Atherosclerosis 286 (2019) 150–153

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Editorial

Accelerated atherosclerotic cardiovascular risk in type 1 diabetes mellitus: Time for a new idea?

ARTICLE INFO

Keywords:
Diabetes
Cardiovascular risk

Go to any on-line calculator for the risk of a future event from atherosclerotic cardiovascular disease (ASCVD) – and you will see a button for “Diabetes”, yes or no [1]. It's odd. Diabetes, here meaning diabetes mellitus, is a syndrome caused by two major diseases that are as pathogenically distinct from each other as they are from central or nephrogenic diabetes insipidus. Typically, a smoldering autoimmune attack on pancreatic β-cells causes type 1 diabetes mellitus (T1DM), which is therefore an autoimmune disease of absolute insulin deficiency [2–4]. By contrast, patients with type 2 diabetes mellitus (T2DM) are hyperinsulinemic, from either endogenous overproduction of the hormone or copious exogenous administration, and they are often obese. The clinical issue in T2DM and related syndromes of overnutrition is the failure of tissues outside the pancreas to respond normally to insulin – a problem sometimes called pathway-selective insulin resistance and responsiveness (SEIRR) or imbalanced insulin action [5–7]. Many authors have correctly noted that the obesity epidemic now affects many patients with T1DM, leading to insulin resistance for handling glucose [8] on top of their autoimmune destruction of pancreatic β-cells. Only about one-third of obese individuals with pathway-selective insulin resistance progress to frank T2DM, and the event that tips them over appears to be an inability of their pancreases to hypersecrete enough insulin to adequately manage their metabolism of glucose. But the so-called pancreatic “failure” in T2DM patients is neither autoimmune nor absolute: patients with advanced T2DM often exhibit supernormal basal and peak concentrations of endogenous insulin in their plasma [9]. These and other superficial similarities between T1DM and T2DM should not obscure their fundamental differences. How, then, can T1DM and T2DM be lumped together in ASCVD risk assessment as if they were somehow a single entity? More importantly, from the standpoint of therapeutic strategies, are the processes that accelerate ASCVD risk in T1DM and T2DM the same, or are the processes different but just happen to increase ASCVD risk to approximately the same numerical extent?

Excess ASCVD risk in T2DM seems to be explained by known causal agents, meaning apolipoprotein-B (apoB)-containing lipoproteins that become retained, or trapped, within the arterial wall, and by known exacerbators (recently listed in table 1 of reference [10]). A cohort study last year from the Swedish National Diabetes Register followed patients with T2DM, but who were otherwise relatively healthy at baseline. Of that cohort, the patients with T2DM who had just five factors within target ranges – plasma low-density lipoprotein cholesterol concentration (causal), and blood level of glycated hemoglobin ($HgbA_{1c}$), albuminuria, smoking, and blood pressure (exacerbators) – showed little or no excess risk of heart attacks, strokes, or premature death compared with the general population during 5.7 years of follow-up [11]. Excess ASCVD risk in T1DM, however, has been neither explained nor corrected [12]. Two recent mechanistic studies from Hagensen et al., the latter one in this issue of *Atherosclerosis,* shed light on novel pathogenic processes but also highlight long-standing questions and suggest at least one mystery regarding properties of LDL in T1DM that we had not previously recognized [13,14].

The fact that we are even discussing ASCVD risk in T1DM – and in other conditions that used to block a long lifespan, such as sickle-cell anemia and acquired immunodeficiency syndrome – indicates how far we have come in helping these patients. From ancient times until the discovery of insulin in 1922, patients with T1DM died within months from ketoacidosis, even when under expert care for that era [15]. From the mid-1920s until roughly the 1970s, death came predominantly from diabetic nephropathy [16,17]. With better glycemic control, aggressive evidence-based blood pressure management, and less smoking, the incidence of new nephropathy per patient per year of T1DM has plummeted [16]. Patients with T1DM are now living long enough to develop clinically significant ASCVD, and their risk is high [18].

