Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies

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Individuals with type 2 diabetes mellitus have increased cardiovascular disease risk compared with those without diabetes. Treatment of the residual risk, other than blood pressure and LDL-cholesterol control, remains important as the rate of diabetes increases worldwide. The accelerated atherosclerosis and cardiovascular disease in diabetes is likely to be multifactorial and therefore several therapeutic approaches can be considered. Results of mechanistic studies done in vitro and in vivo—animals and people—can provide important insights with the potential to improve clinical management decisions and outcomes. In this Review, we focus on three areas in which pathophysiological considerations could be particularly informative—ie, the roles of hyperglycaemia, diabetic dyslipidaemia (other than the control of LDL-cholesterol concentrations), and inflammation (including that in adipose tissue) in the acceleration of vascular injury.

Introduction

Several mechanisms are likely to contribute to the accelerated atherosclerosis and increased cardiovascular disease risk noted in patients with type 2 diabetes mellitus. We focus on areas in which basic mechanistic studies have high relevance to present clinical controversies to understand and address cardiovascular disease risk in people with diabetes. We assess pathophysiological information linking hyperglycaemia, diabetic dyslipidaemia (other than the control of LDL cholesterol concentrations), and inflammation to the accelerated vascular injury and cardiovascular disease risk in type 2 diabetes and discuss clinical considerations.

Hyperglycaemia and the vessel wall

Although a consistent association between glycaemic control and cardiovascular disease has been noted in epidemiological studies, the effect of tight glycaemic control did not seem to reduce the cardiovascular risk in clinical trials.  Intensive glycaemic control in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study was stopped because of an increase in the number of cardiovascular deaths. A formal analysis of the results has not yet been reported. The ADVANCE (Action in Diabetes and Vascular Disease) study will provide information about whether a good glycaemic control is of benefit for cardiovascular disease. Results of basic studies in vitro, in animal models, and in patients with diabetes mellitus suggest several mechanisms by which hyperglycaemia might affect atherogenesis at the level of the artery wall (figure 1).

Hyperglycaemia can lead to vascular complications by several mechanisms. First, high glucose concentrations can activate nuclear factor-κB (NF-κB), which in turn can increase the expression of various genes in the endothelial cells, monocyte-derived macrophages, and vascular smooth-muscle cells. Advanced glycation end-products (AGEs)—including protein cross-links, fluorophors, and other low molecular-weight residues—are formed by sustained exposure of proteins and lipids to high concentrations of glucose, which can generate reactive oxygen species. Ligation of AGEs to specific cell-surface receptors can regulate gene expression in vessel-wall cells.

Glucose increases oxidative stress, which has several possible harmful effects on the artery wall—eg, auto-oxidation of glucose leads to the formation of several reactive oxygen species, such as the superoxide anion, which can promote LDL oxidation in vitro. Indirect observational evidence suggests that lipoprotein oxidation might be increased in patients with type 2 diabetes and is related to glycaemic control. However, many of the studies relied on non-specific assays of oxidative stress. The absence of highly specific markers in collagen, plasma, or urine from individuals with diabetes does not support a generalised increase in oxidative stress in diabetes. Glycoxidation reactions are thought to contribute to macrovascular disease in diabetes by damaging tissues in the local microenvironment of the arterial wall. The pathways leading to these reactions include the generation of superoxide in the mitochondria, NADPH generation by monocyte-derived macrophages, or a redox-sensitive mechanism that generates hydroxyl radicals. Accumulation of the products of hydroxyl radicals locally in arterial tissue of diabetic monkeys is consistent with a redox-sensitive mechanism.

Postprandial hyperglycaemia as an important index of glycaemic exposure and potential oxidative stress has had a resurgence in interest. 24 h excretion of 8-iso-prosta-
glandin F2—an indicator of free radical production derived from arachidonic acid in cell membranes—was increased in patients with diabetes compared with those who are non-diabetic controls. The concentrations of this prostaglandin were highest in patients with the greatest glycaemic variability. Moreover, this variability was a strong predictor of total free radical production, whereas postprandial blood glucose concentrations were not. Indeed, fluctuations in blood glucose concentrations accelerated atherosclerosis in apolipoprotein-E-deficient mice. Further studies are needed to assess the importance of oxidative stress that results from glycaemic variability.

