Insulin Resistance and Atherosclerosis: Implications for Insulin-Sensitizing Agents

Antonino Di Pino[1]* and Ralph A. DeFronzo[1]*

[1]Diabetes Division, University of Texas Health Science Center and Texas Diabetes Institute, San Antonio, Texas 78229

ORCiD numbers: 0000-0003-3839-1724 (R. A. DeFronzo).

(*A.D.P. and R.A.D. contributed equally to this review.)

ABSTRACT Patients with type 2 diabetes mellitus (T2DM) are at high risk for macrovascular complications, which represent the major cause of mortality. Despite effective treatment of established cardiovascular (CV) risk factors (dyslipidemia, hypertension, procoagulant state), there remains a significant amount of unexplained CV risk. Insulin resistance is associated with a cluster of cardiometabolic risk factors known collectively as the insulin resistance (metabolic) syndrome (IRS). Considerable evidence, reviewed herein, suggests that insulin resistance and the IRS contribute to this unexplained CV risk in patients with T2DM. Accordingly, CV outcome trials with pioglitazone have demonstrated that this insulin-sensitizing thiazolidinedione reduces CV events in high-risk patients with T2DM. In this review the roles of insulin resistance and the IRS in the development of atherosclerotic CV disease and the impact of the insulin-sensitizing agents and of other antihyperglycemic medications on CV outcomes are discussed. ***(Endocrine Reviews 40: 1447 – 1467, 2019)***

Multiple studies have demonstrated that insulin resistance is a strong predictor of atherosclerotic cardiovascular (CV) disease (ASCVD) (1–11) and have been summarized in a recent meta-analysis by Gast *et al.* (12). Bressler *et al.* (3), using the euglycemic insulin clamp, were the first to conclusively demonstrate that normal glucose-tolerant (NGT) individuals with diffuse coronary artery disease were markedly insulin resistant compared with NGT individuals with clean coronary arteries, whereas the Insulin Resistance Atherosclerosis Study was the first epidemiologic study to document the relationship between insulin resistance and CVD in a large multiethnic cohort (5), after adjustment for confounding factors, including glucose tolerance, fasting insulin, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, smoking, hypertension, and body mass index. Similarly, in the Botnia study (6), insulin resistance was an independent predictor of increased risk of CVD in nondiabetic subjects during a follow-up period of 6.9 years. Similar observations have been made in the Verona Diabetes Study (7), the Bruneck study (8), the Malmö study (9), and the Atherosclerosis Risk in Communities (ARIC) study (10). Of note, in the ARIC study, insulin resistance also was associated with an increased incidence of atrial fibrillation. In the San Antonio Heart Study, insulin resistance, quantified with homeostatic model assessment of insulin resistance (HOMA-IR), was significantly and independently associated with an increased risk of CV outcomes in a large population of Mexican American and non-Hispanic whites without T2DM at baseline (11); the magnitude of the association of stroke and coronary artery disease with HOMA-IR was similar. The strong association between insulin resistance and adverse CV outcomes in nondiabetic individuals and individuals with T2DM has been summarized in several meta-analyses (12–14). In the meta-analsyis by Gast *et al.* (12), coronary heart disease risk in nondiabetic individuals increased by 46% for an increase in HOMA-IR of 1 SD.

ISSN Print: 0163-769X
ISSN Online: 1945-7189
Printed: in USA

Received: 15 May 2018
Accepted: 18 October 2018
First Published Online: 3 May 2019

ESSENTIAL POINTS

- Insulin resistance is a characteristic feature of type 2 diabetes mellitus (T2DM)
- Insulin resistance is associated with a cluster of cardiometabolic risk factors that contribute to the increased risk of cardiovascular disease in patients with T2DM
- The molecular etiology of the insulin resistance directly contributes to the development of atherosclerotic cardiovascular disease by inhibiting nitric oxide production (endothelial dysfunction) and stimulating the MAPK pathway
- Insulin resistance in T2DM accounts for the unexplained cardiovascular risk that cannot be attributed to the classic cardiovascular risk factors
- Thiazolidinediones are the only true insulin-sensitizing antidiabetic drugs and at least one drug, pioglitazone, in this class has been shown to reduce cardiovascular events and retard the atherosclerotic process in high-risk patients with T2DM
- The glucagon-like peptide receptor agonists and SGLT2 inhibitors have been shown to reduce cardiovascular events in high-risk patients with T2DM, but their cardiovascular benefit appears to be mediated via mechanisms other than amelioration of insulin resistance

Etiologic Links Between Insulin Resistance and ASCVD

Three mechanisms account for the strong association between insulin resistance and ASCVD: (i) the basic molecular etiology of the insulin resistance (15–24), (ii) the compensatory hyperinsulinemia that occurs in response to the insulin resistance (22, 25–31), and (iii) the association between insulin resistance and a cluster of cardiometabolic abnormalities, each of which is an independent risk factor for ASCVD (25–27, 32, 33). This cardiometabolic cluster has been called the "metabolic syndrome" (27), but in the subsequent discussion it is referred to as the "insulin resistance syndrome" (IRS), because the underlying insulin resistance is the etiologic factor responsible for the development of each of the individual cardiometabolic disturbances.

Molecular etiology of insulin resistance

In order for insulin to work, it must first bind to the insulin receptor on the cell membrane surface (34–36), resulting in tyrosine phosphorylation of IRS-1/IRS-2, activation of phosphatidylinositol 3-kinase (PI_3K) (37), and ultimately augmentation of glucose transport (38). Because insulin signaling plays a pivotal role in activating nitric oxide, which is a potent vasodilator and antiatherogenic agent (25, 26), impaired insulin signaling not only inhibits glucose metabolism, but it also promotes hypertension and atherogenesis.

In insulin-resistant states, including obesity, impaired glucose tolerance, and early T2DM, the β-cell reads the severity of insulin resistance and augments its secretion of insulin in an attempt to offset the defect in insulin action (25, 26, 39, 40). Insulin, especially at high levels, is a potent growth factor (26, 28, 32, 41–43) that exerts its growth-promoting effects via the MAPK pathway (18, 19, 22, 28), which catalyzes the phosphorylation of transcription factors that (i) stimulate vascular smooth muscle cell growth, proliferation, and differentiation (34), (ii) activate inflammatory pathways, including IκB/nuclear factor κB (NF-κB), and c-Jun N-terminal kinase (23, 44), and (iii) cause insulin resistance (45, 46). Despite the presence of severe resistance in the IRS-1/PI_3K/Akt pathway, the MAPK pathway, which is activated by Sch, retains normal sensitivity to insulin and is hyperstimulated by the elevated plasma insulin concentrations that are present in individuals with the IRS, in nondiabetic subjects with obesity, in individuals who are prediabetic, and in subjects with T2DM early in the natural history of the disease (24, 47, 48) (Fig. 1). Of note, the same insulin signaling defects that are present in skeletal muscle of individuals with T2DM and individuals with obesity (19, 23, 44, 49) (Fig. 1) have been demonstrated in arterial vascular smooth muscle cells (20–23, 28). Not surprisingly, endothelial dysfunction, which reflects nitric oxide deficiency, is a characteristic feature of insulin-resistant states, including diabetes, prediabetes, and obesity (50–52), and is a central mechanism linking insulin resistance and ASCVD at the cellular level. Insulin resistance also stimulates endothelin-1 production, further promoting increased vasoconstrictor tone and atherogenesis (53).

In summary, the basic molecular insulin signaling defect that is responsible for impaired glucose metabolism in insulin-resistant individuals is intimately related to the development of coronary atherogenesis, and the atherogenic process is exacerbated by the hyperinsulinemia that occurs as the β-cell attempts to compensate for the defect in insulin action (Fig. 1).

Hyperinsulinemia and atherosclerosis

In vitro and *in vivo* studies have demonstrated that insulin, especially at high concentrations, can

accelerate the atherosclerotic process by multiple mechanisms, including (i) stimulation of *de novo* lipogenesis leading to increased very LDL synthesis/secretion (54–57) secondary to activation of SREBP-1C and inhibition of acetyl–coenzyme A carboxylase (58, 59), (ii) vascular smooth muscle cell growth and proliferation (19–22, 29, 30, 60, 61), (iii) activation of genes involved in inflammation (42, 61–64), (iv) increased collagen synthesis (41, 42, 65), and (v) enhanced LDL cholesterol transport into arterial smooth muscle cells (66, 67). Consistent with these *in vitro* actions of insulin, many *in vivo* studies have demonstrated that chronic insulin administration in chickens (68), rabbits (69), and dogs (70) accelerates the atherogenic process. Furthermore, insulin infusion for 7 to 10 days, while maintaining euglycemia, leads to the development of hypertension (71), whereas short-term physiologic hyperinsulinemia in humans causes marked sodium retention (72). Lastly, insulin therapy in humans uniformly is associated with weight gain (73, 74), often in association with the emergence of diabetic dyslipidemia and hypertension (75). Obesity is an insulin-resistant state (25, 26), is the primary factor responsible for the current epidemic of diabetes, and is a major risk factor for CVD (76, 77). Deposition of fat in the arterial wall causes inflammation (64, 78, 79), which directly promotes atherogenesis (80–83) and causes endothelial dysfunction (84), which is associated with accelerated atherosclerosis and insulin resistance (85, 86). The ORIGIN study (87) commonly is cited as proof that insulin does not promote atherosclerosis. However, the mean insulin replacement dose in the ORIGIN study was ~34 U/d, which is close to the daily insulin secretory amount (~30 to 35 U/d) in NGT individuals (88). In contrast, many patients with T2DM require >100 U/d to normalize the HbA1c (<6.5% to 7.0%) (73, 89–91), and the resultant high insulin levels are capable of activating the multiple atherogenic and inflammatory pathways, as described above. As an example, in the study of Henry *et al.* (73) the mean daily insulin dose required to reduce the HbA1c from 7.7% to 5.1% was 100 ± 24 U/d and was associated with a weight gain of 8.6 kg during a period of 6 months.

It has been suggested that insulin resistance may be a defense mechanism that protects the CV system from nutrient overload, especially in high-risk subjects with long-standing diabetes and severe insulin resistance (92). In such individuals the authors argue that high-dose insulin therapy would increase myocardial lipid content (93), overloading the electron transport chain, and would result in mitochondrial dysfunction and increased generation of reactive oxygen species (ROS) (93, 94). Furthermore, the increased glucose flux would (i) cause glucolipotoxicity, further contributing to the mitochondrial dysfunction, and cause endoplasmic reticulum stress (94, 95), (ii) increase flux into the polyol and hexosamine pathways (95, 96), and (iii) activate the inflammasome (97). Although this may be a relevant consideration in long-standing patients with T2DM following the initiation of high-dose insulin therapy, it is difficult to image such a scenario in the prediabetic stage and early in the natural history of T2DM, when insulin resistance is severe and already maximally established (25, 26). Furthermore, the atherosclerotic process targets the vascular (arterial) smooth muscle cells, and the nutrient overload hypothesis may be more relevant to myocardial dysfunction and heart failure (see the

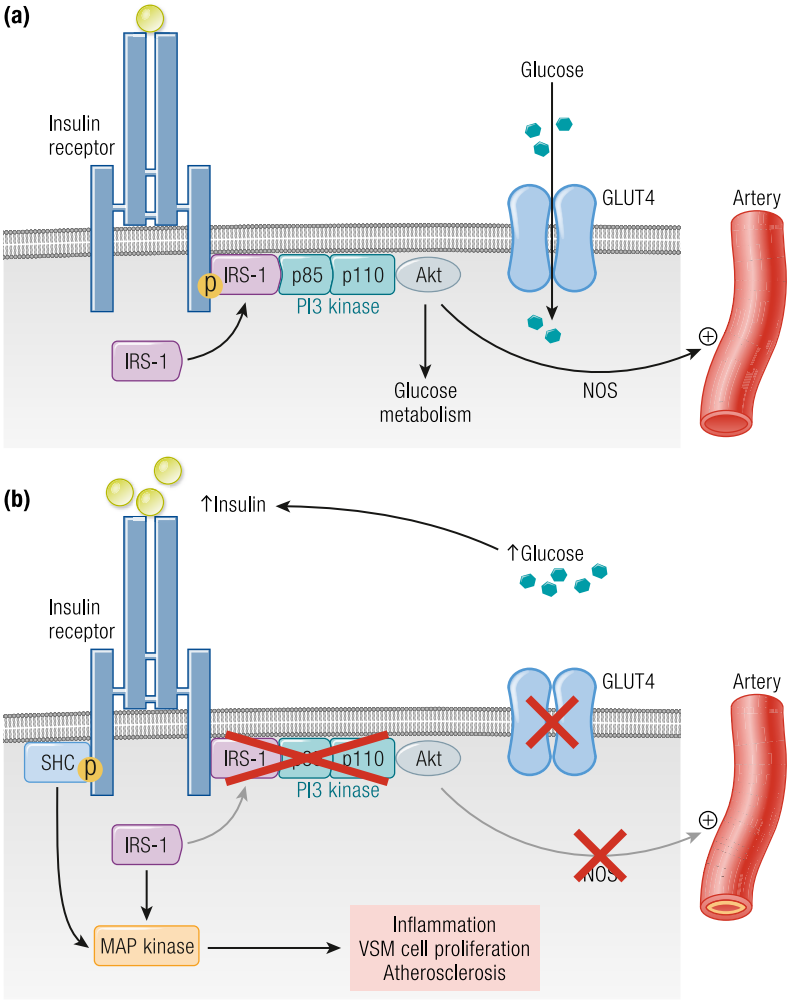


Figure 1. (a) Insulin signal transduction system in individuals with normal glucose tolerance (see text for a detailed discussion). NOS, nitric oxide synthase. (b) In individuals with T2DM, insulin signaling is impaired at the level of IRS-1, leading to decreased glucose transport/phosphorylation/metabolism and impaired nitric oxide synthase activation/endothelial dysfunction. At the same time, insulin signaling through the MAPK pathway remains normally sensitive to insulin. The compensatory hyperinsulinemia (due to insulin resistance in the IRS-1/PI3K pathway) results in excessive stimulation of the MAPK pathway, which is involved in inflammation, vascular smooth muscle cell proliferation, and atherogenesis (see text for a more detailed discussion). SHC, Src homology collagen. [DeFronzo RA: From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 58:773–795, 2009. American Diabetes Association, Diabetes, 2009. Copyright and all rights reserved. Material from this publication has been used with the permission of the American Diabetes Association.]

subsequent discussion) than to the development of atherosclerosis.