While hyperglycemia (or hyperglycemia variability) drives microvascular disease in both T1DM and T2DM, the role of excess glucose *per se* in accelerating ASCVD in the two conditions may differ [12,18,19]. Randomized controlled trials of intensive glucose-lowering in middle-aged, high-risk patients with established T2DM and co-morbidities failed to show significant reductions in ASCVD events [19]. These findings indicate that aggressive glucose lowering started late in the disease does not help cardiovascular endpoints [19]. Alternatively, it has also been suggested that the results of those trials may mean that hyperglycemia is not a major driver of macrovascular risk in T2DM [19], whereas hyperlipidemia and hypertension clearly are – and have become a focus of successful preventive therapies.

In contrast, the DCCT/EDIC study, a key randomized controlled trial of 6.5 years of intensive glucose-lowering with exogenous insulin in a relatively young cohort of patients with T1DM, showed that the initial period of intensive glycemic management markedly and persistently reduced the risk of ASCVD events during long-term follow-up after the

https://doi.org/10.1016/j.atherosclerosis.2019.04.207
Received 3 April 2019; Accepted 4 April 2019
Available online 14 April 2019

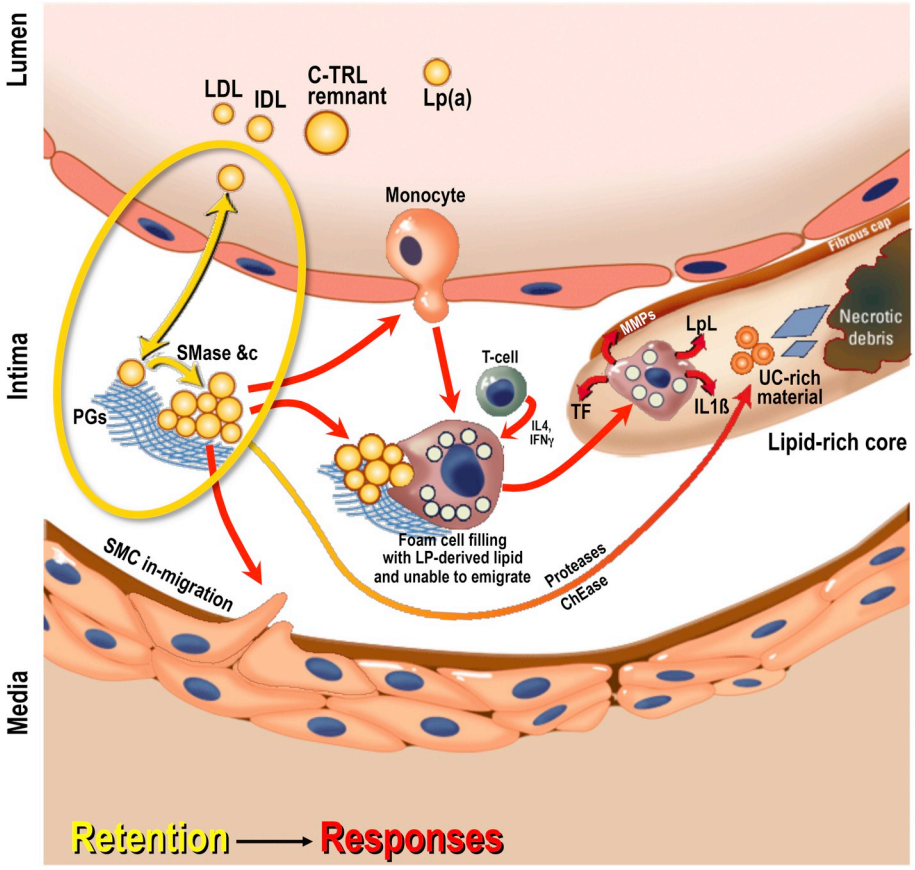

Fig. 1. The response-to-retention model of initiation and progression of atherosclerosis.
Arrows are color-coded to indicate crucial mechanisms in the retention of cholesterol-rich atherogenic apolipoprotein-B-lipoproteins within the arterial wall, which is the key initiating step in atherogenesis (yellow) and then local responses to the retained and modified lipoproteins that lead to plaque growth and evolution (red). The yellow oval encompasses processes that affect LDL retention in vivo, as assessed by Hagensen et al. [13,14] – namely, movement of LDL across the endothelium, adherence to proteoglycans (PGs) within the arterial wall, and early modifications of LDL within the arterial wall that enhance retention. ChEase, cholesteryl esterase; C-TRL, cholesterol- and triglyceride-rich apoB-containing lipoprotein; IFN, interferon; IL, interleukin; LP, lipoprotein; Lp(a), lipoprotein(a); LPL, lipoprotein lipase; MMPs, matrix metalloproteinases; PGs, proteoglycans; SMase, sphingomyelinase; SMC, smooth muscle cell; TF, tissue factor; UC, unesterified cholesterol. Adapted from Ref. [24] with permission.