Glucose and the endothelium

An important initial event in the pathogenesis of atherosclerosis is the adhesion of circulating monocytes to arterial endothelial cells, followed by their transmigration into the subendothelial space along a chemotactic gradient (figure 1). Hyperglycaemia enhances monocyte adhesion to cultured aortic endothelial cells by activation of NF-κB, which increases the expression of several inflammatory genes, including adhesion molecules that promote monocyte adhesion to the endothelial cells (figure 1). Expression of adhesion molecules might result from impaired nitric oxide production, since agents that increase the production of nitric oxide reduce the expression of adhesion molecules. Glucose-mediated and AGE-mediated inhibition of nitric oxide production by endothelial cells is associated with impaired endothelial-dependent relaxation, an early marker of vascular injury. In addition to substantial impairment of endothelium-dependent relaxation, diabetic mice show evidence of increased peroxynitrite generation, nitrotyrosine expression, and lipid peroxidation in the aortic tissues. Hyperglycaemia and AGES stimulate the production of superoxide by endothelial cells, partly by activation of NADPH oxidase, thereby providing a link between hyperglycaemia, AGES, and oxidative stress.

Glucose and monocyte-derived macrophages

Both high glucose concentrations and AGES are associated with an increased state of activation of circulating monocytes in vitro and in vivo. Monocytes grown in the presence of high glucose concentrations or isolated from individuals with poorly controlled diabetes are in an activated and inflammatory state, as shown, for example, by the increased expression of cytokines—interleukin 1β, and interleukin 6—and expression of CD36 and monocyte chemoattractant protein 1. These inflammatory changes are associated with induction of protein-kinase C, NF-κB activation, and increased release of superoxide, and all three could play a part in the oxidative stress that occurs in the presence of hyperglycaemia.

Monocytes entering the endothelial space in response to chemotactic factors, proliferate and differentiate into intimal macrophages, which accumulate in the artery wall in diabetes (figure 1). Hyperglycaemia is not sufficient to stimulate macrophage proliferation in lesions of atherosclerosis or in isolated murine macrophages; in combination with hyperlipidaemia, it stimulates macrophage proliferation by a pathway that might include glucose-dependent oxidation of LDL.

Arterial wall macrophages can accumulate lipid from modified forms of LDL, which are taken up by scavenger receptors. The modifications include LDL that has become oxidised as a result of glucose-mediated oxidative stress and AGE-modified LDL. Additionally, AGE-modified albumin can inhibit the selective uptake of cholesteryl esters from HDL, an essential step in reverse cholesterol transport. Thus, modification of lipoproteins and other proteins resulting from an increased exposure to high glucose concentrations can change the delivery and removal of lipids from macrophages in a way that is likely to promote atherosclerosis.

Glucose and vascular smooth-muscle cells

High glucose concentrations can stimulate the proliferation of vascular smooth-muscle cells in vitro. As atherosclerotic lesions progress, smooth-muscle cells migrate from the media to the intima, in which they proliferate, generate growth factors, and participate in the formation of a fibrous cap. Similar findings were noted after exposure of cells to AGES and high insulin concentrations, which often accompany hyperglycaemia in type 2 diabetes.

Vascular smooth-muscle cells generate several matrix molecules that are implicated in atherogenesis. Vascular proteoglycans bind atherogenic lipoproteins, leading to

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**Figure 1: Possible mechanisms by which glucose and advanced glycation end-products (AGEs) can affect atherogenesis in diabetes**

EC = endothelial cell. SMC = smooth-muscle cell. *Glucose and †AGEs have been proven to affect various steps in these pathways.
Diabetic dyslipidaemia and the vessel wall

Diabetic dyslipidaemia is strongly related to atherosclerosis. Even though patients with type 2 diabetes might not have substantially increased concentrations of LDL-cholesterol compared with matched individuals without diabetes, a cornerstone of the management of cardiovascular disease risk in diabetes is the use of LDL-cholesterol-lowering drugs—ie, statins. These drugs generally reduce cardiovascular disease events by 25–50% but the excess residual cardiovascular disease risk remains for treated patients with diabetes compared with those without diabetes. Some of this residual risk could be attributed to lipoprotein abnormalities in patients with type 2 diabetes that are not adequately managed by statin treatment. Type 2 diabetes is characterised by reduced HDL-cholesterol concentrations, increased triglyceride-rich lipoprotein concentrations, and abnormalities in the composition of HDL, LDL, and triglyceride-rich lipoprotein particles (panel). 41-44