Multiple studies have demonstrated that insulin resistance is a characteristic feature of nonalcoholic fatty liver disease (NAFLD), even in lean subjects with the disease, and that the insulin resistance involves muscle, liver, and adipose tissue (98–100). Furthermore, patients with nonalcoholic steatohepatitis (NASH) are at increased risk for CVD (101, 102). In addition to insulin resistance, individuals with NASH are characterized by multiple other cariovascular risk factors, including dyslipidemia and inflammation (99).

IRS: a cardiometabolic cluster of CV risk factors

Insulin resistance is associated with a cluster of CV/metabolic abnormalities, which collectively have been referred to as the IRS (26, 27, 103) (Table 1). Each individual component of the IRS is an independent risk factor for ASCVD and, as discussed previously, the molecular etiologies of the insulin resistance and compensatory hyperinsulinemia promote vascular smooth muscle growth and proliferation, inflammation, and atherogenesis (16–18, 26).

CV risk factors and the IRS

Hypertension, a major risk factor for ASCVD, is a characteristic feature of the IRS, and multiple studies have demonstrated that insulin resistance is a characteristic feature of hypertension (103–108). Reduced plasma HDL cholesterol, elevated plasma triglycerides, and small dense LDL cholesterol particles each are independent risk factors for ASCVD (27, 103, 109, 110) and are causally related to the underlying insulin resistance (26, 108, 111–113). Collectively, these three lipid disturbances represent the characteristic diabetic dyslipidemia (108–113). Nitric oxide is a potent vasodilator and antiatherogenic agent (114) and is deficient in insulin-resistant subjects (115–117), contributing to the accelerated atherosclerosis (86, 118–120). Furthermore, insulin-resistant states, such as T2DM, are associated with a number of clotting factor abnormalities, including increased PAI-1, elevated fibrinogen levels, and increased platelet stickiness, which are important CV risk factors and are related to the underlying insulin resistance in nondiabetic subjects as well as in subjects with diabetes (121, 122).

Obesity, especially visceral obesity, is a classic insulin-resistant state (25, 26, 110), is strongly related to the development of ASCVD (74, 75, 123), and is the major factor driving the epidemic of T2DM (124, 125). The development of insulin resistance in individuals with obesity is intimately related to the concept of lipotoxicity (Table 2), which refers to the deleterious effect of excess tissue and plasma lipid accumulation that occurs when energy intake exceeds energy consumption and from *de novo* lipogenesis (25–27). Elevated plasma free fatty acid (FFA) levels are an integral component of the IRS and lead to (i) increased tissue lipid deposition, including in vascular tissues (126–131), (ii) activation of inflammatory pathways (132), and (iii) induction of insulin resistance (132–135). Excess fat accumulation in adipocytes incites inflammation, enhances the secretion of insulin resistance–provoking and proinflammatory/prothrombotic cytokines (TNFα, PAI-1, resistin) that promote atherogenesis, and inhibits the secretion of the insulin-sensitizing molecule adiponectin (127). Altered fat topography, especially excess visceral fat accumulation, is strongly associated with ASCVD and insulin resistance (122, 127–137), although in humans the underlying mechanisms responsible for this association have yet to be defined. In rodents, removal of visceral fat prevents insulin resistance (138, 139) and, interestingly, prolongs longevity (140). Intra-abdominal adipocytes manifest both accelerated lipogenesis and enhanced lipolysis, as well as increased secretion of inflammatory cytokines (141, 142). Most recently, NAFLD, which is present in ~50% to 60% of patients with T2DM, has been shown to be a major independent CV risk factor (143, 144). Whether NAFLD leads to the development of insulin resistance or results from insulin resistance is a subject of debate (99, 100). Intramyocardial fat deposition and increased pericardial and epicardial fat also have been shown to be associated with insulin resistance (145–150), and progressively increasing pericoronary fat volumes strongly correlate with the number of IRS components (105). Furthermore, the insulin-sensitizing agent rosiglitazone markedly enhances myocardial insulin sensitivity in insulin-resistant patients with T2DM (151). Diastolic dysfunction also is strongly correlated with insulin resistance (145, 152, 153) and is improved by the insulin-sensitizing agent pioglitazone (145).

Low-grade inflammation is a well-established feature of the IRS, obesity, and T2DM (154–156). Adipose tissue, and to lesser extent muscle tissue, is infiltrated by proinflammatory M2 macrophages (157). The IκB/NF-κB and TLR-4 pathways (64, 158, 159), as well as the MAPK and c-Jun N-terminal kinase pathways (19–21), are stimulated, and all of these inflammatory abnormalities are associated with insulin resistance and accelerated atherosclerosis (26). Prospective studies have demonstrated that in individuals with the IRS, increasing levels of high-sensitivity C-reactive protein add independent prognostic information about future CV risk, confirming the relationship between inflammation, insulin resistance, and CV events (160).

The results of the Relationship Between Insulin Sensitivity and Cardiovascular Disease (RISC) study are especially informative (33). Using the gold standard euglycemic insulin clamp (161), these investigators demonstrated that insulin resistance was closely associated with the load of CV risk factors (11). The 3-year follow-up of the RISC study demonstrated that

the presence and severity of insulin resistance predicted deterioration of glucose tolerance (31), risk of elevated systolic blood pressure in women (162), and development of albuminuria (163), a known risk factor for CVD (164, 165). Cross-sectional data from the RISC study confirmed the relationship between insulin resistance and other CV risk parameters, including fatty liver and carotid intima–media thickness (IMT), known predictors of CVD in populations with and without diabetes (166, 167). Low-grade inflammation also has been reported to be a component of the cardiometabolic risk profile (168). Insulin resistance, obesity, central fat accumulation, and a hyperinsulinemic response during an oral glucose tolerance test all were independent contributors to the clustering of cardiometabolic risk factors in the RISC study (33).

Quantitative assessment of insulin resistance in the IRS

Studies by Reaven (27, 104), Stienstra *et al.* (97), and DeFronzo and colleagues (25, 26, 32, 36, 103, 107, 108, 169) have provided abundant proof that insulin resistance is a characteristic feature of each individual component of the IRS (Table 1). Using the euglycemic insulin clamp to quantitate insulin sensitivity, nondiabetic individuals with obesity and lean individuals with T2DM have been shown to be markedly insulin resistant, and the defect in insulin action primarily affects the nonoxidative (glycogen synthetic) pathway of glucose disposal (16, 25, 32, 48, 170–172) (Fig. 2). Furthermore, both nondiabetic individuals with obesity and lean individuals with T2DM manifest a moderate to severe defect in the insulin signaling pathway (Fig. 1) (16, 19, 25, 26, 173, 174). Prediabetic individuals with impaired glucose tolerance also manifest insulin resistance involving the glycogen synthetic pathway and share the same insulin signaling defect as subjects with obesity and with T2DM (39, 174, 175). Similarly, hypertension (102–106) and diabetic dyslipidemia (increased plasma triglyceride and FFA concentrations, decreased HDL cholesterol, small dense LDL particles) (27, 108–111, 176) are insulin-resistant states characterized by impaired insulin-mediated glucose disposal involving the nonoxidative pathway of glucose disposal and reduced insulin signaling. Hypercholesterolemia *per se* is not an insulin-resistant state but, when present, acts synergistically with other components of the IRS to accelerate atherogenesis (177–179). As discussed previously, multiple studies (1–3, 27, 143) have demonstrated that normal glucose-tolerant individuals with coronary artery disease are as resistant to insulin as are individuals with T2DM and nondiabetic individuals with obesity (Fig. 2). Similar to skeletal muscle, the myocardium of individuals with T2DM with and without coronary artery disease and nondiabetic individuals with coronary artery disease (144, 145, 151) has been shown to be resistant to insulin-stimulated glucose disposal. The demonstration that nondiabetic individuals with the IRS are at the same high risk for experiencing a CV event as individuals with diabetes (4) emphasizes the importance of recognizing insulin resistance as a major CV equivalent that deserves specific therapy with insulin-sensitizing agents (see the subsequent discussion).

Table 1. Syndrome of Insulin Resistance

• Obesity (especially visceral)
• Glucose intolerance (impaired glucose tolerance, impaired fasting glucose, T2DM)
• Hypertension
• Dyslipidemia (high triacylglyerol, low HDL, small dense LDL particles)
• Endothelial dysfunction
• Prothrombotic state
• NAFLD/NASH
• Lipotoxicity
• Inflammation
• ASCVD
• Hyperinsulinemia
• Insulin resistance

Insulin resistance and ASCVD: unexplained CV risk

Despite the identification of multiple pathophysiologic disturbances (Table 1), a large percentage of the risk for ASCVD in patients with T2DM remains undefined (180, 181). This is exemplified by the study of D'Agostino *et al.* (182), who analyzed six large prospective CV epidemiologic studies (Fig. 3). Using the Framingham Cardiovascular Risk Engine (183), they reported that the classic risk factors for ASCVD only could explain 69% of observed CV events, leaving 31% unexplained. Similarly, in the ARIC study (10), which examined the relationship between carotid IMT and recognized CV factors (hypertension, dyslipidemia, obesity, impaired glucose tolerance), only ~70% of the increase in carotid IMT could be accounted for (Fig. 3). What is responsible for the unaccounted ~30% of the risk for CVD (182, 183) and carotid IMT (10)? We postulate that insulin resistance (Fig. 2) and the basic molecular etiology of the insulin resistance (Fig. 1) account for most of this unaccounted CV risk.

Although utilization of medications, such as angiotensin-converting enzyme inhibitors, other antihypertensive medications, statins, and platelet inhibitory agents, has reduced the incidence of atherosclerotic CV complications, there remain as-of-yet unidentified CV risk factors, in addition to the classical risk factors, that contribute to the high CV risk among

Table 2. Lipotoxicity

• Elevated plasma nonesterified fatty acids
• Increased tissue fat content
• Altered fat topography
• Adiposopathy

optimally treated patients. Medical therapy typically is directed against a single risk factor or multiple CV risk factors and does not specifically target the underlying pathophysiological defect, that is, insulin resistance, that is responsible for the generation of the cardiometabolic abnormality. This is evident from a recent publication from the National Swedish Registry (180) in which CV mortality declined significantly in individuals with T2DM from 1998 to 2014, but remained markedly higher and reached a plateau compared with NGT individuals. We hypothesize that failure to correct the cellular/molecular abnormality responsible for the insulin resistance explains, at least in part, the failure to reduce the CV risk to a level observed in the nondiabetic population.

Insulin resistance and the IRS also have been shown to be associated with subclinical ASCVD. In a retrospective analysis of 10,153 occupational patients, insulin resistance was independently associated with the coronary calcium score, which is a strong predictor of coronary artery disease, and this association persisted after adjustment for other CV risk factors and preexisting CVD (184). Other studies, including the Framingham Offspring Study, also have demonstrated a strong association between the coronary calcium score, insulin resistance, and inflammatory cytokines in nondiabetic individuals (185–188). A similar association between insulin resistance and coronary artery disease in nondiabetic individuals has been demonstrated with ultrasound (189).

Insulin resistance and heart failure

The IRS also has been reported to be associated with an increased incidence of heart failure in individuals without diabetes and without a prior history of myocardial infarction (190). Similar results have been reported from a large community-based sample of elderly adults (191). Different mechanisms may explain the association between insulin resistance and heart failure. Insulin is a growth factor and has been shown to impact cardiac structure (192, 193). Furthermore, insulin activates the sympathetic nervous system and enhances the ability of angiotensin II to activate the MAPK pathway (194, 195). In the Cardiovascular Health Study, a positive association between the fasting plasma insulin concentration vs adverse echocardiographic features and risk of subsequent heart failure was reported (196). Similar results were reported in the ARIC study in patients with and without antecedent myocardial infarction (10). Insulin resistance, assessed by HOMA-IR, also has been shown to be associated with peripheral arterial disease (197).

Insulin Resistance, T2DM, and CVD

T2DM is a cardiometabolic disease that affects both the microvasculature (retinopathy, nephropathy, neuropathy) and macrovasculature (heart attack, stroke) (25, 26). The microvascular complications are related to two factors: (i) the magnitude of elevation in blood glucose concentration, as reflected by the HbA1c, and (ii) the duration of elevation of the HbA1c (198, 199). In contrast, the macrovascular complications are only weakly related to the level of glucose control (199) and represent the major cause of mortality, with heart attack and stroke accounting for ~75% of all deaths (200, 201). The failure of intensive glycemic control in the ACCORD (89), ADVANCE (90), and VADT (91) studies to significantly reduce heart attack and stroke provides further support that hyperglycemia is a weak risk factor for CVD, although it could be argued that it would be difficult for any glucose-lowering therapy to slow the progression of and reverse advanced fibrotic, lipid-laden plaques. Furthermore, insulin was the primary antidiabetic agent used in these prior trials (89–91), and even small increases in the fasting plasma insulin concentration are associated with the induction of severe insulin resistance (26, 47, 48) and weight gain (73, 74), which are risk factors for ASCVD (26, 76, 77). Furthermore, when used in high doses, insulin can accelerate the atherogenic process (see the previous discussion). Of particular importance, it currently is well established that events portending accelerated atherosclerosis are under way long before the formal diagnosis of diabetes is established, that is, in the prediabetic state as well as in insulin-resistant NGT subjects (5–11, 202–207).

