]. However, over the years, several clinical trials have failed to demonstrate benefits in terms of cardiovascular endpoints Fibrates have been used over the years to increase HDL-C, and their effects were evaluated in several clinical trials (the most representative are the FIELD—Fenofibrate Intervention and Event Lowering in Diabetes; ACCORD—Action to Control Cardiovascular Risk in Diabetes; VA-HIT—Veterans Administration HDL Intervention Trial, and the HHS—Helsinki Heart Study), although have failed in showing a significant CV risk decrease despite an HDL-C increase [44].

4. CETP Inhibitors

Although torcetrapib was effective in raising HDL-C and ApoA-I and reducing LDL-C with and without an added statin [45], phase 3 trials failed to demonstrate effects on atherosclerosis burden and cardiovascular deaths (RADIANCE and ILLUMINATE trials) [46][47]. Moreover, because of an excess of overall mortality and cardiovascular events, the development of torcetrapib was halted [45]. The excess deaths and adverse cardiovascular events in patients taking torcetrapib have been attributed to off-target effects independent from

CETP inhibition [45][48]. Moreover, meta-analysis based on clinical trials carried out with niacin, statins, fibrates and CETP inhibitors have exhibited no decreases in CV mortality [49][50].

References

1. Zhou, H.; Gong, Y.; Wu, Q.; Ye, X.; Yu, B.; Lu, C.; Jiang, W.; Ye, J.; Fu, Z. Rare Diseases Related with Lipoprotein Metabolism. Adv. Exp. Med. Biol. 2020, 1276, 171–188.
2. Gordon, D.J.; Probstfield, J.L.; Garrison, R.J.; Neaton, J.D.; Castelli, W.P.; Knoke, J.D.; Jacobs, D.R.; Bangdiwala, S.; Tyroler, H.A. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989, 79, 8–15.
3. Franceschini, G. Epidemiologic evidence for high-density lipoprotein cholesterol as a risk factor for coronary artery disease. Am. J. Cardiol. 2001, 88, 9–13.
4. Voight, B.F.; Peloso, G.M.; Orho-Melander, M.; Frikke-Schmidt, R.; Barbalic, M.; Jensen, M.K.; Hindy, G.; Hólm, H.; Ding, E.L.; Johnson, T.; et al. Plasma HDL cholesterol and risk of myocardial infarction: A mendelian randomisation study. Lancet 2012, 380, 572–580.
5. Haase, C.L.; Tybjærg-Hansen, A.; Qayyum, A.A.; Schou, J.; Nordestgaard, B.G.; Frikke-Schmidt, R. LCAT, HDL Cholesterol and Ischemic Cardiovascular Disease: A Mendelian Randomization Study of HDL Cholesterol in 54,500 Individuals. J. Clin. Endocrinol. Metab. 2012, 97, E248–E256.
6. Zhong, S.; Sharp, D.S.; Grove, J.S.; Bruce, C.; Yano, K.; Curb, J.D.; Tall, A.R. Increased coronary heart disease in Japanese-American men with mutation in the cholesteryl ester transfer protein gene despite increased HDL levels. J. Clin. Investig. 1996, 97, 2917–2923.
7. Curb, J.D.; Abbott, R.D.; Rodriguez, B.L.; Masaki, K.; Chen, R.; Sharp, D.S.; Tall, A.R. A prospective study of HDL-C and cholesteryl ester transfer protein gene mutations and the risk of coronary heart disease in the elderly. J. Lipid Res. 2004, 45, 948–953.
8. Kajani, S.; Curley, S.; McGillicuddy, F.C. Unravelling HDL—Looking beyond the Cholesterol Surface to the Quality Within. Int. J. Mol. Sci. 2018, 19, 1971.
9. Calabresi, L.; Gomaraschi, M.; Franceschini, G. Endothelial Protection by High-Density Lipoproteins. Arter. Thromb. Vasc. Biol. 2003, 23, 1724–1731.
10. Cervellati, C.; Vigna, G.B.; Trentini, A.; Sanz, J.M.; Zimetti, F.; Dalla Nora, E.; Morieri, M.L.; Zuliani, G.; Passaro, A. Paraoxonase-1 activities in individuals with different HDL circulating levels: Implication in reverse cholesterol transport and early vascular damage. Atherosclerosis 2019, 285, 64–70.
11. Godsland, I.F. Biology: Risk factor modification by OCs and HRT lipids and lipoproteins. Maturitas 2004, 47, 299–303.