Triglyceride-rich lipoproteins

The triglyceride-rich lipoproteins—which can be increased in the fasting or postprandial state—in patients with type 2 diabetes are VLDL and metabolites of VLDL, and chylomicron remnants. The role of these lipoproteins in diabetic atherosclerosis remains controversial. Triglyceride concentrations vary inversely with HDL-cholesterol concentrations, confounding interpretations related to increases in concentrations of triglyceride-rich lipoproteins to atherosclerosis. 42,43 Post-prandial triglyceride concentrations might be a better predictor of cardiovascular disease events than fasting triglyceride concentrations, independently of HDL cholesterol concentrations. 44-46 A proatherogenic effect of triglyceride-rich lipoproteins in the vessel wall is supported by substantial in-vitro evidence (figure 2). Triglyceride-rich lipoproteins enhance the proinflammatory phenotype of endothelial cells and macrophages and produce apoptosis in endothelial cells. 47-49 They increase expression of tumour necrosis factor α (TNFα) and adhesion receptors in macrophages, resulting in increased adherence of monocytes and monocyte-derived macrophages to endothelial cells. 50 Apolipoprotein CIII—a component of triglyceride-rich lipoproteins and an inhibitor of lipoprotein lipase—increases adhesion of monocytic cells to endothelial cells. 51-53 Chylomicron remnants and triglyceride-rich lipoproteins produce lipid accumulation in macrophages. 53 Uptake of the lipid-rich VLDL particles is favoured by macrophages, promoting lipid accumulation. 54 Disruption of the VLDL receptor expression in macrophages reduces atherosclerosis in cholesterol-fed mice, whereas VLDL receptor expression in VLDL receptor-deficient mice increases atherosclerosis. 55 Reduction in triglyceride-rich lipoprotein concentrations and hyperlipidaemia prevented disruption of atherosclerotic plaques in a mouse model of type 1 diabetes. 56 Increased concentrations of postprandial remnant lipoprotein particles have been proven to contribute to impaired arterial compliance. 57 The fatty-acid composition of chylomicron remnants affects their uptake and the induction of lipid accumulation in macrophages. 58 The ability of triglyceride-rich lipoprotein particles to induce an inflammatory phenotype in macrophages might be enhanced by lipolytic release of fatty acids from VLDL. 59 Increased concentrations of free fatty acids are another component of diabetic dyslipidaemia and accompany increased triglyceride concentrations. Fatty acids can directly lead to changes in the composition of the extracellular matrix produced by arterial smooth-muscle cells in a manner that favours increased immobilisation and retention of lipoproteins. 60 Excess free-fatty-acid delivery to peripheral tissues can worsen insulin resistance and might play a part in
activation of the inflammatory processes through activation of toll-like receptors. Free fatty acids are proven to impair endothelium-dependent vasodilation and disrupt the function of cellular sterol transporters that are important for reverse cholesterol transport. However, data suggest that in some circumstances physiological lipolysis of triglyceride-rich lipoproteins might have beneficial anti-inflammatory effects. In some model systems, the lipolytic release of fatty acids can provide a ligand for nuclear hormone receptors—such as the peroxisome-proliferator-activated receptor (PPAR)γ—which are implicated in the inhibition of inflammation. Taken together, these results suggest that inappropriate generation or handling of fatty acids, or both, might represent a fundamental abnormality in diabetes, leading to accelerated atherosclerosis.

**LDL**

Patients with type 2 diabetes might not have substantially higher concentrations of LDL cholesterol than matched individuals without diabetes, but for any LDL-cholesterol concentration, those with diabetes generally have an increase in LDL particles because small, dense lipid-poor LDL particles accumulate in the circulation. Each LDL particle contains one apolipoprotein-B molecule and therefore patients with type 2 diabetes will also have a parallel increase in concentrations of apolipoprotein B. An increased number of LDL particles, measured directly or indirectly by concentrations of apolipoprotein B, might contribute to atherogenesis and cardiovascular disease risk. An increase in the number of LDL particles in diabetes can be treated by statins. However, a separate issue is whether or not small, dense LDL particles are inherently more atherogenic on a per-particle basis than the larger buoyant particles. An increased atherogenicity of small, dense LDL particles is supported by results of in-vitro studies, showing that small LDL particles rapidly enter the arterial wall and can be toxic to endothelial cells, cause greater production of procoagulant factors, be oxidised more readily, and be more readily immobilised by proteoglycans present in the arterial wall than can the large buoyant particles. The small particles do not bind very well to the LDL receptor, which might lead to impaired clearance by the liver. How these in-vitro results translate to the in-vivo milieu, however, remains unclear. A satisfactory in-vivo model for testing atherogenicity of small, dense LDL particles on a per-particle basis compared with large particles is needed.