Insulin Resistance in CVD and Therapeutic Interventions

Lifestyle intervention

Sedentary lifestyle (208) and obesity (209) are insulin-resistant states associated with the IRS and increased CV mortality (76, 210–212). Consequently, weight loss and increased physical activity are recommended both by the American Heart Association (213) and American Diabetes Association (214) to reduce CV events and prevent the development of T2DM by improving insulin sensitivity and preserving β-cell function.

The Look AHEAD trial was a randomized controlled study designed to compare an intensive lifestyle intervention vs a diabetes support and education program in patients who are overweight/obese with T2DM on the development of CVD. Although modest benefits on CV risk factors (improved biomarkers of glucose and lipid control, less sleep apnea, reduced liver fat, increased fitness, and enhanced insulin sensitivity) and improved quality of life were observed, the trial was stopped because of lack of CV benefit after a median follow-up of 9.6 years (215, 216). During the first year of the Look AHEAD trial, subjects lost ~8.6% of body weight, and waist circumference decreased by 8 cm. At the study's end, the percentage weight loss was ~6.0% and the reduction in waist circumference was only 2 cm. This weight regain and increase in waist circumference (*i.e.*, visceral fat) could have obscured any CV benefit.

The Diabetes Prevention Program employed an intensive lifestyle intervention to delay/prevent T2DM in participants with impaired glucose tolerance, a group at high risk for ASCVD (217). Partipants lost ~7 kg during the first year, the incidence of T2DM was reduced by 58% after 3 years, and the CV risk profile improved (218). However, by 10 years, participants had regained ~5 kg and no reduction in CV events was observed (217). As reviewed in two meta-analyses, a major problem with lifestyle interventions has been the inability to sustain the weight loss on a long-term basis (219, 220). The results of a meta-analysis sugest that implementation of a Mediterranean diet can improve adherence and is associated with favorable effects on multiple components of the IRS (221). Consistent with this, a recent study from Spain provided evidence that the Mediterranean diet caused a significant reduction in CV events (222).

Insulin-sensitizing antidiabetic medications: thiazolidinediones

The only true sensitizing antidiabetic agents are the thiazolidinediones (TZDs) (25, 26, 126, 151, 169, 173, 223–225) and, of these, the only one that is readily available worldwide is pioglitazone. Metformin is not a true insulin-sensitizing agent (225, 226). Two large prospective clinical trials (227–229) and two prospective anatomical studies (230, 231) have demonstrated that pioglitazone reduces CV events (227–229) and promotes the regression of atherosclerotic lesions (230, 231), respectively.

The Prospective Pioglitazone Clinical Trial in Microvascular Events (PROactive) study (227) was the first study to demonstrate the beneficial effect of any antidiabetic agent to reduce CV events. In 5238 patients with T2DM with a prior CV event and who were treated with pioglitazone or placebo for a period of 34.5 months, the "main secondary" major adverse CV event (MACE; CV mortality, nonfatal myocardial infarction, nonfatal stroke) endpoint was reduced by 16% [hazard ratio (HR), 0.84; $P < 0.027$], although the primary endpoint (3-point MACE plus coronary and leg revascularization) did not reach statistical significance (HR, 0.90; 95% CI, 0.80 to 1.02; $P = 0.09$) because of an increase in leg revascularization. However, it is well established that peripheral vascular disease is refractory to all therapeutic interventions, including glucose-lowering, lipid-lowering, and blood pressure–lowering therapy (232, 233). Furthermore, by preventing death, myocardial infarction, and stroke, pioglitazone would make more people available for leg revascularization (234). Analysis of all double-blind, placebo-controlled pioglitazone studies (228) revealed a decrease in CV events in individuals without a prior history of CV events (HR, 0.78; $P = 0.005$). Consistent with these observations, pioglitazone reduced coronary atherosclerotic plaque volume in the PERISCOPE trial (231) and decreased carotid IMT in the CHICAGO trial (230). In the IRIS study (229), 3876 nondiabetic, insulin-resistant (HOMA-IR >3.0) individuals with a recent (≤6 months) stroke or transient ischemic attack were treated with pioglitazone or placebo for 4.8 years. Pioglitazone-treated subjects experienced a 24% decrease (HR, 0.76; $P = 0.007$) in recurrent stroke plus CV events, and HOMA-IR declined by 24% ($P < 0.0001$).

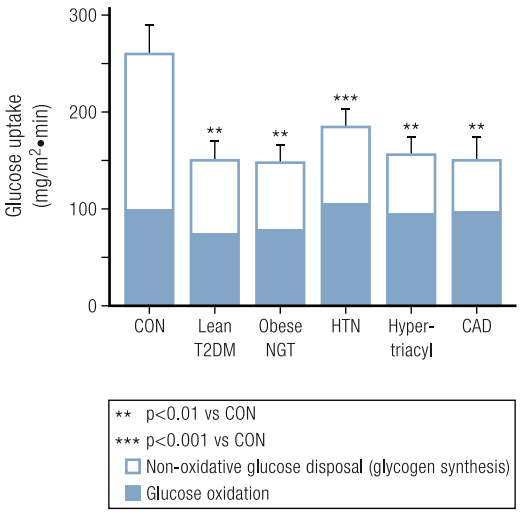


Figure 2. Insulin-stimulated glucose disposal (40 mU/m^2·min euglycemic-hyperinsulemic clamp) in lean healthy controls (CON), NGT participants with obesity (NGT), lean drug-naive individuals with T2DM (T2DM), lean normal glucose-tolerant participants with hypertension (HTN), NGT participants who are hypertriacylglycerolemic (Hypertriacyl) participants, and nondiabetic subjects with coronary artery disease (CAD). Open (white) sections represent nonoxidative glucose disposal (glycogen synthesis); filled (black) sections represent glucose oxidation. **$P < 0.01$ vs CON; ***$P < 0.001$ vs CON. To change glucose uptake into SI units, divide by 180. [Adapted with permission from DeFronzo RA: Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. Diabetologia 2010;53:1270–1287. Illustration presentation copyright Endocrine Society 2019.]

Unfortunately, the correlation between improved insulin sensitivity and decrease in CV events was not reported, but such an analysis would be of great clinical and pathophysiologic importance. In a recently published real-world study in Finland (235) involving 33,054 subjects with T2DM treated with pioglitazone and a similar number of propensity-matched individuals, pioglitazone reduced CV risk by 42% and non–CV risk by 37%. Finally, a meta-analysis of randomized control trials reported that pioglitazone significantly reduced the MACE endpoint in people with insulin resistance, prediabetes, and T2DM (236).

In summary, multiple studies demonstrate that the insulin-sensitizing antidiabetic agent pioglitazone reduces atherosclerotic CV events in association with enhanced insulin sensitivity. Improved glucose control cannot explain the reduction in stroke and myocardial infarction because the decrease in HbA1c was quite modest in the PROactive study (227), and subjects in the IRIS trial were not diabetic (229). Pioglitazone can prevent atherosclerotic CV complications by multiple mechanisms: (i) reversal of the basic molecular disturbances responsible for the insulin resistance and accelerated atherosclerosis, including inhibition of the MAPK pathway and stimulation of the IRS-1/PI3K pathway, leading to enhanced insulin sensitivity and a reduction in hyperinsulinemia (25, 26, 126, 173, 237–239); (ii) suppression of multiple inflammatory pathways (IκB/NF-κB, TLR-4, TNFα) and reduced generation of ROS (127, 155, 156, 240–245) that are associated with insulin resistance; (iii) correction of diabetic dyslipidemia (decrease in plasma triacylglycerol, increase in HDL cholesterol, conversion of small dense LDL particles to larger more buoyant, less dense LDL particles), which is associated with amelioration of the insulin resistance (246, 247); (iv) reduction in the plasma FFA concentration (94, 126, 237–239) and mobilization of FFA out of tissues (126–128, 224, 238, 239, 248), including arterial smooth muscle cells; (v) improved endothelial dysfunction and enhanced nitric oxide generation, which are directly related to the insulin-sensitizing effect of the TZDs (249–251); (vi) increased production of the insulin-sensitizing adipocytokine adiponectin (127, 238, 252–254); (vii) stimulation of peroxisome proliferator–activated receptor γ (PPARγ) (223, 242, 243), the master regulator of mitochondrial biogenesis (243); this leads to enhanced intracellular fat oxidation and reduced skeletal and arterial smooth muscle fat content, resulting in improved insulin sensitivity, reduced inflammatory cytokines and ROS generation, and inhibition of atherogenesis (241, 242); and (viii) reduced plasma FFAs and intramyocellular fatty acyl–coenzyme A derivatives, which are intimately associated with the development of insulin resistance and activation of intracellular pathways involved in atherogenesis (19, 126, 127, 132–134, 224, 240). Although not well appreciated, analysis of atherosclerotic plaques reveals large amounts of nonesterified fatty acids (81–83), which stimulate inflammatory pathways involved in atherogenesis (64, 78, 79, 255, 256).

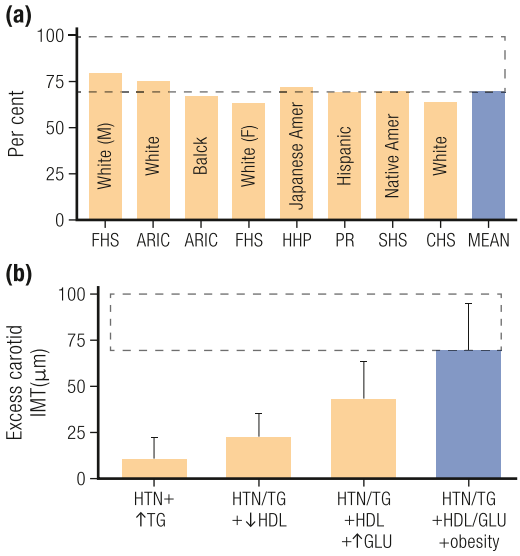


Figure 3. (a) Predictive value (%) of CVD (ASCVD) using the Framingham risk engine in the Framingham Heart Study (FHS), the ARIC study, the Honolulu Heart Program (HHP), the Puerto Rico Heart Health Program (PR), the Strong Heart Study (SHS), and the Cardiovascular Health Study (CHS). On mean, the Framingham risk engine predicts only 69% of the risk of a future CV event. (b) Excess carotid IMT in relationship to the individual components of the insulin resistance (metabolic) syndrome as listed. Amer, American; F, female; GLU, glucose; HTN, hypertension; M, male; TG, triacylglycerol. Fields in dotted lines represent the unexplained risk [(a), 31%; (b), 30%]. [(a) Adapted with permission from D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P: Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 286:180–187, 2001. Illustration presentation copyright Endocrine Society 2019. (b) Adapted with permission from Golden SH, Folsom AR, Coresh J, Sharrett AR, Szklo M, Brancati F: Risk factor groupings related to insulin resistance and their synergistic effects on subclinical atherosclerosis: the Atherosclerosis Risk in Communities Study. Diabetes 51:3069–3076, 2002. Illustration presentation copyright Endocrine Society 2019.]

Th use of TZDs has been limited in part by uncertainty about the risk for development of heart failure, especially in susceptible patients with diastolic dysfunction (257). In the PROactive study involving 5238 patients with T2DM with a previous CV event or multiple CV risk factors, an increased incidence of "heart failure" was observed, but these patients did not experience any increase in CV events (227, 258, 259). Heart failure in patients with T2DM is an ominous sign with a 5-year survival rate of 12.5% (259). Therefore, it is likely that these individuals really had peripheral edema, not heart failure, and that following diuresis the benefical CV effects of pioglitazone were observed. Although fat weight gain is common with

pioglitazone, the HbA1c consistently declines, and the greater is the weight gain, the greater are the improvements in insulin secretion and insulin sensitivity (126, 239, 260). Of note, increased weight gain in the PROactive study was associated with reduced CV mortality (227). Lastly, the 10-year follow-up of a Food and Drug Administration (FDA)–mandated study involving 193,099 patients failed to demonstrate any association of pioglitazone with bladder cancer (261).

CV outcome trials with rosiglitazone have been more controversial. Similar to pioglitazone, rosiglitazone is a potent insulin sensitizer (173, 262), improves β-cell function (260, 263, 264), effectively reduces and maintains the reduction in HbA1c [reviewed in Ref. (1)] for up to 5 years (263), and reduces circulating levels of inflammatory cytokines (265, 266). In a meta-analysis of 42 trials by Nissen and Wolski (267), rosiglitazone was associated with a significant increase (HR, 1.43; $P = 0.03$) in myocardial risk and borderline significant increase in ASCVD-related death (HR, 1.64; $P = 0.06$). A retrospective data analysis by GlaxoSmithKline (268) confirmed that the incidence of myocardial infarction in rosiglitazone-treated patients with T2DM was increased (HR, 1.31; $P = 0.05$), and an FDA analysis (269) of individual patient data provided by GlaxoSmithKline demonstrated that rosiglitazone was associated with a significant increase in all ischemic events (HR, 1.40; 95% CI, 1.1 to 1.8). In the only prospective trial (RECORD) with rosiglitazone (270) in 4447 patients with T2DM (mean follow-up of 5.5 years), the HR for the primary endpoint (hospitalization or death from CV causes) was 1.08 (95% CI, 0.89 to 1.31). In the recently published VADT (271), rosiglitazone was associated with a significant decrease in the risk of the ASCVD composite outcome (any major CV event) (HR, 0.63; 95% CI, 0.49 to 0.81). In the VICTORY study (272), which evaluated the atherosclerotic burden via ultrasound in 193 patients with T2DM, no difference in atherosclerosis progression was observed between rosiglitazone and placebo. In the DREAM trial (273), although not designed to evaluate ASCVD events, a trend for increased myocardial infarction was observed in the rosiglitazone group (HR, 1.65; 95% CI, 0.79 to 4.03). In a meta-analysis of trials in which rosiglitazone was added to insulin-treated patients with T2DM, no difference in CV events was observed compared with insulin monotherapy (274).