12. Titov, V.N.; Tvorogova, M.G.; Kantardzhian, I.G.; Alamdarova, I.A.; Negovskaia, A.V. High density lipoprotein cholesterol in sec-ondary hyperlipoproteinemias. Lab Delo. 1983, 12, 11–17.
13. Inazu, A.; Jiang, X.C.; Haraki, T.; Yagi, K.; Kamon, N.; Koizumi, J.; Mabuchi, H.; Takeda, R.; Takata, K.; Moriyama, Y. Genetic cholesteryl ester transfer protein deficiency caused by two prevalent mutations as a major determinant of increased levels of high density lipoprotein cholesterol. J. Clin. Investig. 1994, 94, 1872–1882.
14. Arai, T.; Tsukada, T.; Murase, T.; Matsumoto, K. Particle size analysis of high density lipoproteins in patients with genetic cholesteryl ester transfer protein deficiency. Clin. Chim. Acta 2000, 301, 103–117.
15. Gangabadage, C.S.; Zdunek, J.; Tessari, M.; Nilsson, S.; Olivecrona, G.; Wijmenga, S.S. Structure and Dynamics of Human Apolipoprotein CIII. J. Biol. Chem. 2008, 283, 17416–17427.
16. Pollin, T.I.; Damcott, C.M.; Shen, H.; Ott, S.H.; Shelton, J.; Horenstein, R.B.; Post, W.; McLenithan, J.C.; Bielak, L.F.; Peyser, P.A.; et al. A Null Mutation in Human APOC3 Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection. Science 2008, 322, 1702–1705.
17. Crosby, J.H.; Peloso, G.M.; Auer, P.L.; Crosslin, D.R.; Stitziel, N.; Lange, L.A.; Lu, Y.; Tang, Z.Z.; Zhang, H.; Hindy, G.; et al. Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease. N. Engl. J. Med. 2014, 371, 22–31.
18. Bochem, A.; Van Capelleveen, J.; Dallinga-Thie, G.; Schimmel, A.; Motazacker, M.; Tietjen, I.; Singaraja, R.; Hayden, M.; Kastelein, J.; Stroes, E.; et al. Two novel mutations in apolipoprotein C3 underlie atheroprotective lipid profiles in families. Clin. Genet. 2013, 85, 433–440.
19. Yu, L.; Dai, Y.; Mineo, C. Novel Functions of Endothelial Scavenger Receptor Class B Type I. Curr. Atheroscler. Rep. 2021, 23, 1–9.
20. Shen, W.-J.; Azhar, S.; Kraemer, F.B. SR-B1: A Unique Multifunctional Receptor for Cholesterol Influx and Efflux. Annu. Rev. Physiol. 2018, 80, 95–116.
21. Hildebrand, R.B.; Lammers, B.; Meurs, I.; Korporaal, S.J.; De Haan, W.; Zhao, Y.; Kruijt, J.K.; Praticò, D.; Schimmel, A.W.; Holleboom, A.G.; et al. Restoration of High-Density Lipoprotein Levels by Cholesteryl Ester Transfer Protein Expression in Scavenger Receptor Class B Type I (SR-BI) Knockout Mice Does Not Normalize Pathologies Associated with SR-BI Deficiency. Arter. Thromb. Vasc. Biol. 2010, 30, 1439–1445.
22. Hoekstra, M.; Meurs, I.; Koenders, M.; Out, R.; Hildebrand, R.B.; Kruijt, J.K.; Van Eck, M.; Van Berkel, T.J.C. Absence of HDL cholesteryl ester uptake in mice via SR-BI impairs an adequate adrenal glucocorticoid-mediated stress response to fasting. J. Lipid Res. 2008, 49, 738–745.
23. Chadwick, A.C.; Sahoo, D. Functional Characterization of Newly-Discovered Mutations in Human SR-BI. PLoS ONE 2012, 7, e45660.