end of the intervention period [12,20,21]. Remarkably, 30 years later, ASCVD events were still 30% lower in the group that had been intensively treated for that initial 6.5 years – and the decrease in $HgbA_{1c}$ statistically accounted for *all* of the ASCVD benefit [21]. Levels of $HgbA_{1c}$ often associate with known causal factors and exacerbators of ASCVD, but a recent mediation analysis indicated that approximately half of the effect of $HgbA_{1c}$ on ASCVD events in this cohort was independent of traditional ASCVD risk factors [12]. Along similar lines, a Mendelian randomization study in non-diabetic subjects showed that small, lifelong increases in nonfasting plasma glucose concentrations exacerbate the risk of ASCVD events [22]. How might hyperglycemia *per se* exacerbate the risk of ASCVD events in T1DM – or in non-diabetics who inherit minor glucose-raising alleles?

Prior studies established that the key initiating event in ASCVD is the retention, or trapping, of cholesterol-rich apoB-containing lipoproteins within the arterial wall [10,23,24]. Retained and modified apoB-lipoproteins within the artery wall trigger a series of strikingly maladaptive cellular responses that accelerate further lipoprotein retention and lesion development (Fig. 1). Early attempts to develop animal models of accelerated atherosclerosis in T1DM involved the administration of alloxan, a toxin for pancreatic β-cells, to cholesterol-fed rabbits. But the strategy paradoxically protected the animals' arteries, owing to the abnormal development of huge lipoproteins that were too large to cross the endothelium and enter the intima [25]. Thus, these animals did not mimic the human condition. The long-standing lack of a suitable animal model of accelerated atherosclerosis in T1DM has hindered research into this important clinical problem [26].

Recently, however, the Akita mouse model of T1DM was shown to exhibit accelerated atherosclerosis when made deficient in LDL receptors [26,27] – apparently without the development of gigantic lipoproteins. The Akita mouse is not autoimmune, but carries a single copy of a mutation in the *Ins2* gene ($Ins2^{Akita}$; mice have two separate insulin genes). The mutation impedes proper folding of murine proinsulin-2 so that the protein accumulates in the endoplasmic reticulum of pancreatic β-cells, triggering apoptosis. The animals become hypoinsulinemic and hyperglycemic. When also made deficient in LDL receptors and placed on an atherogenic diet, Akita mice become more hypercholesterolemic and more hypertriglyceridemic than the normoglycemic, LDL receptor-deficient controls. These Akita mice also develop more severe atherosclerosis [26,27]. One might conclude that their worsened hyperlipidemia could entirely explain their accelerated atherosclerosis – a result that would not mimic human T1DM [12].