In non-human primates fed fat-modified diets, LDL-particle size was not independently atherogenic. Results from studies of healthy individuals and those with coronary heart disease showed that both large and small LDL particles are related to atherosclerosis and cardiovascular disease.

**HDL**

Individuals with type 2 diabetes mellitus have reduced HDL cholesterol and circulating apolipoprotein AI—the major apolipoprotein in HDL cholesterol. Abnormalities in the size and composition of the HDL particle have also been noted in diabetic patients. HDL and apolipoprotein AI remove excess cholesterol from atherosclerotic plaque cells, and their reduced concentrations in diabetes would be expected to have a
detrimental effect on cholesterol content in vessel walls (figure 2). The cell type of most interest is the monocyte-derived macrophage because cholesterol-ester-engorged macrophages (ie, foam cells) are hallmarks of the atherosclerotic plaque. Removal of cholesterol from macrophages is thought to be an important first step in the process of reverse cholesterol transport, and might be important for the prevention of progression and for regression of atherosclerotic plaques.\textsuperscript{77} The HDL particle and its apolipoprotein-AI component might act through distinct cellular sterol transporters for removal of cholesterol from cells. The HDL particle seems to rely mainly on the ATP-binding cassette transporter G1 to facilitate sterol efflux, and expression of this transporter in cells can be inhibited by exposure to glycosylated proteins.\textsuperscript{78} Additionally, glycation of apolipoprotein AI, which acts mainly through the ATP-binding cassette transporter AI, suppresses its ability to remove cholesterol from cells.\textsuperscript{79} HDL has anti-inflammatory and antioxidant properties in cells of the vessel wall.\textsuperscript{76,77} Monocyte-derived macrophages isolated from individuals with low HDL cholesterol concentrations manifest a proinflammatory phenotype.\textsuperscript{79}

In addition to changes in HDL-cholesterol and apolipoprotein-AI concentrations, patients with type 2 diabetes have changes in HDL composition. HDL is the most heterogeneous and complex of all lipoprotein particles, and changes in its composition might affect HDL atheroprotective properties (figure 2).\textsuperscript{79} In isolated cells, HDL particles of different sizes and composition show different abilities to remove cholesterol from cells.\textsuperscript{80} Changes in the content of many proteins associated with HDL, for example paraoxonase (opposes oxidation of lipoprotein lipid),\textsuperscript{81} might change its atheroprotective properties.\textsuperscript{82} Compositional abnormalities of HDL isolated from patients with type 2 diabetes have been linked to impaired antiatherogenic properties.\textsuperscript{74} Cholesterol-ester transfer protein inhibition with torcetrapib did not protect against cardiovascular disease events, underscoring the notion that HDL-particle composition might be more important than HDL-cholesterol concentrations for reduction of cardiovascular disease risk.\textsuperscript{82}

Mice without apolipoprotein AI and with very low HDL cholesterol concentrations have increased rates of atherosclerosis because of both reduced cholesterol transport and increased inflammation.\textsuperscript{83} Conversely, increased expression of apolipoprotein AI with high HDL-cholesterol concentrations reduces the amount of atherosclerosis in the apolipoprotein-E−/− mouse—a model of accelerated and progressive atherosclerosis.\textsuperscript{84} An increase in HDL-cholesterol concentrations in patients with type 2 diabetes has been linked to reduced carotid atherosclerosis.\textsuperscript{85,86} HDL has been proven to improve mobilisation and function of endothelial precursor cells\textsuperscript{87} and to protect the myocardium from ischaemia and reperfusion injury.\textsuperscript{88}

**Glycaemia versus hyperlipidaemia in atherosclerosis**

The roles of hyperglycaemia and hyperlipidaemia in atherogenesis have been difficult to separate in animal models of diabetes. Hyperlipidaemia is usually exacerbated by the onset of hyperglycaemia—eg, in mouse models of LDL-receptor deficiency and apolipoprotein-E deficiency—thereby confounding the effect of hyperglycaemia. However, in two animal models, hyperglycaemia seems to have an independent role.\textsuperscript{89,90} First, fat-fed diabetic pigs had more atherosclerosis than equally dyslipidaemic fat-fed animals without diabetes.\textsuperscript{90} Second, consumption of a cholesterol-free diet by LDL-receptor-deficient mice with a novel form of diabetes induced by a β-cell-directed viral antigen resulted in hyperglycaemia without changes in lipids and lipoproteins.\textsuperscript{91} Hyperglycaemia was associated with lesion initiation. Addition of increasing amounts of dietary cholesterol led to dyslipidaemia, which was the major factor in atherosclerosis progression, independent of hyperglycaemia.\textsuperscript{91}