24. Brunham, L.R.; Tietjen, I.; Bochem, A.E.; Singaraja, R.R.; Franchini, P.L.; Radomski, C.; Mattice, M.; Legendre, A.; Hovingh, G.K.; Kastelein, J.J.P.; et al. Novel mutations in scavenger receptor BI associated with high HDL cholesterol in humans. Clin. Genet. 2011, 79, 575–581.
25. Vergeer, M.; Korporaal, S.J.; Franssen, R.; Meurs, I.; Out, R.; Hovingh, G.K.; Hoekstra, M.; Sierts, J.A.; Dallinga-Thie, G.M.; Motazacker, M.M.; et al. Genetic Variant of the Scavenger Receptor BI in Humans. N. Engl. J. Med. 2011, 364, 136–145.
26. Schilcher, I.; Ledinski, G.; Radulović, S.; Hallström, S.; Eichmann, T.; Madl, T.; Zhang, F.; Leitinger, G.; Kolb-Lenz, D.; Darnhofer, B.; et al. Endothelial lipase increases antioxidative capacity of high-density lipoprotein. Biochim. Biophys. Acta BBA Mol. Cell Biol. Lipids 2019, 1864, 1363–1374.
27. Jahangiri, A.; Rader, D.J.; Marchadier, D.; Curtiss, L.K.; Bonnet, D.J.; Rye, K.-A. Evidence that endothelial lipase remodels high density lipoproteins without mediating the dissociation of apolipoprotein A-I. J. Lipid Res. 2005, 46, 896–903.
28. Schilcher, I.; Kern, S.; Hrzenjak, A.; Eichmann, T.O.; Stojakovic, T.; Scharnagl, H.; Duta-Mare, M.; Kratky, D.; Marsche, G.; Frank, S. Impact of Endothelial Lipase on Cholesterol Efflux Capacity of Serum and High-density Lipoprotein. Sci. Rep. 2017, 7, 12485.
29. Escolà-Gil, J.C.; Chen, X.; Julve, J.; Quesada, H.; Santos, D.; Metso, J.; Tous, M.; Jauhiainen, M.; Blanco-Vaca, F. Hepatic lipase- and endothelial lipase-deficiency in mice promotes macrophage-to-feces RCT and HDL antioxidant properties. Biochim. et Biophys. Acta BBA Mol. Cell Biol. Lipids 2013, 1831, 691–697.
30. Edmondson, A.C.; Brown, R.J.; Kathiresan, S.; Cupples, L.A.; Demissie, S.; Manning, A.K.; Jensen, M.K.; Rimm, E.B.; Wang, J.; Rodrigues, A.; et al. Loss-of-function variants in endothelial lipase are a cause of elevated HDL cholesterol in humans. J. Clin. Investig. 2009, 119, 1042–1050.
31. Khetarpal, S.A.; Edmondson, A.C.; Raghavan, A.; Neeli, H.; Jin, W.; Badellino, K.O.; Demissie, S.; Manning, A.K.; DerOhannessian, S.L.; Wolfe, M.L.; et al. Mining the LIPG Allelic Spectrum Reveals the Contribution of Rare and Common Regulatory Variants to HDL Cholesterol. PLoS Genet. 2011, 7, e1002393.
32. Wu, Z.; Lou, Y.; Qiu, X.; Liu, Y.; Lu, L.; Chen, Q.; Jin, W. Association of cholesteryl ester transfer protein (CETP) gene polymorphism, high density lipoprotein cholesterol and risk of coronary artery disease: A meta-analysis using a Mendelian randomization approach. BMC Med. Genet. 2014, 15, 1–17.
33. Lu, H.; Inazu, A.; Moriyama, Y.; Higashikata, T.; Kawashiri, M.-A.; Yu, W.; Huang, Z.; Okamura, T.; Mabuchi, H. Haplotype analyses of cholesteryl ester transfer protein gene promoter: A clue to an unsolved mystery of TaqIB polymorphism. J. Mol. Med. 2003, 81, 246–255.