Instead, Hagensen et al. examined additional explanations for the effects of T1DM, using the Akita model to focus on the earliest stages of atherogenesis (Fig. 1, yellow oval). In the first of their mechanistic studies, Hagensen et al. injected fluorescently labeled LDL from healthy non-diabetic human donors into living wild-type and Akita mice [13]. Aortas of the Akita mice accumulated, or retained, two to eight times as much labeled LDL as did the aortas of wild-type control mice. Related findings had been previously reported [28], but not in an animal model in which T1DM had been shown so clearly to accelerate atherosclerosis (reviewed in Ref. [13]). Microarray profiling of the Akita aortas did not show differential levels of mRNAs known to be involved in arterial retention of LDL, although one extracellular matrix candidate, *Prg4,* was identified in an exploratory analysis [13]. Thus, the nature of the alterations in Akita aortae that accelerate LDL retention remain unknown [13] but should be a fruitful area for further study. Delaying the development of these arterial changes by early intensive glucose management could contribute to the long-lasting ASCVD benefit in the DCCT/EDIC study.

In their second mechanistic study, Hagensen et al. looked at the other participant in arterial retention of LDL – namely, LDL itself [14]. They injected living Akita mice with fluorescently labeled LDL from human patients with T1DM – or with labeled LDL from healthy, non-diabetic control volunteers. LDL from T1DM patients was retained in

the aortae more than four times as much as was the control LDL [14]. It is a particularly important finding, given that patients with T1DM do not typically exhibit elevated plasma concentrations of LDL. But the quality of their LDL is different. Why?

Numerous prior studies have focused on non-enzymatic glycation of LDL as a potential atherogenic change (reviewed in Ref. [14]) – a process that could fit with clinical findings from the DCCT/EDIC study implicating hyperglycemia in accelerated ASCVD risk in T1DM [12,20,21]. But the new study from Hagensen et al. provides evidence to suggest that glycation may not be the key change in LDL in patients with T1DM. First, the degree of LDL (or apoB) glycation in their study was low – below the limits of detection in their assay. This finding is consistent with the relatively short half-life of LDL in plasma: two days, compared with three months for the hemoglobin in each red blood cell. Second, accelerated LDL retention in murine aortae did not correlate with the patients' glycated hemoglobin levels. Third, although artificial glycation of LDL in vitro increased its retention in arteries, the degree of glycation vastly exceeded what occurs in human patients [14]. Additionally, the degree of LDL glycation in non-diabetics who inherit minor glucose-raising alleles must be miniscule, yet these people also show increased ASCVD events [22].

So these are the mysteries: why do arteries of T1DM animals (and presumably people) retain more LDL than do arteries in normoglycemic controls? [13,28] And what makes LDL from human patients with T1DM much more prone to retention in arteries than is LDL from healthy control subjects? [14].

Perhaps we need a new idea, beyond just glycation. Extrapolating from the work by Hagensen et al. [13,14] and others, here are a few suggestions. First, integrity of the endothelial barrier to LDL entry into the arterial subintima might play a role [29,30]. Second, agents to block LDL retention to arterial matrix have been reported [31] but have not been tested yet in T1DM. Third, strategies are now available to improve LDL quality [32], though again not tested in T1DM. One tempting possibility is icosapent ethyl, which decreases ASCVD events through unknown mechanisms [33,34], perhaps by altering the composition of LDL and other atherogenic apoB-containing lipoproteins. Fourth, if hyperglycemia is the key exacerbator of ASCVD risk in T1DM, then we should expect the problem to be solved as, say, closed-loop systems improve. Based on data in humans, starting early may be particularly important [19–21,35].

The "harvest of sorrow" in T1DM goes on [17], though thankfully delayed to later in life. We hope that these recent insights will allow even long-term harm from T1DM to become more medically tractable.

Financial support

This work was supported by the Swedish Heart-Lung Foundation (Hjärt-Lungfonden).

Conflict of interest

A.D.R. serves on scientific advisory board of Astra Zeneca. K.J.W. reports an ownership interest in Hygieia, Inc., and in Gemphire Therapeutics, Inc., serves on the Medical and Scientific Advisory Board of Gemphire Therapeutics, Inc., and has filed patent applications on methods to alter the susceptibility of LDL to aggregate.