**Chronic subclinical inflammation and the vessel wall**

Evidence ranging from pathological studies in people to in-vivo mouse models has established the role of inflammatory cells (such as macrophages and T lymphocytes) and inflammatory mechanisms (such as cytokine release) in the pathogenesis of atherosclerosis.\textsuperscript{92} Because type 2 diabetes and atherosclerosis are chronic conditions that take decades to arise, the cause and effect are difficult to discern (figure 3). Inflammation is implicated in the pathogenesis of type 2 diabetes and atherosclerosis.\textsuperscript{93,94} Since diabetes promotes atherosclerosis and increases cardiovascular events, a distinction might exist between inflammation that fosters diabetes and inflammation that arises after the type 2 diabetes and promotes atherosclerosis directly (figure 3). Most of the inflammatory mechanisms discussed also seem to be implicated in the atherosclerosis seen in prediabetic and non-diabetic states. Although the evidence implicating inflammation in atherosclerosis and type 2 diabetes is wide-ranging, a specific mechanism or an integrated framework has not been identified to explain precisely why patients with diabetes are at increased risk of inflammation or atherosclerosis.

**Mechanisms of inflammation in diabetic atherosclerosis**

The endothelium—as the cellular interface between the circulation and hyperglycaemia and dyslipidaemia that characterise type 2 diabetes mellitus—responds to hyperglycaemia and dyslipidaemia by showing an inflammatory response.\textsuperscript{95} Most of the responses induced in atherosclerosis are common to both diabetic and non-diabetic atherosclerosis. Classic proatherosclerotic endothelial responses—adhesion-molecule expression, secretion of chemokines, and coagulation proteins
Macrophage biology in type-2 diabetes mellitus and atherosclerosis

The available data suggests cellular responses to injury, inflammation, and metabolism might converge on control points that are important in atherosclerosis. A central regulator of inflammation is NF-κB, a transcriptional complex activated by various stimuli, including cytokines, oxidised LDL, lipopolysaccharide, and oxidative stress (figure 4). NF-κB is reported to regulate LDL oxidative modification, chemokine and cytokine expression, macrophage growth and differentiation, apoptosis, and vascular smooth-muscle cell proliferation. NF-κB, its regulatory proteins (eg, inhibitor κB), and distal targets (eg, c-Jun N-terminal kinase) have all been strongly implicated in insulin sensitivity and in atherosclerosis (figure 4). NF-κB might have a role in the common pathway, linking many inputs that are activated in type 2 diabetes mellitus to atherosclerotic responses. It is activated by factors commonly abnormal in type 2 disease mellitus, including fatty acids, glucose, AGE pathways, and some toll like receptors—a family of pattern recognition receptors expressed in various inflammatory cells. Several NF-κB-regulated targets are implicated in diabetic atherosclerosis, including TNFα, which increases insulin resistance, toll-like receptors, and resistin. In mice, inhibition of NF-κB activation can improve insulin sensitivity and reduce atherosclerosis; this inhibition (eg, by high-dose salicylates) is also being investigated in people. PPARγ’s anti-inflammatory and antiatherosclerotic effects in vitro and in mice might work through NF-κB inhibition (figure 4).

Several mechanistic pathways have been proposed for how glucose brings about cellular injury and subsequent inflammation. Cells that do not have the ability to counter the increase in intracellular glucose concentrations might activate pathways of cellular injury and inflammation. These mechanisms include activation of protein-kinase C, formation of polyols, which promotes intracellular oxidative stress, and increased hexosamine activation, with subsequent increases in reactive oxidant species and mitochondrial stress. Although much of this evidence was linked to diabetic microvascular disease, increased flux of free fatty acids into the endothelium might cause macrovascular disease through similar pathways, inducing inflammation.

All secretory and membrane proteins, many nutrients, and many pathogens pass through the endoplasmic reticulum. Several lines of study implicate endoplasmic reticulum stress in the promotion of inflammation. Hypoxia, hyperglycaemia, and increased fatty-acid concentrations can all induce endoplasmic reticulum stress and a specific cellular process known as the....