Overall, the results do not support a beneficial effect of rosiglitazone on adverse CV events in patients with T2DM, and, because of CV safety concerns, the European Medicine Agency removed rosiglitazone from the market (275), whereas the FDA placed severe restrictions on its use (276). What explains the beneficial results of pioglitazone on ASCVD, whereas the results with rosiglitazone can, at best, be viewed as neutral? One obvious difference is the divergent effects of the two drugs on plasma lipid levels (247, 277, 278). Rosiglitazone increases total and LDL cholesterol levels and has no significant effect on the plasma triglyceride concentration. In contrast, pioglitazone is neutral with respect to total and LDL cholesterol and significantly reduces plasma triglyceride levels. Furthermore, pioglitazone reduces the concentration of small atherogenic LDL particles (278) and lipoprotein(a) levels (279). Although both TZDs increase HDL cholesterol, the increase with pioglitazone is approximately twice as great as that with rosiglitazone (247, 280). These different effects on the plasma lipid profile most likely are explained by the overlapping but also unique gene expression of the two TZDs and by the ability of pioglitazone to partially activate PPARα (280, 281). Another difference between the two TZDs is the consistent improvement in endothelial function observed with pioglitazone vs the more inconsistent results noted with rosiglitazone (282). In summary, it could be argued that if it were not for rosiglitazone's adverse effects on lipid metabolism, the drug's insulin-sensitizing effect might have resulted in a decrease in adverse CV events.

Metformin

Metformin is commonly referred to as an insulin-sensitizing agent. However, studies utilizing the euglycemic insulin clamp have failed to demonstrate that metformin enhances insulin sensitivity in peripheral tissues, including muscle (225, 226, 283–285), in the absence of weight loss (Fig. 4). The average weight loss after 6 to 12 months of metformin therapy is ~1.5 to 2.0 kg, which can account for the observed improvement in insulin sensitivity reported in some studies. Moreover, as reviewed by Natali and Ferrannini (225), in contrast to the uniform improvement in insulin action with TZDs, reports of enhanced insulin sensitivity with metformin are more sporadic and, when observed, changes in body weight were not provided. As suggested from previous studies, the biguanide's major mechanism of action in T2DM is the suppression the elevated rate of hepatic gluconeogenesis (283, 284) (Fig. 4). It is noteworthy that following the intravenous administration of radiolabeled metformin, using positron emission tomography, the biguanide can be shown to accumulate in liver and distal small bowel and not in muscle (286). There remains uncertainty about whether metformin reduces risk of CVD among patients with T2DM, for whom it is recommended as first-line drug. In the UKPDS (287), diabetic patients randomized to metformin experienced a 39% relative risk reduction in fatal/nonfatal myocardial infarction (metformin, 11% vs conventional therapy, 18%) and a 36% relative risk reduction in all-cause mortality (metformin, 13.6% vs conventional therapy, 20.6%). However, the patient population consisted of only 342 patients with obesity with T2DM, and the number of CV events was very small. By today's standards, the results of the UKPDS

would not be accepted as evidence of a CV benefit of metformin. Moreover, a beneficial effect on CV events has not been observed in other clinical studies with metformin, that is, the ADOPT study (263), which included twice the number of patients as the UKPDS (n = 818). On the contrary, subjects receiving metformin in the ADOPT study experienced more CV events than did subjects receiving glyburide, although this difference was not statistically significant. Similarly, in metformin-treated subjects who also were receiving concomitant therapy with a sulfonylurea in the UKPDS, a significant increase in CV events was reported (288). This emphasizes the problem of interpreting results from studies that are markedly underpowered to detect a clinically significant difference in cardiac event rates. In a meta-analysis of randomized controlled trials with patients with T2DM comparing any dose and preparation of metformin with placebo or lifestyle intervention, metformin was slightly favored in all outcomes, with the exception of stroke (289); however, no endpoint achieved statistical significance (all-cause mortality HR, 0.96; CV death HR, 0.97; myocardial infarction HR, 0.89; stroke HR, 1.04; peripheral vascular disease HR, 0.81).

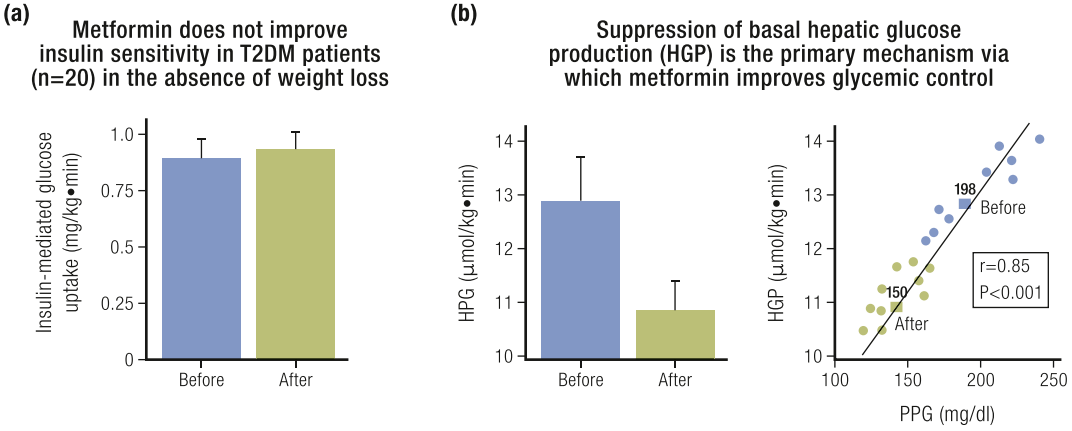
In summary, at the present time it is unclear whether metformin has any CV benefit.

Sodium-glucose cotransporter 2 inhibitors

In the EMPA REG OUTCOME trial (290) the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin reduced the MACE endpoint by 14% (HR, 0.86; $P = 0.04$) and hospitalization for heart failure by 35% (HR, 0.65; $P = 0.002$) in 7020 high-risk individuals with T2DM with a prior CV event. The reduction in 3-point MACE primarily was driven by a 38% reduction in CV mortality, whereas myocardial infarction and stroke did not change significantly. Potential mechanisms responsible for the marked reduction in CV mortality have been reviewed (291, 292). Because the reduction in CV events was evident within 1 to 3 months after the start of empagliflozin, it is unlikely that the early beneficial CV effects can be explained by an antiatherogenic mechanism. The improvement in insulin sensitivity following a treatment with SGLT2 inhibitors has been observed in animal diabetic models (293, 294) and human T2DM studies (295) within 2 weeks. The most likely explanation for the increase in insulin sensitivity is the reduction in plasma glucose concentration resulting in amelioration of glucotoxicity. However, the improvement in insulin sensitivity was modest, ~25% to 30%, and unlikely to explain the rapid and dramatic reduction in CV mortality and hospitalization for heart failure. SGLT2 inhibitors block Na^+-glucose cotransport in the proximal tubule, resulting in a modest decrease in the intravascular volume and preload reduction (291, 296). The SGLT2 inhibitors also reduce systolic/diastolic blood pressure and decrease aortic stiffness (291, 296), resulting in substantial afterload reduction. These hemodynamic effects are rapid in onset and most likely explain, at least in part, the marked reduction in CV mortality observed within 1 to 3 months after initiation of empagliflozin in the EMPA REG OUTCOME trial. Consistent with this scenario, empagliflozin treatment of 3 months decreased left ventricular mass and improved diastolic dysfunction (297). However, the slope of the curve relating the incidence of CV events to time changes significantly after year 1 of empagliflozin therapy, suggesting that mechanisms other than hemodynamic ones contribute to the CV benefits reported in the EMPA REG OUTCOME trial (290). Most recently, the results of CANVAS/CANVAS-R (298) have been published and, similar to the EMPA REG OUTCOME trial, demonstrated a 13% decrease (HR, 0.87; $P < 0.001$) in the MACE endpoint, although the reduction in CV mortality was modest and not statistically significant. A surprising result in the CANVAS study was the almost twofold increased risk for lower-extremity amputations with canagliflozin compared with placebo (HR, 1.97; 95% CI, 1.41 to 2.75; $P < 0.001$). The amputations were observed more often in men and in patients with a history of prior amputation, neuropathy, and peripheral vascular disease (298). It is noteworthy that in the recently published CREDENCE study (299), which demonstrated a 34% decrease in the renal composite outcome [dialysis, kidney transplantation, renal death, eGFR < 15 mL/min*1.73 m^2, doubling of serum creatinine (HR, 0.66; 95% CI, 0.53 to 0.91; $P < 0.001$)], no increase in lower-extremity amputations was observed in individuals with T2DM who had manifest diabetic kidney on entry into the study. The metabolic effects of canagliflozin have been less well studied compared with dapagliflozin and empagliflozin (295, 300), but it is reasonable to expect that the reduction in plasma glucose concentration secondary to glucosuria would lead to amelioration of glucotoxicity and a modest improvement in insulin sensitivity. Nonetheless, as previously reviewed (291), we think that hemodynamic factors—decreased preload and afterload reduction—represent the most likely mechanism responsible for the beneficial effect of SGLT2 inhibitors on 3-point MACE. A number of other potential mechanisms have been put forward to explain the CV benefits of the SGLT2 inhibitors (291), of which the "ketone hypothesis" (301) has received considerable attention. However, at the present time all of these mechanisms remain unproven.

Recently, the results of the DECLARE study (302), which had two primary endpoints, were published. Hospitalization for heart failure plus cardiovascular mortality was significantly reduced (HR, 0.83; 95% CI, 0.73 to 0.95; $P = 0.005$), whereas MACE was not significantly reduced (HR, 0.93; 95% CI, 0.84 to 1.03; $P = 0.17$). In a subgroup analysis (303), diabetic individuals

Figure 4. Effect of metformin on insulin sensitivity and hepatic glucose production in T2DM. (a) Metformin has no effect to improve muscle insulin sensitivity (measured with euglycemic insulin clamp) in individuals with T2DM in the absence of weight loss. (b) The primary effect via which metformin reduces the HbA1c in T2DM is related to the suppression of hepatic glucose production via inhibition of gluconeogenesis (284). [Reproduced with permission from Cusi K, DeFronzo RA. Metformin: a review of its metabolic effects. Diabetes Reviews 6:89–131, 1998. ©1998 by the American Diabetes Association® Diabetes Review 6:89–131, 1998. Reprinted with permission from the American Diabetes Association®.]



with a prior MI experienced a 16% decrease in recurrent MI (HR, 0.84; 95% CI, 0.72 to 0.99; $P = 0.048$). These results are consistent with two real-world studies (CVD REAL-1 and CVD REAL-2), have shown that this SGLT2 inhibitor also reduces the MACE endpoint and CV mortality (304–306).

Glucagon-like peptide-1 receptor agonists and DPP4 inhibitors

Two glucagon-like peptide-1 (GLP-1) receptor agonists (RAs), liraglutide (LEADER study) (by 13%, $P = 0.01$) (307) and semaglutide (SUSTAIN-6 study) (by 26%, $P = 0.02$) (308), have been shown to significantly reduce 3-point MACE in a high CV-risk population with T2DM. In the LEADER study the decrease in CV events primarily was driven by a 22% reduction in CV mortality ($P = 0.007$), whereas nonfatal myocardial infarction (by 12%, $P = 0.11$) and nonfatal stroke (by 11%, $P = 0.30$) decreased but not significantly. In the SUSTAIN-6 study the primary outcome (3-point MACE) was driven by a 39% decline in nonfatal stroke ($P = 0.04$) and a 26% reduction in nonfatal myocardial infarction ($P = 0.12$) without any benefit on CV mortality. Unlike the EMPA REG OUTCOME trial, separation of the Kaplan–Meier curves did not occur until after year 1, suggesting that the CV benefit was more related to antiatherogenic benefits than to any hemodynamic benefits of the two GLP-1 RAs. GLP-1 RAs improve many CV risk factors (obesity, hypertension, dyslipidemia, inflammation, visceral/hepatic fat, hyperglycemia), but the magnitude of improvement in these CV risk factors was modest in the LEADER and SUSTAIN-6 studies and unlikely to explain the reduction in primary outcome (3-point MACE) when reviewed individually. GLP-1 RAs do not have a direct insulin-sensitizing effect (309, 310), although they can ameliorate insulin resistance secondary to their effect to promote weight loss. Nonetheless, it seems unlikely that the magnitude of the weight loss would enhance insulin sensitivity sufficiently to have a major impact on the atherosclerotic process (216). However, when viewed collectively, the modest improvement in multiple components of the IRS (blood pressure, dyslipidemia, visceral/hepatic fat), when combined with the weight loss and associated improvement in insulin sensitivity, could have exerted a significant antiatherogenic effect. In a large 3-year randomized controlled trial in 2254 adults who were obese/overweight with prediabetes, liraglutide (3 mg/d) caused a significant, durable reduction in multiple components of the IRS, which correlated with enhanced insulin sensitivity measured with both HOMA-IR and the Matsuda index (311).