34. Boes, E.; Coassin, S.; Kollerits, B.; Heid, I.M.; Kronenberg, F. Genetic-epidemiological evidence on genes associated with HDL cholesterol levels: A systematic in-depth review. Exp. Gerontol. 2009, 44, 136–160.
35. Weissglas-Volkov, D.; Pajukanta, P. Genetic causes of high and low serum HDL-cholesterol. J. Lipid Res. 2010, 51, 2032–2057.
36. Kuwano, T.; Bi, X.; Cipollari, E.; Yasuda, T.; Lagor, W.R.; Szapary, H.J.; Tohyama, J.; Millar, J.S.; Billheimer, J.T.; Lyssenko, N.N.; et al. Overexpression and deletion of phospholipid transfer protein reduce HDL mass and cholesterol efflux capacity but not macrophage reverse cholesterol transport. J. Lipid Res. 2017, 58, 731–741.
37. Oates, C.P.; Koenig, D.; Rhyne, J.; Bogush, N.; O'Connell, J.; Mitchell, B.D.; Miller, M. Novel polymorphisms associated with hyperalphalipoproteinemia and apparent cardioprotection. J. Clin. Lipidol. 2018, 12, 110–115.
38. Huggins, G.S.; Papandonatos, G.; Erar, B.; Belalcazar, L.M.; Brautbar, A.; Ballantyne, C.; Kitabchi, A.E.; Wagenknecht, L.E.; Knowler, W.C.; Pownall, H.; et al. Do Genetic Modifiers of High-Density Lipoprotein Cholesterol and Triglyceride Levels also Modify Their Response to a Lifestyle Intervention in the Setting of Obesity and Type-2 Diabetes Mellitus? Circ. Cardiovasc. Genet. 2013, 6, 391–399.
39. Barter, P.; Genest, J. HDL cholesterol and ASCVD risk stratification: A debate. Atherosclerosis 2019, 283, 7–12.
40. Boekholdt, S.M.; Arsenault, B.J.; Hovingh, G.K.; Mora, S.; Pedersen, T.R.; LaRosa, J.C.; Welch, K.; Amarenco, P.; DeMicco, D.A.; Tonkin, A.M.; et al. Levels and Changes of HDL Cholesterol and Apolipoprotein A-I in Relation to Risk of Cardiovascular Events Among Statin-Treated Patients. Circulation 2013, 128, 1504–1512.
41. Agerholm-Larsen, B.; Tybjærg-Hansen, A.; Schnohr, P.; Steffensen, R.; Nordestgaard, B.G. Common Cholesteryl Ester Transfer Protein Mutations, Decreased HDL Cholesterol, and Possible Decreased Risk of Ischemic Heart Disease. Circulation 2000, 102, 2197–2203.
42. Ko, D.T.; Alter, D.A.; Guo, H.; Koh, M.; Lau, G.; Austin, P.C.; Booth, G.L.; Hogg, W.; Jackevicius, C.A.; Lee, D.; et al. High-Density Lipoprotein Cholesterol and Cause-Specific Mortality in Individuals without Previous Cardiovascular Conditions. J. Am. Coll. Cardiol. 2016, 68, 2073–2083.
43. Garg, A.; Sharma, A.; Krishnamoorthy, P.; Garg, J.; Virmani, D.; Sharma, T.; Stefanini, G.; Kostis, J.B.; Mukherjee, D.; Sikorskaya, E. Role of Niacin in Current Clinical Practice: A Systematic Review. Am. J. Med. 2017, 130, 173–187.
44. Franceschini, G.; Favari, E.; Calabresi, L.; Simonelli, S.; Bondioli, A.; Adorni, M.P.; Zimetti, F.; Gomaraschi, M.; Coutant, K.; Rossomanno, S.; et al. Differential effects of fenofibrate and

extended-release niacin on high-density lipoprotein particle size distribution and cholesterol efflux capacity in dyslipidemic patients. J. Clin. Lipidol. 2013, 7, 414–422.

45. Tall, A.R.; Rader, D.J. Trials and Tribulations of CETP Inhibitors. Circ. Res. 2018, 122, 106–112.
46. Bots, M.L.; Visseren, F.; Evans, G.W.; Riley, W.A.; Revkin, J.H.; Tegeler, C.H.; Shear, C.L.; Duggan, W.T.; Vicari, R.M.; Grobbee, D.E.; et al. Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): A randomised, double-blind trial. Lancet 2007, 370, 153–160.
47. Barter, P.J.; Rye, K.-A.; Tardif, J.-C.; Waters, D.D.; Boekholdt, S.M.; Breazna, A.; Kastelein, J.J. Effect of Torcetrapib on Glucose, Insulin, and Hemoglobin A 1c in Subjects in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) Trial. Circulation 2011, 124, 555–562.
48. Clerc, R.G.; Stauffer, A.; Weibel, F.; Hainaut, E.; Perez, A.; Hoflack, J.-C.; Bénardeau, A.; Pflieger, P.; Garriz, J.M.; Funder, J.W.; et al. Mechanisms underlying off-target effects of the cholesteryl ester transfer protein inhibitor torcetrapib involve L-type calcium channels. J. Hypertens. 2010, 28, 1676–1686.
49. Salahuddin, T.; Kittelson, J.; Tardif, J.-C.; Shah, P.K.; Olsson, A.G.; Nicholls, S.J.; Leitersdorf, E.; Leiter, L.A.; Kallend, D.; Black, D.M.; et al. Association of high-density lipoprotein particle concentration with cardiovascular risk following acute coronary syndrome: A case-cohort analysis of the dal-Outcomes trial. Am. Hear. J. 2020, 221, 60–66.
50. Noto, D.; Cefalu', A.B.; Averna, M.R. Beyond Statins: New Lipid Lowering Strategies to Reduce Cardiovascular Risk. Curr. Atheroscler. Rep. 2014, 16, 1–10.