References

[1] American College of Cardiology (ACC), ASCVD Risk Estimator Plus, (2019) https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/ , Accessed date: 27 March 2019.
[2] W. Gepts, Pathologic anatomy of the pancreas in juvenile diabetes mellitus, Diabetes 14 (1965) 619–633, https://doi.org/10.2337/diab.14.10.619.
[3] G.F. Bottazzo, B.M. Dean, J.M. McNally, E.H. MacKay, P.G.F. Swift, D.R. Gamble, In situ characterization of autoimmune phenomena and expression of HLA molecules in the pancreas in diabetic insulitis, N. Engl. J. Med. 313 (1985) 353–360, https://doi.org/10.1056/NEJM198508083130604.
[4] A. Pugliese, Autoreactive T cells in type 1 diabetes, J. Clin. Investig. 127 (2017) 2881–2891, https://doi.org/10.1172/JCI94549.
[5] M.K. Hellerstein, J.-M. Schwarz, R.A. Neese, Regulation of hepatic de novo lipogenesis in humans, Annu. Rev. Nutr. 16 (1996) 523–557, https://doi.org/10.1146/annurev.nu.16.070196.002515.
[6] X. Wu, K.J. Williams, NOX4 pathway as a source of selective insulin resistance and responsiveness, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 1236–1245, https://doi.org/10.1161/ATVBAHA.111.244525.
[7] K.J. Williams, X. Wu, Imbalanced insulin action in chronic over nutrition: clinical harm, molecular mechanisms, and a way forward, Atherosclerosis 247 (2016) 225–282, https://doi.org/10.1016/j.atherosclerosis.2016.02.004.
[8] P. Bjornstad, M. Schäfer, U. Truong, M. Cree-Green, L. Pyle, A. Baumgartner, Y. Garcia Reyes, A. Maniatis, S. Nayak, R.P. Wadwa, L.P. Browne, J.E.B. Reusch, K.J. Nadeau, Metformin improves insulin sensitivity and vascular health in youth with type 1 diabetes mellitus: randomized controlled trial, Circulation 138 (2018) 2895–2907, https://doi.org/10.1161/CIRCULATIONAHA.118.035525.
[9] W.J. Pories, G.L. Dohm, Diabetes: have we got it all wrong? Hyperinsulinism as the culprit: surgery provides the evidence, Diabetes Care 35 (2012) 2438–2442, https://doi.org/10.2337/dc12-0684.
[10] J. Borén, K.J. Williams, The central role of arterial retention of cholesterol-rich apoB-containing lipoproteins in the pathogenesis of atherosclerosis: a triumph of simplicity, Curr. Opin. Lipidol. 27 (2016) 473–483, https://doi.org/10.1097/MOL.0000000000000330.
[11] A. Rawshani, A. Rawshani, S. Franzén, N. Sattar, B. Eliasson, A.-M. Svensson, B. Zethelius, M. Miftaraj, D.K. McGuire, A. Rosengren, S. Gudbjörnsdottir, Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes, N. Engl. J. Med. 379 (2018) 633–644, https://doi.org/10.1056/NEJMoa1800256.
[12] I. Bebu, B.H. Braffett, T.J. Orchard, G.M. Lorenzi, J.M. Lachinthe DCCT/EDIC Research Group, Mediation of the effect of glycemia on the risk of CVD outcomes in type 1 diabetes: the DCCT/EDIC Study, Diabetes Care (2019), https://doi.org/10.2337/dc18-1613.
[13] M.K. Hagensen, M.B. Mortensen, M. Kjolby, N.L. Stillits, L.B. Steffensen, J.F. Bentzon, Type 1 diabetes increases retention of low-density lipoprotein in the atherosclerosis-prone area of the murine aorta, Atherosclerosis 263 (2017) 7–14, https://doi.org/10.1016/j.atherosclerosis.2017.05.019.