Both the myocardium and vasculature express GLP-1 receptors (312, 313) and GLP-1 RAs exert multiple beneficial effects on CV function: (i) direct effect to augment myocardial function; (ii) vasodilatory effect on small vessel blood flow secondary to enhanced nitric oxide production; (iii) inhibitory effect on the atherogenic process; (iv) altered autonomic nervous system balance favoring parasympathetic activity; (v) reduced myocardial injury after an ischemic insult (314–323); and (vi) direct anti-inflammatory actions on the myocardium and blood vessels (314). In animal models, GLP-1 RAs have been shown to directly slow the atherogenic process (324–326). Although the cellular/molecular mechanisms responsible for these antiatherogenic effects remain to be elucidated, they could have contributed to the decrease in CV events in the LEADER and SUSTAIN-6 studies.

Recently, the results of the EXSCEL trial have been published (327), and from a purely statistical standpoint sustained-release exenatide was shown to be CV neutral in high-risk individuals with T2DM (HR = 0.90, $P = 0.06$). However, the median duration of exposure in the exenatide group compared with the amount of time that they were expected to be on the GLP-1 RA was 76%, most likely because the study was initiated with the old preparation of Bydureon, which is very cumbersome to use and because of a higher drop in rate of SGLT2 inhibitors and GLP-1 RAs in the placebo group. When viewed in the context of these two factors, it could be argued that the EXSCEL trial was a positive study with respect to CV protection. The results of the recently published REWIND study (328) with dulaglutide are consistent with those of LEADER (307) and SUSTAIN-6 (308) and demonstrate a 12% decrease in the MACE endpoint (HR, 0.88; 95% CI, 0.79 to 0.99; $P = 0.026$).

Although not yet published, the CV results of the FREEDOM trial (329) have been stated to be neutral. The neutral result of the FREEDOM (and possibly EXSCEL) trial stand in contrast to those of the LEADER and SUSTAIN-6 trials. The reasons underlying these different results are unclear, but exenatide has only ~50% homology with human GLP-1, whereas liraglutide and semaglutide (which are very similar in structure) both are closely homologous to human GLP-1. Although the ELIXA study (330) failed to demonstrate any CV benefit, lixisenatide is short acting, in the range of 4 to 6 hours, and the patient population (acute coronary syndrome) was very different than prior CV trials of GLP-1 RAs in diabetes. The result of the REWIND trial (331) with dulaglutide may help to clarify whether the observed antiatherogenic effects of the GLP-1 RAs represent a class effect.

The DPP4 inhibitors exert their major effect by inhibiting glucagon secretion by the pancreatic α-cells and to a lesser extent by increasing insulin secretion (332–336). The DPP4 inhibitors have no insulin-sensitizing effect (335, 336). Four CV outcome trials have been reported with the DPP4 inhibitors [SAVOR-TIMI (saxagliptin), ESAMINE (alogliptin), TECOS (sitagliptin) and CARMELINA (linogliptin)] (337–340), and all four have failed to demonstrate any CV protective effect in patients with T2DM with established ASCVD.

Summary

Macrovascular complications (heart attack and stroke) remain the major cause of mortality in individuals with the IRS, in nondiabetic people with obesity, and in prediabetic subjects and subjects with T2DM, and the increase in CV mortality cannot be fully accounted for by the classic CV risk factors. Considerable evidence suggests that insulin resistance and the basic molecular etiology of the insulin resistance can explain a major component of the unexplained CV risk in these populations. CV outcome trials have demonstrated that three classes of antidiabetic agents can reduce 3-point MACE: TZDs (pioglitazone), GLP-1 RAs (liraglutide, semaglutide), and SGLT2 inhibitors (empagliflozin, canagliflozin). Of these three classes, strong evidence supports that the insulin-sensitizing agent pioglitazone exerts its antiatherogenic effect by improving insulin resistance and multiple components of the IRS. The current recommended approach in T2D management still focuses on lowering the plasma glucose concentration rather than correcting the underlying metabolic abnormalities that cause the hyperglycemia. However, we now have antidiabetes medications that, in addition to lowering the plasma glucose concentration, also improve CV risk factors and CV events in subjects with T2DM with established CVD. Thus, these agents should be favored over agents that lower plasma glucose but have no beneficial effects on CV risk factors or CVD. As opposed to pioglitazone, it seems unlikely that either the SGLT2 inhibitors or GLP-1 RAs exert their CV protective effects by enhancing insulin sensitivity. This raises the intriguing possibility that combination therapy with pioglitazone plus either a SGLT2 inhibitor or GLP-1 RA could provide an additive or even synergistic effect to reduce CV events in high-risk individuals (323).

References and Notes

1. Reaven GM, Knowles JW, Leonard D, Barlow CE, Willis BL, Haskell WL, Maron DJ. Relationship between simple markers of insulin resistance and coronary artery calcification. *J Clin Lipidol*. 2017; **11**(4):1007–1012.
2. Fakhrzadeh H, Sharifi F, Alizadeh M, Arzaghi SM, Tajallizade-Khoob Y, Tootee A, Alatab S, Mirarefin M, Badamchizade Z, Kazemi H. Relationship between insulin resistance and subclinical atherosclerosis in individuals with and without type 2 diabetes mellitus. *J Diabetes Metab Disord*. 2016; **15**(1):41.
3. Bressler P, Bailey SR, Matsuda M, DeFronzo RA. Insulin resistance and coronary artery disease. *Diabetologia*. 1996;**39**(11):1345–1350.
4. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;**339**(4):229–234.
5. Howard G, O'Leary DH, Zaccaro D, Haffner S, Rewers M, Hamman R, Selby JV, Saad MF, Savage P, Bergman R; The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. Insulin sensitivity and atherosclerosis. *Circulation*. 1996;**93**(10):1809–1817.
6. Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;**24**(4): 683–689.

7. Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, Saggiani F, Poli M, Perbellini S, Raffaelli A, Cacciatori V, Santi L, Targher G, Bonadonna R, Muggeo M. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care*. 2002;**25**(7):1135–1141.
8. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Meigs JB, Bonadonna RC, Muggeo M. Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in Caucasian subjects from the general population: the Bruneck study. *Diabetes Care*. 2007;**30**(2):318–324.
9. Hedblad B, Nilsson P, Janzon L, Berglund G. Relation between insulin resistance and carotid intima-media thickness and stenosis in non-diabetic subjects. Results from a cross-sectional study in Malmö, Sweden. *Diabet Med*. 2000;**17**(4):299–307.
10. Golden SH, Folsom AR, Coresh J, Sharrett AR, Szklo M, Brancati F. Risk factor groupings related to insulin resistance and their synergistic effects on subclinical atherosclerosis: the atherosclerosis risk in communities study. *Diabetes*. 2002;**51**(10):3069–3076.
11. Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. *Diabetes Care*. 2002;**25**(7):1177–1184.
12. Gast KB, Tjeerdema N, Stijnen T, Smit JW, Dekkers OM. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. *PLoS One*. 2012;**7**(12):e52036.
13. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;**56**(14):1113–1132.
14. Sarwar N, Sattar N, Gudnason V, Danesh J. Circulating concentrations of insulin markers and coronary heart disease: a quantitative review of 19 Western prospective studies. *Eur Heart J*. 2007;**28**(20):2491–2497.
15. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. *Physiol Rev*. 2018;**98**(4):2133–2223.
16. Bajaj M, Defronzo RA. Metabolic and molecular basis of insulin resistance. *J Nucl Cardiol*. 2003;**10**(3):311–323.
17. Rask-Madsen C, Li Q, Freund B, Feather D, Abramov R, Wu IH, Chen K, Yamamoto-Hiraoka J, Goldenbogen J, Sotiropoulos KB, Clermont A, Geraldes P, Dall'Osso C, Wagers AJ, Huang PL, Rekhter M, Scalia R, Kahn CR, King GL. Loss of insulin signaling in vascular endothelial cells accelerates atherosclerosis in apolipoprotein E null mice. *Cell Metab*. 2010;**11**(5):379–389.
18. Jiang ZY, Lin YW, Clemont A, Feener EP, Hein KD, Igarashi M, Yamauchi T, White MF, King GL. Characterization of selective resistance to insulin signaling in the vasculature of obese Zucker (*fa/fa*) rats. *J Clin Invest*. 1999;**104**(4):447–457.
19. Cusi K, Maezono K, Osman A, Pendergrass M, Patti ME, Pratipanawatr T, DeFronzo RA, Kahn CR, Mandarino LJ. Insulin resistance differentially affects the PI 3-kinase- and MAP kinase-mediated signaling in human muscle. *J Clin Invest*. 2000;**105**(3):311–320.
20. Sasaoka T, Rose DW, Jhun BH, Saltiel AR, Draznin B, Olefsky JM. Evidence for a functional role of Shc proteins in mitogenic signaling induced by insulin, insulin-like growth factor-1, and epidermal growth factor. *J Biol Chem*. 1994;**269**(18):13689–13694.
21. Hsueh WA, Law RE. Insulin signaling in the arterial wall. *Am J Cardiol*. 1999;**84**(1A):21J–24J.
22. Wang CC, Goalstone ML, Draznin B. Molecular mechanisms of insulin resistance that impact cardiovascular biology. *Diabetes*. 2004;**53**(11):2735–2740.
23. Draznin B. Molecular mechanisms of insulin resistance: serine phosphorylation of insulin receptor substrate-1 and increased expression of p85α: the two sides of a coin. *Diabetes*. 2006;**55**(8):2392–2397.
24. King GL, Park K, Li Q. Selective insulin resistance and the development of cardiovascular diseases in diabetes: the 2015 Edwin Bierman Award Lecture. *Diabetes*. 2016;**65**(6):1462–1471.
25. DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;**58**(4):773–795.
26. DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. *Diabetologia*. 2010;**53**(7):1270–1287.
27. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;**37**(12):1595–1607.
28. Sasaoka T, Ishiki M, Sawa T, Ishihara H, Takata Y, Imamura T, Usui I, Olefsky JM, Kobayashi M. Comparison of the insulin and insulin-like growth factor 1 mitogenic intracellular signaling pathways. *Endocrinology*. 1996;**137**(10):4427–4434.
29. Pfeifle B, Ditschuneit H. Effect of insulin on growth of cultured human arterial smooth muscle cells. *Diabetologia*. 1981;**20**(2):155–158.
30. Leitner JW, Kline T, Carel K, Goalstone M, Draznin B. Hyperinsulinemia potentiates activation of p21Ras by growth factors. *Endocrinology*. 1997;**138**(5):2211–2214.
31. Ferrannini E, Natali A, Muscelli E, Nilsson PM, Golay A, Laasko M, Beck-Mielsen H, Mari H; RISC Investigators. Natural history and physiological determinants of changes in glucose tolerance in a non-diabetic population: the RISC study. *Diabetologia*. 2011;**54**(6):1507–1516.
32. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;**14**(3):173–194.
33. Ferrannini E, Balkau B, Coppack SW, Dekker JM, Mari A, Nolan J, Walker M, Natali A, Beck-Nielsen H; RISC Investigators. Insulin resistance, insulin response, and obesity as indicators of metabolic risk. *J Clin Endocrinol Metab*. 2007;**92**(8):2885–2892.
34. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. *Nat Rev Mol Cell Biol*. 2006;**7**(2):85–96.
35. White MF, Livingston JN, Backer JM, Lauris V, Dull TJ, Ullrich A, Kahn CR. Mutation of the insulin receptor at tyrosine 960 inhibits signal transmission but does not affect its tyrosine kinase activity. *Cell*. 1988;**54**(5):641–649.
36. DeFronzo R. Pathogenesis of type 2 diabetes: metabolic and molecular implications for identifying diabetes genes. *Diabetes Rev*. 1997;**5**(3):177–269.
37. Sun XJ, Miralpeix M, Myers MG Jr, Glasheen EM, Backer JM, Kahn CR, White MF. Expression and function of IRS-1 in insulin signal transmission. *J Biol Chem*. 1992;**267**(31):22662–22672.
38. Ruderman NB, Kapeller R, White MF, Cantley LC. Activation of phosphatidylinositol 3-kinase by insulin. *Proc Natl Acad Sci USA*. 1990;**87**(4):1411–1415.
39. Abdul-Ghani MA, Jenkinson CP, Richardson DK, Tripathy D, DeFronzo RA. Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epidemiology Study. *Diabetes*. 2006;**55**(5):1430–1435.
40. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Pettiti M, Natali A, Mari A, DeFronzo RA. Predominant role of reduced beta-cell sensitivity to glucose over insulin resistance in impaired glucose tolerance. *Diabetologia*. 2003;**46**(9):1211–1219.
41. King GL, Goodman AD, Buzney S, Moses A, Kahn CR. Receptors and growth-promoting effects of insulin and insulinlike growth factors on cells from bovine retinal capillaries and aorta. *J Clin Invest*. 1985;**75**(3):1028–1036.
42. Coletta DK, Balas B, Chavez AO, Baig M, Abdul-Ghani M, Kashyap SR, Folli F, Tripathy D, Mandarino LJ, Cornell JE, Defronzo RA, Jenkinson CP. Effect of acute physiological hyperinsulinemia on gene expression in human skeletal muscle in vivo. *Am J Physiol Endocrinol Metab*. 2008;**294**(5):E910–E917.
43. Tokudome T, Horio T, Yoshihara F, Suga S, Kawano Y, Kohno M, Kangawa K. Direct effects of high glucose and insulin on protein synthesis in cultured cardiac myocytes and DNA and collagen synthesis in cardiac fibroblasts. *Metabolism*. 2004;**53**(6):710–715.
44. Hirosumi J, Tuncman G, Chang L, Görgün CZ, Uysal KT, Maeda K, Karin M, Hotamisligil GS. A central role for JNK in obesity and insulin resistance. *Nature*. 2002;**420**(6913):333–336.
45. Del Prato S, Leonetti F, Simonson DC, Sheehan P, Matsuda M, DeFronzo RA. Effect of sustained physiologic hyperinsulinaemia and hyperglycaemia on insulin secretion and insulin sensitivity in man. *Diabetologia*. 1994;**37**(10):1025–1035.
46. Iozzo P, Pratipanawatr T, Pijl H, Vogt C, Kumar V, Pipek R, Matsuda M, Mandarino LJ, Cusi KJ, DeFronzo RA. Physiological hyperinsulinemia impairs insulin-stimulated glycogen synthase activity and glycogen synthesis. *Am J Physiol Endocrinol Metab*. 2001;**280**(5):E712–E719.
47. Calanna S, Urbano F, Piro S, Zagami RM, Di Pino A, Spadaro L, Purrello F, Rabuazzo AM. Elevated plasma glucose-dependent insulinotropic polypeptide associates with hyperinsulinemia in metabolic syndrome. *Eur J Endocrinol*. 2012;**166**(5):917–922.
48. Kanat M, Mari A, Norton L, Winnier D, DeFronzo RA, Jenkinson C, Abdul-Ghani MA. Distinct β-cell defects in impaired fasting glucose and impaired glucose tolerance. *Diabetes*. 2012;**61**(2):447–453.
49. Liu YF, Herschkovitz A, Boura-Halfon S, Ronen D, Paz K, Leroith D, Zick Y. Serine phosphorylation proximal to its phosphotyrosine binding domain inhibits insulin receptor substrate 1 function and promotes insulin resistance. *Mol Cell Biol*. 2004;**24**(21):9668–9681.
50. Zeng G, Nystrom FH, Ravichandran LV, Cong LN, Kirby M, Mostowski H, Quon MJ. Roles for insulin receptor, PI3-kinase, and Akt in insulin-signaling pathways related to production of nitric oxide in human vascular endothelial cells. *Circulation*. 2000;**101**(13):1539–1545.
51. Muris DM, Houben AJ, Schram MT, Stehouwer CD. Microvascular dysfunction is associated with a higher incidence of type 2 diabetes mellitus: a systematic review and meta-analysis. *Arterioscler Thromb Vasc Biol*. 2012;**32**(12):3082–3094.
52. Matsuzawa Y, Lerman A. Endothelial dysfunction and coronary artery disease: assessment, prognosis, and treatment. *Coron Artery Dis*. 2014;**25**(8):713–724.