**Figure 3:** The intersection of inflammation, type 2 diabetes mellitus, and atherosclerosis

**Figure 4:** Macrophage biology in type-2 diabetes mellitus and atherosclerosis

FFA=free fatty acids. AGEs=advanced glycation end-products. ROS=reactive oxygen species. ER=endoplasmic reticulum. aP2=adipocyte protein 2. JNK=c-Jun N-terminal kinase. PPARs=peroxisome-proliferator-activated receptors. IκBα= inhibitor κB. AP1=activator protein 1. NF-κB=nuclear factor κB.
Adipose tissue inflammation

Adipose tissue is a biologically active endocrine and paracrine organ. The theory that it could be involved in diabetic atherosclerosis has many implications for the intersection of inflammation, atherosclerosis, and type 2 diabetes mellitus, especially since clinical data suggests that adiposity is a core defect in the metabolic abnormalities that arise before and during diabetes. Inflammation in adipose tissue might contribute to abnormal metabolism and atherosclerosis in type 2 diabetes.

Oxidative stress, endoplasmic reticulum stress, and NF-kB activation pathways also operate in adipocytes. Oxidative stress and inflammation in adipose tissue can be exacerbated by hyperglycaemia. Fatty acids released from adipose tissue might signal to macrophages through pathways that involve toll-like receptors, leading to NF-kB activation. Many of the same pathways involved in the recruitment of leucocytes to the arterial wall also recruit inflammatory cells to fat, including monocyte chemoattractant protein 1. Indeed, mice deficient in C-C chemokine receptor-2—ie, the receptor for monocyte chemoattractant protein 1—are afforded some degree of protection from diet-induced insulin resistance and induction of inflammation. Excess lipid accumulation in other tissues—eg, skeletal muscle and the liver—might modulate inflammation, contributing to insulin resistance and atherosclerosis.

Increased concentrations of inflammatory cytokines released from visceral fat in diabetes and obesity can act directly on the liver to increase the circulating concentrations of proinflammatory molecules such as C-reactive protein and serum amyloid A. C-reactive protein might directly amplify injury at the vessel wall and serum amyloid A unfavourably modifies the composition and function of HDL. The expression of adipose tissue apolipoproteins, which affect adipocyte lipid metabolism, is modified by inflammatory cytokines. Several adipocyte-specific mediators have been implicated in the inflammation contributing to insulin resistance and atherosclerosis. Leptin is an adipocyte-specific signal that seems to exert systemic proinflammatory effects. It produces proinflammatory changes in endothelial cells and macrophages, and its administration to apolipoprotein-E-deficient mice promotes atherosclerosis. Adiponectin, which circulates in the plasma in various multimeric forms, restricts inflammatory and atherosclerotic responses. Adiponectin concentrations are reduced in obesity and diabetes, and the treatment of apolipoprotein-E-deficient mice with an adiponectin-expressing adenovirus has proven to reduce atherosclerotic plaque formation. Adiponectin is present at higher concentrations in the subcutaneous fat adipocytes than in visceral fat adipocytes, one of many examples that suggest both depot-specific differences in fat and increased pathogenicity from visceral fat.

Conclusions

Data from in-vitro and animal model studies support the argument that the absence of intensive glycaemic control in the ACCORD trial should not eliminate hyperglycaemia as an important therapeutic target for reduction of cardiovascular disease in diabetes; the absence of effect might relate to an unfavourable benefit to risk ratio of the presently available glucose-lowering treatments in the patients recruited for that trial. In the ACCORD trial, the elderly at risk patients might have had increased susceptibility to the adverse effects of hypoglycaemia, off-target drug effects, or the risk imposed by ectopic fat deposition that usually accompany intensification of glucose-lowering treatments. The lipid arm of the ACCORD trial will provide information about the value of adding a fibrate (which can increase HDL concentrations) to statin treatment in patients with type 2 diabetes. Information obtained from animal models about the complexity of HDL metabolism and HDL’s potent atheroprotective effect argues that, despite the apparent failure of torcetrapib, other mechanisms for increasing HDL-cholesterol concentrations warrant assessment. Although therapeutic interventions in people can never be as targeted or specific as the experimental manipulations achievable in isolated cells or in animal models, pathophysiological and mechanistic information from these models provide key insights for the design and assessment of new treatment options to reduce cardiovascular disease in type 2 diabetes.


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