[14] M.K. Hagensen, M.B. Mortensen, M. Kjolby, J. Palmfeldt, J.F. Bentzon, S. Gregersen, Increased retention of LDL from type 1 diabetic patients in atherosclerosis-prone areas of the murine arterial wall, Atherosclerosis (2019) 156–162, https://doi.org/10.1016/j.atherosclerosis.2019.02.027.
[15] F.J. Poynton, Five cases of diabetes mellitus in young children, Br. Med. J. 1 (1923) 277–279.
[16] P. Rossing, The changing epidemiology of diabetic microangiopathy in type 1 diabetes, Diabetologia 48 (2005) 1439–1444, https://doi.org/10.1007/s00125-005-1836-x.
[17] E.A. Gale, Type 1 diabetes in the young: the harvest of sorrow goes on, Diabetologia 48 (2005) 1435–1438, https://doi.org/10.1007/s00125-005-1833-0.
[18] S.D. de Ferranti, I.H. de Boer, V. Fonseca, C.S. Fox, S.H. Golden, C.J. Lavie, S.N. Magge, N. Marx, D.K. McGuire, T.J. Orchard, B. Zinman, R.H. Eckel, Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association, Circulation 130 (2014) 1110–1130, https://doi.org/10.1161/CIR.0000000000000034.
[19] J.S. Skyler, R. Bergenstal, R.O. Bonow, J. Buse, P. Deedwania, E.A. Gale, B.V. Howard, M.S. Kirkman, M. Kosiborod, P. Reaven, R.S. Sherwin, Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association, Diabetes Care 32 (2009) 187–192, https://doi.org/10.2337/dc08-9026.
[20] D.M. Nathan, P.A. Cleary, J.Y. Backlund, S.M. Genuth, J.M. Lachin, T.J. Orchard, P. Raskin, B. Zinman, The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes, N. Engl. J. Med. 353 (2005) 2643–2653, https://doi.org/10.1056/NEJMoa052187.
[21] The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up, Diabetes Care 39 (2016) 686–693, https://doi.org/10.2337/dc15-1990.
[22] M. Benn, A. Tybjærg-Hansen, M.I. McCarthy, G.B. Jensen, P. Grande, B.G. Nordestgaard, Nonfasting glucose, ischemic heart disease, and myocardial infarction: a Mendelian randomization study, J. Am. Coll. Cardiol. 59 (2012) 2356–2365, https://doi.org/10.1016/j.jacc.2012.02.043.
[23] K.J. Williams, I. Tabas, The response-to-retention hypothesis of early atherogenesis, Arterioscler. Thromb. Vasc. Biol. 15 (1995) 551–561, https://doi.org/10.1161/01.ATV.15.5.551.
[24] K.J. Williams, I. Tabas, Lipoprotein retention—and clues for atheroma regression, Arterioscler. Thromb. Vasc. Biol. 25 (2005) 1536–1540, https://doi.org/10.1161/01.ATV.0000174795.62387.d3.
[25] B.G. Nordestgaard, D.B. Zilversmit, Large lipoproteins are excluded from the arterial wall in diabetic cholesterol-fed rabbits, J. Lipid Res. 29 (1988) 1491–1500.
[26] C. Zhou, B. Pridgen, N. King, J. Xu, J.L. Breslow, Hyperglycemic Ins2^{Akita}Ldlr$^{-/-}$ mice show severely elevated lipid levels and increased atherosclerosis: a model of type 1 diabetic macrovascular disease, J. Lipid Res. 52 (2011) 1483–1493, https://doi.org/10.1194/jlr.M014092.