53. Wilkes JJ, Hevener A, Olefsky J. Chronic endothelin-1 treatment leads to insulin resistance in vivo. *Diabetes*. 2003;**52**(8):1904–1909.
54. Koopmans SJ, Kushwaha RS, DeFronzo RA. Chronic physiologic hyperinsulinemia impairs suppression of plasma free fatty acids and increases de novo lipogenesis but does not cause dyslipidemia in conscious normal rats. *Metabolism*. 1999;**48**(3):330–337.
55. Tobey TA, Greenfield M, Kraemer F, Reaven GM. Relationship between insulin resistance, insulin secretion, very low density lipoprotein kinetics, and plasma triglyceride levels in normotriglyceridemic man. *Metabolism*. 1981;**30**(2):165–171.
56. Winhofer Y, Krssák M, Jankovic D, Anderwald CH, Reiter G, Hofer A, Trattnig S, Luger A, Krebs M. Short-term hyperinsulinemia and hyperglycemia increase myocardial lipid content in normal subjects. *Diabetes*. 2012;**61**(5):1210–1216.
57. Scherer T, Lindtner C, O'Hare J, Hackl M, Zielinski E, Freudenthaler A, Baumgartner-Parzer S, Tödter K, Heeren J, Krššák M, Scheja L, Fürnsinn C, Buettner C. Insulin regulates hepatic triglyceride secretion and lipid content via signaling in the brain. *Diabetes*. 2016;**65**(6):1511–1520.
58. Azzout-Marniche D, Bécard D, Guichard C, Foretz M, Ferré P, Foufelle F. Insulin effects on sterol regulatory-element-binding protein-1c (SREBP-1c) transcriptional activity in rat hepatocytes. *Biochem J*. 2000;**350**(Pt 2):389–393.
59. Lucero D, Miksztowicz V, Macri V, López GH, Friedman S, Berg G, Zago V, Schreier L. Overproduction of altered VLDL in an insulin-resistance rat model: influence of SREBP-1c and PPAR-α. *Clin Investig Arterioscler*. 2015;**27**(4):167–174.
60. Nakao J, Ito H, Kanayasu T, Murota S. Stimulatory effect of insulin on aortic smooth muscle cell migration induced by 12-L-hydroxy-5,8,10,14-eicosatetraenoic acid and its modulation by elevated extracellular glucose levels. *Diabetes*. 1985;**34**(2):185–191.
61. Golovchenko I, Goalstone ML, Watson P, Brownlee M, Draznin B. Hyperinsulinemia enhances transcriptional activity of nuclear factor-κB induced by angiotensin II, hyperglycemia, and advanced glycosylation end products in vascular smooth muscle cells. *Circ Res*. 2000;**87**(9):746–752.
62. Hajra L, Evans AI, Chen M, Hyduk SJ, Collins T, Cybulsky MI. The NF-κB signal transduction pathway in aortic endothelial cells is primed for activation in regions predisposed to atherosclerotic lesion formation. *Proc Natl Acad Sci USA*. 2000;**97**(16):9052–9057.
63. Hsueh WA. Insulin signals in the arterial wall. *J Cardiol*. 1999;**84**(1):21–24.
64. Reyna SM, Ghosh S, Tantiwong P, Meka CS, Eagan P, Jenkinson CP, Cersosimo E, Defronzo RA, Coletta DK, Sriwijitkamol A, Musi N. Elevated Toll-like receptor 4 expression and signaling in muscle from insulin-resistant subjects. *Diabetes*. 2008;**57**(10):2595–2602.
65. Lindsey JB, House JA, Kennedy KF, Marso SP. Diabetes duration is associated with increased thin-cap fibroatheroma detected by intravascular ultrasound with virtual histology. *Circ Cardiovasc Interv*. 2009;**2**(6):543–548.
66. Stout RW. The effect of insulin on the incorporation of sodium (1-^{14}C)-acetate into the lipids of the rat aorta. *Diabetologia*. 1971;**7**(5):367–372.
67. Porter KE, Riches K. The vascular smooth muscle cell: a therapeutic target in type 2 diabetes? *Clin Sci (Lond)*. 2013;**125**(4):167–182.
68. Stamler J, Pick R, Katz LN. Effect of insulin in the induction and regression of atherosclerosis in the chick. *Circ Res*. 1960;**8**(3):572–576.
69. Duff GL, McMillan GC. The effect of alloxan diabetes on experimental cholesterol atherosclerosis in the rabbit. *J Exp Med*. 1949;**89**(6):611–630.
70. Cruz AB Jr, Amatuzio DS, Grande F, Hay LJ. Effect of intra-arterial insulin on tissue cholesterol and fatty acids in alloxan-diabetic dogs. *Circ Res*. 1961;**9**(1):39–43.
71. Meehan WP, Buchanan TA, Hsueh W. Chronic insulin administration elevates blood pressure in rats. *Hypertension*. 1994;**23**(6 Pt 2):1012–1017.
72. DeFronzo RA, Goldberg M, Agus ZS. The effects of glucose and insulin on renal electrolyte transport. *J Clin Invest*. 1976;**58**(1):83–90.
73. Henry RR, Gumbiner B, Ditzler T, Wallace P, Lyon R, Glauber HS. Intensive conventional insulin therapy for type II diabetes. Metabolic effects during a 6-mo outpatient trial. *Diabetes Care*. 1993;**16**(1):21–31.
74. Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, Levy JC. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med*. 2007;**357**(17):1716–1730.
75. Purnell JQ, Dev RK, Steffes MW, Cleary PA, Palmer JP, Hirsch IB, Hokanson JE, Brunzell JD. Relationship of family history of type 2 diabetes, hypoglycemia, and autoantibodies to weight gain and lipids with intensive and conventional therapy in the Diabetes Control and Complications Trial. *Diabetes*. 2003;**52**(10):2623–2629.
76. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med*. 1999;**341**(15):1097–1105.
77. Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB. Annual deaths attributable to obesity in the United States. *JAMA*. 1999;**282**(16):1530–1538.
78. Sinha S, Perdomo G, Brown NF, O'Doherty RM. Fatty acid-induced insulin resistance in L6 myotubes is prevented by inhibition of activation and nuclear localization of nuclear factor κB. *J Biol Chem*. 2004;**279**(40):41294–41301.
79. Bhatt BA, Dube JJ, Dedousis N, Reider JA, O'Doherty RM. Diet-induced obesity and acute hyperlipidemia reduce IκBα levels in rat skeletal muscle in a fiber-type dependent manner. *Am J Physiol Regul Integr Comp Physiol*. 2006;**290**(1):R233–R240.
80. Wang L, Gill R, Pedersen TL, Higgins LJ, Newman JW, Rutledge JC. Triglyceride-rich lipoprotein lipolysis releases neutral and oxidized FFAs that induce endothelial cell inflammation. *J Lipid Res*. 2009;**50**(2):204–213.
81. Felton CV, Crook D, Davies MJ, Oliver MF. Relation of plaque lipid composition and morphology to the stability of human aortic plaques. *Arterioscler Thromb Vasc Biol*. 1997;**17**(7):1337–1345.
82. Felton CV, Crook D, Davies MJ, Oliver MF. Dietary polyunsaturated fatty acids and composition of human aortic plaques. *Lancet*. 1994;**344**(8931):1195–1196.
83. Stachowska E, Dołęgowska B, Chlubek D, Wesołowska T, Ciechanowski K, Gutowski P, Szumiłowicz H, Turowski R. Dietary trans fatty acids and composition of human atheromatous plaques. *Eur J Nutr*. 2004;**43**(5):313–318.
84. Steinberg HO, Tarshoby M, Monestel R, Hook G, Cronin J, Johnson A, Bayazeed B, Baron AD. Elevated circulating free fatty acid levels impair endothelium-dependent vasodilation. *J Clin Invest*. 1997;**100**(5):1230–1239.
85. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature*. 1993;**362**(6423):801–809.
86. Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. *Diabetes Metab Res Rev*. 2006;**22**(6):423–436.
87. Gerstein HC, Bosch J, Dagenais GR, Díaz R, Jung H, Maggioni AP, Pogue J, Probstfield J, Ramachandran A, Riddle MC, Rydén LE, Yusuf S; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;**367**(4):319–328.
88. Eaton RP, Allen RC, Schade DS, Standefer JC. "Normal" insulin secretion: the goal of artificial insulin delivery systems? *Diabetes Care*. 1980;**3**(2):270–273.
89. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;**358**(24):2545–2559.
90. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;**358**(24):2560–2572.
91. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;**360**(2):129–139.
92. Nolan CJ, Ruderman NB, Kahn SE, Pedersen O, Prentki M. Insulin resistance as a physiological defense against metabolic stress: implications for the management of subsets of type 2 diabetes. *Diabetes*. 2015;**64**(3):673–686.
93. Hoehn KL, Salmon AB, Hohnen-Behrens C, Turner N, Hoy AJ, Maghzal GJ, Stocker R, Van Remmen H, Kraegen EW, Cooney GJ, Richardson AR, James DE. Insulin resistance is a cellular antioxidant defense mechanism. *Proc Natl Acad Sci USA*. 2009;**106**(42):17787–17792.
94. Muoio DM, Neufer PD. Lipid-induced mitochondrial stress and insulin action in muscle. *Cell Metab*. 2012;**15**(5):595–605.
95. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 2005;**54**(6):1615–1625.
96. Chess DJ, Stanley WC. Role of diet and fuel overabundance in the development and progression of heart failure. *Cardiovasc Res*. 2008;**79**(2):269–278.
97. Stienstra R, Tack CJ, Kanneganti TD, Joosten LA, Netea MG. The inflammasome puts obesity in the danger zone. *Cell Metab*. 2012;**15**(1):10–18.
98. Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic VA, Shiffman ML, Clore JN. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology*. 2001;**120**(5):1183–1192.
99. Yki-Järvinen H. Liver fat in the pathogenesis of insulin resistance and type 2 diabetes. *Dig Dis*. 2010;**28**(1):203–209.
100. Bugianesi E, Gastaldelli A, Vanni E, Gambino R, Cassader M, Baldi S, Ponti V, Pagano G, Ferrannini E,