[27] M.M. Bjørklund, A.K. Hollensen, M.K. Hagensen, F. Dagnæs-Hansen, C. Christoffersen, J.G. Mikkelsen, J.F. Bentzon, Induction of atherosclerosis in mice and hamsters without germline genetic engineering, Circ. Res. 114 (2014) 1684–1689, https://doi.org/10.1161/CIRCRESAHA.114.302937.
[28] K.N. Litwak, W.T. Cefalu, J.D. Wagner, Chronic hyperglycemia increases arterial low-density lipoprotein metabolism and atherosclerosis in cynomolgus monkeys, Metabolism 47 (1998) 947–954.
[29] E.D. Bartels, C. Christoffersen, M.W. Lindholm, L.B. Nielsen, Altered metabolism of LDL in the arterial wall precedes atherosclerosis regression, Circ. Res. 117 (2015) 933–942, https://doi.org/10.1161/CIRCRESAHA.115.307182.
[30] J.R. Kraehling, J.H. Chidlow, C. Rajagopal, M.G. Sugiyama, J.W. Fowler, M.Y. Lee, X. Zhang, C.M. Ramírez, E.J. Park, B. Tao, K. Chen, L. Kuruvilla, B. Larriveé, E. Folta-Stogniew, R. Ola, N. Rotllan, W. Zhou, M.W. Nagle, J. Herz, K.J. Williams, A. Eichmann, W.L. Lee, C. Fernández-Hernando, W.C. Sessa, Genome-wide RNAi screen reveals ALK1 mediates LDL uptake and transcytosis in endothelial cells, Nat. Commun. 7 (2016) 13516, https://doi.org/10.1038/ncomms13516.
[31] R. Sarduy, V. Brito, A. Castillo, Y. Soto, T. Griñan, S. Marleau, A.M. Vázquez, Dose-dependent induction of an idiotypic cascade by anti-glycosaminoglycan monoclonal antibody in apoE$^{-/-}$ mice: association with atheroprotection, Front. Immunol. 8 (2017) 232, https://doi.org/10.3389/fimmu.2017.00232.
[32] M. Ruuth, S.D. Nguyen, T. Vihervaara, M. Hilvo, T.D. Laajala, P.K. Kondadi, A. Gisterå, H. Lähteenmäki, T. Kittilä, J. Huusko, M. Uusitupa, U. Schwab, M.J. Savolainen, J. Sinisalo, M.-L. Lokki, M.S. Nieminen, A. Jula, M. Perola, S. Ylä-Herttula, L. Rudel, A. Öörni, M. Baumann, A. Baruch, R. Laaksonen, D.F.J. Ketelhuth, T. Aittokallio, M. Jauhiainen, R. Käkelä, J. Borén, K.J. Williams, P.T. Kovanen, K. Öörni, Susceptibility of low-density lipoprotein particles to aggregate depends on particle lipidome, is modifiable, and associates with future cardiovascular deaths, Eur. Heart J. 39 (2018) 2562–2573, https://doi.org/10.1093/eurheartj/ehy319.
[33] D.L. Bhatt, P.G. Steg, M. Miller, E.A. Brinton, T.A. Jacobson, S.B. Ketchum, R.T. Doyle, R.A. Juliano, L. Jiao, C. Granowitz, J.-C. Tardif, C.M. Ballantyne, For the REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia, N. Engl. J. Med. 380 (2019) 11–22, https://doi.org/10.1056/NEJMoa1812792.
[34] J.J.P. Kastelein, E.S.G. Stroes, FISHing for the miracle of eicosapentaenoic acid, N. Engl. J. Med. 380 (2019) 89–90, https://doi.org/10.1056/NEJMe1814004.
[35] K. Dahl-Jørgensen, J.R. Larsen, K.F. Hanssen, Atherosclerosis in childhood and adolescent type 1 diabetes: early disease, early treatment? Diabetologia 48 (2005) 1445–1453, https://doi.org/10.1007/s00125-005-1832-1.

Ajay D. Rao
Section of Endocrinology, Diabetes, & Metabolism, Department of Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA
Center for Metabolic Disease and Research, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA

Cherie Lisa Vaz
Section of Endocrinology, Diabetes, & Metabolism, Department of Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, PA, USA

Kevin Jon Williams*
Department of Molecular and Clinical Medicine, Sahlgrenska Academy of the University of Gothenburg, Göteborg, 413 45, Sweden
E-mail address: Kevin-Jon.Williams@wlab.gu.se.

* Corresponding author. Göteborgs universitet, Sahlgrenska University Hospital, SE-413, Göteborg, 413 45, Sweden.