Rizzetto M. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. *Diabetologia*. 2005;**48**(4):634–642.
101. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med*. 2010;**363**(14):1341–1350.
102. Misra VL, Khashab M, Chalasani N. Nonalcoholic fatty liver disease and cardiovascular risk. *Curr Gastroenterol Rep*. 2009;**11**(1):50–55.
103. Miranda PJ, DeFronzo RA, Califf RM, Guyton JR. Metabolic syndrome: evaluation of pathological and therapeutic outcomes. *Am Heart J*. 2005;**149**(1):20–32.
104. Reaven G. Insulin resistance, hypertension, and coronary heart disease. *J Clin Hypertens (Greenwich)*. 2003;**5**(4):269–274.
105. Sironi AM, Pingitore A, Ghione S, De Marchi D, Scattini B, Positano V, Muscelli E, Ciociaro D, Lombardi M, Ferrannini E, Gastaldelli A. Early hypertension is associated with reduced regional cardiac function, insulin resistance, epicardial, and visceral fat. *Hypertension*. 2008;**51**(2):282–288.
106. Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, Pedrinelli R, Brandi L, Bevilacqua S. Insulin resistance in essential hypertension. *N Engl J Med*. 1987;**317**(6):350–357.
107. Solini AD. Insulin resistance, hypertension, and cellular ion transport systems. *Acta Diabetol*. 1992;**29**(3–4):196–200.
108. DeFronzo RA. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia and atherosclerosis. *Neth J Med*. 1997;**50**(5):191–197.
109. Rana JS, Visser ME, Arsenault BJ, Després JP, Stroes ES, Kastelein JJ, Wareham NJ, Boekholdt SM, Khaw KT. Metabolic dyslipidemia and risk of future coronary heart disease in apparently healthy men and women: the EPIC-Norfolk prospective population study. *Int J Cardiol*. 2010;**143**(3):399–404.
110. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;**16**(2):434–444.
111. Jeppesen J, Hollenbeck CB, Zhou MY, Coulston AM, Jones C, Chen YD, Reaven GM. Relation between insulin resistance, hyperinsulinemia, postheparin plasma lipoprotein lipase activity, and postprandial lipemia. *Arterioscler Thromb Vasc Biol*. 1995;**15**(3):320–324.
112. Sheu WH, Shieh SM, Fuh MM, Shen DD, Jeng CY, Chen YD, Reaven GM. Insulin resistance, glucose intolerance, and hyperinsulinemia. Hypertriglyceridemia versus hypercholesterolemia. *Arterioscler Thromb*. 1993;**13**(3):367–370.
113. Galvan AQ, Santoro D, Natali A, Sampietro T, Boni C, Masoni A, Buzzigoli G, Ferrannini E. Insulin sensitivity in familial hypercholesterolemia. *Metabolism*. 1993;**42**(10):1359–1364.
114. Steinberg HO, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release. *J Clin Invest*. 1994;**94**(3):1172–1179.
115. Kashyap SR, Roman LJ, Lamont J, Masters BS, Bajaj M, Suraamornkul S, Belfort R, Berria R, Kellogg DL Jr, Liu Y, DeFronzo RA. Insulin resistance is associated with impaired nitric oxide synthase activity in skeletal muscle of type 2 diabetic subjects. *J Clin Endocrinol Metab*. 2005;**90**(2):1100–1105.
116. Kashyap SR, Lara A, Zhang R, Park YM, DeFronzo RA. Insulin reduces plasma arginase activity in type 2 diabetic patients. *Diabetes Care*. 2008;**31**(1):134–139.
117. Baron AD. Hemodynamic actions of insulin. *Am J Physiol*. 1994;**267**(2 Pt 1):E187–E202.
118. Brunner H, Cockcroft JR, Deanfield J, Donald A, Ferrannini E, Halcox J, Kiowski W, Lüscher TF, Mancia G, Natali A, Oliver JJ, Pessina AC, Rizzoni D, Rossi GP, Salvetti A, Spieker LE, Taddei S, Webb DJ; Working Group on Endothelins and Endothelial Factors of the European Society of Hypertension. Endothelial function and dysfunction. Part II: Association with cardiovascular risk factors and diseases. A statement by the Working Group on Endothelins and Endothelial Factors of the European Society of Hypertension. *J Hypertens*. 2005;**23**(2):233–246.
119. Naruse K, Shimizu K, Muramatsu M, Toki Y, Miyazaki Y, Okumura K, Hashimoto H, Ito T. Long-term inhibition of NO synthesis promotes atherosclerosis in the hypercholesterolemic rabbit thoracic aorta. PGH2 does not contribute to impaired endothelium-dependent relaxation. *Arterioscler Thromb*. 1994;**14**(5):746–752.
120. Hsueh WA, Lyon CJ, Quiñones MJ. Insulin resistance and the endothelium. *Am J Med*. 2004;**117**(2):109–117.
121. Stegenga ME, van der Crabben SN, Levi M, de Vos AF, Tanck MW, Sauerwein HP, van der Poll T. Hyperglycemia stimulates coagulation, whereas hyperinsulinemia impairs fibrinolysis in healthy humans. *Diabetes*. 2006;**55**(6):1807–1812.
122. Dunn EJ, Philippou H, Ariëns RA, Grant PJ. Molecular mechanisms involved in the resistance of fibrin to clot lysis by plasmin in subjects with type 2 diabetes mellitus. *Diabetologia*. 2006;**49**(5):1071–1080.
123. Smith U. Abdominal obesity: a marker of ectopic fat accumulation. *J Clin Invest*. 2015;**125**(5):1790–1792.
124. Koh-Banerjee P, Wang Y, Hu FB, Spiegelman D, Willett WC, Rimm EB. Changes in body weight and body fat distribution as risk factors for clinical diabetes in US men. *Am J Epidemiol*. 2004;**159**(12):1150–1159.
125. Centers for Disease Control and Prevention. National diabetes fact sheet, 2011. Available at: www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed 17 July 2017.
126. Bajaj M, Baig R, Suraamornkul S, Hardies LJ, Coletta DK, Cline GW, Monroy A, Koul S, Sriwijitkamol A, Musi N, Shulman GI, DeFronzo RA. Effects of pioglitazone on intramyocellular fat metabolism in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2010;**95**(4):1916–1923.
127. Bays H, Mandarino L, DeFronzo RA. Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: peroxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. *J Clin Endocrinol Metab*. 2004;**89**(2):463–478.
128. Bajaj M, Suraamornkul S, Romanelli A, Cline GW, Mandarino LJ, Shulman GI, DeFronzo RA. Effect of a sustained reduction in plasma free fatty acid concentration on intramuscular long-chain fatty acyl-CoAs and insulin action in type 2 diabetic patients. *Diabetes*. 2005;**54**(11):3148–3153.
129. Inoguchi T, Li P, Umeda F, Yu HY, Kakimoto M, Imamura M, Aoki T, Etoh T, Hashimoto T, Naruse M, Sano H, Utsumi H, Nawata H. High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C—dependent activation of NAD(P)H oxidase in cultured vascular cells. *Diabetes*. 2000;**49**(11):1939–1945.
130. Mathew M, Tay E, Cusi K. Elevated plasma free fatty acids increase cardiovascular risk by inducing plasma biomarkers of endothelial activation, myeloperoxidase and PAI-1 in healthy subjects. *Cardiovasc Diabetol*. 2010;**9**(1):9.
131. Wende AR, Symons JD, Abel ED. Mechanisms of lipotoxicity in the cardiovascular system. *Curr Hypertens Rep*. 2012;**14**(6):517–531.
132. Richardson DK, Kashyap S, Bajaj M, Cusi K, Mandarino SJ, Finlayson J, DeFronzo RA, Jenkinson CP, Mandarino LJ. Lipid infusion decreases the expression of nuclear encoded mitochondrial genes and increases the expression of extracellular matrix genes in human skeletal muscle. *J Biol Chem*. 2005;**280**(11):10290–10297.
133. Dresner A, Laurent D, Marcucci M, Griffin ME, Dufour S, Cline GW, Slezak LA, Andersen DK, Hundal RS, Rothman DL, Petersen KF, Shulman GI. Effects of free fatty acids on glucose transport and IRS-1-associated phosphatidylinositol 3-kinase activity. *J Clin Invest*. 1999;**103**(2):253–259.
134. Belfort R, Mandarino L, Kashyap S, Wirfel K, Pratipanawatr T, Berria R, Defronzo RA, Cusi K. Dose-response effect of elevated plasma free fatty acid on insulin signaling. *Diabetes*. 2005;**54**(6):1640–1648.
135. Kim JK, Fillmore JJ, Chen Y, Yu C, Moore IK, Pypaert M, Lutz EP, Kako Y, Velez-Carrasco W, Goldberg IJ, Breslow JL, Shulman GI. Tissue-specific overexpression of lipoprotein lipase causes tissue-specific insulin resistance. *Proc Natl Acad Sci USA*. 2001;**98**(13):7522–7527.
136. Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjöström L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *Br Med J (Clin Res Ed)*. 1984;**289**(6454):1257–1261.
137. Després JP, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis*. 1990;**10**(4):497–511.
138. Gabriely I, Ma XH, Yang XM, Atzmon G, Rajala MW, Berg AH, Scherer P, Rossetti L, Barzilai N. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? *Diabetes*. 2002;**51**(10):2951–2958.
139. Barzilai N, She L, Liu BQ, Vuguin P, Cohen P, Wang J, Rossetti L. Surgical removal of visceral fat reverses hepatic insulin resistance. *Diabetes*. 1999;**48**(1):94–98.
140. Muzumdar R, Allison DB, Huffman DM, Ma X, Atzmon G, Einstein FH, Fishman S, Poduval AD, McVei T, Keith SW, Barzilai N. Visceral adipose tissue modulates mammalian longevity. *Aging Cell*. 2008;**7**(3):438–440.
141. Gastaldelli A, Cusi K, Pettiti M, Hardies J, Miyazaki Y, Berria R, Buzzigoli E, Sironi AM, Cersosimo E, Ferrannini E, Defronzo RA. Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. *Gastroenterology*. 2007;**133**(2):496–506.
142. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;**444**(7121):875–880.
143. Lomonaco R, Bril F, Portillo-Sanchez P, Ortiz-Lopez C, Orsak B, Biernacki D, Lo M, Suman A, Weber MH, Cusi K. Metabolic impact of nonalcoholic steatohepatitis in obese patients with type 2 diabetes. *Diabetes Care*. 2016;**39**(4):632–638.
144. Gaggini M, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E, Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. *Nutrients*. 2013;**5**(5):1544–1560.
145. Clarke GD, Solis-Herrera C, Molina-Wilkins M, Martinez S, Merovci A, Cersosimo E, Chilton RJ,

Iozzo P, Gastaldelli A, Abdul-Ghani M, DeFronzo RA. Pioglitazone improves left ventricular diastolic function in subjects with diabetes. *Diabetes Care*. 2017;**40**(11):1530–1536.
146. Paternostro G, Camici PG, Lammerstma AA, Marinho N, Baliga RR, Kooner JS, Radda GK, Ferrannini E. Cardiac and skeletal muscle insulin resistance in patients with coronary heart disease. A study with positron emission tomography. *J Clin Invest*. 1996;**98**(9):2094–2099.
147. Kankaanpää M, Lehto HR, Pärkkä JP, Komu M, Viljanen A, Ferrannini E, Knuuti J, Nuutila P, Parkkola R, Iozzo P. Myocardial triglyceride content and epicardial fat mass in human obesity: relationship to left ventricular function and serum free fatty acid levels. *J Clin Endocrinol Metab*. 2006;**91**(11):4689–4695.
148. McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, Levine BD, Raskin P, Victor RG, Szczepaniak LS. Cardiac steatosis in diabetes mellitus: a ^{1}H-magnetic resonance spectroscopy study. *Circulation*. 2007;**116**(10):1170–1175.
149. Iacobellis G, Leonetti F. Epicardial adipose tissue and insulin resistance in obese subjects. *J Clin Endocrinol Metab*. 2005;**90**(11):6300–6302.
150. Iozzo P, Chareonthaitawee P, Dutka D, Betteridge DJ, Ferrannini E, Camici PG. Independent association of type 2 diabetes and coronary artery disease with myocardial insulin resistance. *Diabetes*. 2002;**51**(10):3020–3024.
151. Lautamäki R, Airaksinen KE, Seppänen M, Toikka J, Luotolahti M, Ball E, Borra R, Härkönen R, Iozzo P, Stewart M, Knuuti J, Nuutila P. Rosiglitazone improves myocardial glucose uptake in patients with type 2 diabetes and coronary artery disease: a 16-week randomized, double-blind, placebo-controlled study. *Diabetes*. 2005;**54**(9):2787–2794.
152. Fontes-Carvalho R, Ladeiras-Lopes R, Bettencourt P, Leite-Moreira A, Azevedo A. Diastolic dysfunction in the diabetic continuum: association with insulin resistance, metabolic syndrome and type 2 diabetes. *Cardiovasc Diabetol*. 2015;**14**(1):4.
153. von Bibra H, Paulus WJ, St John Sutton M, Leclerque C, Schuster T, Schumm-Draeger PM. Quantification of diastolic dysfunction via the age dependence of diastolic function—impact of insulin resistance with and without type 2 diabetes. *Int J Cardiol*. 2015;**182**:368–374.
154. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocr Rev*. 2002;**23**(5):599–622.
155. Garg R, Tripathy D, Dandona P. Insulin resistance as a proinflammatory state: mechanisms, mediators, and therapeutic interventions. *Curr Drug Targets*. 2003;**4**(6):487–492.
156. Pickup JC, Crook MA. Is type II diabetes mellitus a disease of the innate immune system? *Diabetologia*. 1998;**41**(10):1241–1248.
157. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. *J Clin Invest*. 2003;**112**(12):1785–1788.
158. Barnes PJ, Karin M. Nuclear factor-κB: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med*. 1997;**336**(15):1066–1071.
159. Sriwijitkamol A, Christ-Roberts C, Berria R, Eagan P, Pratipanawatr T, DeFronzo RA, Mandarino LJ, Musi N. Reduced skeletal muscle inhibitor of κBβ content is associated with insulin resistance in subjects with type 2 diabetes: reversal by exercise training. *Diabetes*. 2006;**55**(3):760–767.
160. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation*. 2003;**107**(3):391–397.
161. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol*. 1979;**237**(3):E214–E223.
162. Petrie JR, Malik MO, Balkau B, Perry CG, Højlund K, Pataky Z, Nolan J, Ferrannini E, Natali A; RISC Investigators. Euglycemic clamp insulin sensitivity and longitudinal systolic blood pressure: role of sex. *Hypertension*. 2013;**62**(2):404–409.
163. Pilz S, Rutters F, Nijpels G, Stehouwer CD, Højlund K, Nolan JJ, Balkau B, Dekker JM; RISC Investigators. Insulin sensitivity and albuminuria: the RISC study. *Diabetes Care*. 2014;**37**(6):1597–1603.
164. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, Lee BJ, Perkins RM, Rossing P, Sairenchi T, Tonelli M, Vassalotti JA, Yamagishi K, Coresh J, de Jong PE, Wen CP, Nelson RG; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2012;**380**(9854):1662–1673.
165. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT; Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;**375**(9731):2073–2081.
166. Gastaldelli A, Kozakova M, Højlund K, Flyvbjerg A, Favuzzi A, Mitrakou A, Balkau B; RISC Investigators. Fatty liver is associated with insulin resistance, risk of coronary heart disease, and early atherosclerosis in a large European population. *Hepatology*. 2009;**49**(5):1537–1544.
167. Kozakova M, Natali A, Dekker J, Beck-Nielsen H, Laakso M, Nilsson P, Balkau B, Ferrannini E; RISC Investigators. Insulin sensitivity and carotid intima-media thickness: relationship between insulin sensitivity and cardiovascular risk study. *Arterioscler Thromb Vasc Biol*. 2013;**33**(6):1409–1417.
168. de Rooij SR, Nijpels G, Nilsson PM, Nolan JJ, Gabriel R, Bobbioni-Harsch E, Mingrone G, Dekker JM; Relationship Between Insulin Sensitivity and Cardiovascular Disease (RISC) Investigators. Low-grade chronic inflammation in the relationship between insulin sensitivity and cardiovascular disease (RISC) population: associations with insulin resistance and cardiometabolic risk profile. *Diabetes Care*. 2009;**32**(7):1295–1301.
169. DeFronzo RA. Lilly lecture 1987. The triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes*. 1988;**37**(6):667–687.
170. DeFronzo RA, Gunnarsson R, Björkman O, Olsson M, Wahren J. Effects of insulin on peripheral and splanchnic glucose metabolism in noninsulin-dependent (type II) diabetes mellitus. *J Clin Invest*. 1985;**76**(1):149–155.
171. Bonadonna RC, Groop L, Kraemer N, Ferrannini E, Del Prato S, DeFronzo RA. Obesity and insulin resistance in humans: a dose-response study. *Metabolism*. 1990;**39**(5):452–459.
172. Shulman GI, Rothman DL, Jue T, Stein P, DeFronzo RA, Shulman RG. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by ^{13}C nuclear magnetic resonance spectroscopy. *N Engl J Med*. 1990;**322**(4):223–228.
173. Miyazaki Y, He H, Mandarino LJ, DeFronzo RA. Rosiglitazone improves downstream insulin receptor signaling in type 2 diabetic patients. *Diabetes*. 2003;**52**(8):1943–1950.
174. Pratipanawatr W, Pratipanawatr T, Cusi K, Berria R, Adams JM, Jenkinson CP, Maezono K, DeFronzo RA, Mandarino LJ. Skeletal muscle insulin resistance in normoglycemic subjects with a strong family history of type 2 diabetes is associated with decreased insulin-stimulated insulin receptor substrate-1 tyrosine phosphorylation. *Diabetes*. 2001;**50**(11):2572–2578.
175. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of β-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care*. 2006;**29**(5):1130–1139.
176. Schenk S, Saberi M, Olefsky JM. Insulin sensitivity: modulation by nutrients and inflammation. *J Clin Invest*. 2008;**118**(9):2992–3002.
177. Eliasson B, Cederholm J, Eeg-Olofsson K, Svensson AM, Zethelius B, Gudbjörnsdottir S; National Diabetes Register. Clinical usefulness of different lipid measures for prediction of coronary heart disease in type 2 diabetes: a report from the Swedish National Diabetes Register. *Diabetes Care*. 2011;**34**(9):2095–2100.
178. Taskinen MR. Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia*. 2003;**46**(6):733–749.
179. Howard BV, Robbins DC, Sievers ML, Lee ET, Rhoades D, Devereux RB, Cowan LD, Gray RS, Welty TK, Go OT, Howard WJ. LDL cholesterol as a strong predictor of coronary heart disease in diabetic individuals with insulin resistance and low LDL: the Strong Heart Study. *Arterioscler Thromb Vasc Biol*. 2000;**20**(3):830–835.
180. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson AM, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjörnsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;**376**(15):1407–1418.
181. Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, O'Keeffe LM, Gao P, Wood AM, Burgess S, Freitag DF, Pennells L, Peters SA, Hart CL, Håheim LL, Gillum RF, Nordestgaard BG, Psaty BM, Yeap BB, Knuiman MW, Nietert PJ, Kauhanen J, Salonen JT, Kuller LH, Simons LA, van der Schouw YT, Barrett-Connor E, Selmer R, Crespo CJ, Rodriguez B, Verschuren WM, Salomaa V, Svärdsudd K, van der Harst P, Björkelund C, Wilhelmsen L, Wallace RB, Brenner H, Amouyel P, Barr EL, Iso H, Onat A, Trevisan M, D'Agostino RB Sr, Cooper C, Kavousi M, Welin L, Roussel R, Hu FB, Sato S, Davidson KW, Howard BV, Leening MJ, Leening M, Rosengren A, Dörr M, Deeg DJ, Kiechl S, Stehouwer CD, Nissinen A, Giampaoli S, Donfrancesco C, Kromhout D, Price JF, Peters A, Meade TW, Casiglia E, Lawlor DA, Gallacher J, Nagel D, Franco OH, Assmann G, Dagenais GR, Jukema JW, Sundström J, Woodward M, Brunner EJ, Khaw KT, Wareham NJ, Whitsel EA, Njølstad I, Hedblad B, Wassertheil-Smoller S, Engström G, Rosamond WD, Selvin E, Sattar N, Thompson SG, Danesh J; Emerging Risk Factors Collaboration. Association of cardiometabolic multimorbidity with mortality (published correction appears in *JAMA*. 2015;**314**(11):1179). *JAMA*. 2015;**314**(1):52–60.
182. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;**286**(2):180–187.
183. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary

heart disease using risk factor categories. *Circulation*. 1998;**97**(18):1837–1847.
184. Sung KC, Choi JH, Gwon HC, Choi SH, Kim BS, Kwag HJ, Kim SH. Relationship between insulin resistance and coronary artery calcium in young men and women. *PLoS One*. 2013;**8**(1):e53316.
185. Meigs JB, Larson MG, D'Agostino RB, Levy D, Clouse ME, Nathan DM, Wilson PW, O'Donnell CJ. Coronary artery calcification in type 2 diabetes and insulin resistance: the Framingham Offspring Study. *Diabetes Care*. 2002;**25**(8):1313–1319.
186. Wong ND, Kouwabunpat D, Vo AN, Detrano RC, Eisenberg H, Goel M, Tobis JM. Coronary calcium and atherosclerosis by ultrafast computed tomography in asymptomatic men and women: relation to age and risk factors. *Am Heart J*. 1994; **127**(2):422–430.
187. Qasim A, Mehta NN, Tadesse MG, Wolfe ML, Rhodes T, Girman C, Reilly MP. Adipokines, insulin resistance, and coronary artery calcification. *J Am Coll Cardiol*. 2008;**52**(3):231–236.
188. Yamazoe M, Hisamatsu T, Miura K, Kadowaki S, Zaid M, Kadota A, Torii S, Miyazawa I, Fujiyoshi A, Arima H, Sekikawa A, Maegawa H, Horie M, Ueshima H; SESSA Research Group. Relationship of insulin resistance to prevalence and progression of coronary artery calcification beyond metabolic syndrome components: Shiga epidemiological study of subclinical atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2016;**36**(8):1703–1708.
189. Yoshida M, Takamatsu J, Yoshida S, Tanaka K, Takeda K, Higashi H, Kitaoka H, Ohsawa N. Scores of coronary calcification determined by electron beam computed tomography are closely related to the extent of diabetes-specific complications. *Horm Metab Res*. 1999;**31**(10):558–563.
190. Vardeny O, Gupta DK, Claggett B, Burke S, Shah A, Loehr L, Ramussen-Torvik L, Selvin E, Chang PP, Aguilar D, Solomon SD. Insulin resistance and incident heart failure: the ARIC Study (Atherosclerosis Risk in Communities). *JACC Heart Fail*. 2013;**1**(6): 531–536.
191. Ingelsson E, Sundström J, Arnlöv J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. *JAMA*. 2005;**294**(3):334–341.
192. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV. Impact of diabetes on cardiac structure and function: the Strong Heart Study. *Circulation*. 2000;**101**(19):2271–2276.
193. Sundström J, Lind L, Nyström N, Zethelius B, Andrén B, Hales CN, Lithell HO. Left ventricular concentric remodeling rather than left ventricular hypertrophy is related to the insulin resistance syndrome in elderly men. *Circulation*. 2000;**101**(22):2595–2600.
194. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J Clin Invest*. 1991;**87**(6):2246–2252.
195. Sartori M, Ceolotto G, Papparella I, Baritono E, Ciccariello L, Calò L, Leoni M, Semplicini A. Effects of angiotensin II and insulin on ERK1/2 activation in fibroblasts from hypertensive patients. *Am J Hypertens*. 2004;**17**(7):604–610.
196. Banerjee D, Biggs ML, Mercer L, Mukamal K, Kaplan R, Barzilay J, Kuller L, Kizer JR, Djousse L, Tracy R, Zieman S, Lloyd-Jones D, Siscovick D, Carnethon M. Insulin resistance and risk of incident heart failure: Cardiovascular Health Study. *Circ Heart Fail*. 2013; **6**(3):364–370.
197. Britton KA, Mukamal KJ, Ix JH, Siscovick DS, Newman AB, de Boer IH, Thacker EL, Biggs ML, Gaziano JM, Djoussé L. Insulin resistance and incident peripheral artery disease in the Cardiovascular Health Study. *Vasc Med*. 2012;**17**(2):85–93.
198. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, Rand L, Siebert C; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;**329**(14):977–986.
199. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;**321**(7258):405–412.
200. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO multinational study of vascular disease in diabetes. *Diabetologia*. 2001;**44**(Suppl 2):S14–S21.
201. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njølstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011;**364**(9):829–841.
202. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA*. 1990;**263**(21):2893–2898.
203. Di Pino A, Urbano F, Zagami RM, Filippello A, Di Mauro S, Piro S, Purrello F, Rabuazzo AM. Low endogenous secretory receptor for advanced glycation end-products levels are associated with inflammation and carotid atherosclerosis in prediabetes. *J Clin Endocrinol Metab*. 2016;**101**(4):1701–1709.
204. Brunner EJ, Shipley MJ, Witte DR, Fuller JH, Marmot MG. Relation between blood glucose and coronary mortality over 33 years in the Whitehall Study. *Diabetes Care*. 2006;**29**(1):26–31.
205. Færch K, Bergman B, Perreault L. Does insulin resistance drive the association between hyperglycemia and cardiovascular risk? *PLoS One*. 2012;**7**(6): e39260.
206. Haffner SM, Mykkänen L, Festa A, Burke JP, Stern MP. Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. *Circulation*. 2000;**101**(9):975–980.
207. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med*. 2001; **161**(3):397–405.
208. Koivisto VA, Yki-Järvinen H, DeFronzo RA. Physical training and insulin sensitivity. *Diabetes Metab Rev*. 1986;**1**(4):445–481.
209. DeFronzo RA. Insulin secretion, insulin resistance, and obesity. *Int J Obes*. 1982;**6**(Suppl 1):73–82.
210. Fall T, Hägg S, Ploner A, Mägi R, Fischer K, Draisma HH, Sarin AP, Benyamin B, Ladenvall C, Åkerlund M, Kals M, Esko T, Nelson CP, Kaakinen M, Huikari V, Mangino M, Meirhaeghe A, Kristiansson K, Nuotio ML, Kobl M, Grallert H, Dehghan A, Kuningas M, de Vries PS, de Bruijn RF, Willems SM, Heikkilä K, Silventoinen K, Pietiläinen KH, Legry V, Giedraitis V, Goumidi L, Syvänen AC, Strauch K, Koenig W, Lichtner P, Herder C, Palotie A, Menni C, Uitterlinden AG, Kuulasmaa K, Havulinna AS, Moreno LA, Gonzalez-Gross M, Evans A, Tregouet DA, Yarnell JW, Virtamo J, Ferrières J, Veronesi G, Perola M, Arveiler D, Brambilla P, Lind L, Kaprio J, Hofman A, Stricker BH, van Duijn CM, Ikram MA, Franco OH, Cottel D, Dallongeville J, Hall AS, Jula A, Tobin MD, Penninx BW, Peters A, Gieger C, Samani NJ, Montgomery GW, Whitfield JB, Martin NG, Groop L, Spector TD, Magnusson PK, Amouyel P, Boomsma DI, Nilsson PM, Järvelin MR, Lyssenko V, Metspalu A, Strachan DP, Salomaa V, Ripatti S, Pedersen NL, Prokopenko I, McCarthy MI, Ingelsson E; ENGAGE Consortium. Age- and sex-specific causal effects of adiposity on cardiovascular risk factors. *Diabetes*. 2015;**64**(5):1841–1852.
211. Hägg S, Fall T, Ploner A, Mägi R, Fischer K, Draisma HH, Kals M, de Vries PS, Dehghan A, Willems SM, Sarin AP, Kristiansson K, Nuotio ML, Havulinna AS, de Bruijn RF, Ikram MA, Kuningas M, Stricker BH, Franco OH, Benyamin B, Gieger C, Hall AS, Huikari V, Jula A, Järvelin MR, Kaakinen M, Kaprio J, Kobl M, Mangino M, Nelson CP, Palotie A, Samani NJ, Spector TD, Strachan DP, Tobin MD, Whitfield JB, Uitterlinden AG, Salomaa V, Syvänen AC, Kuulasmaa K, Magnusson PK, Esko T, Hofman A, de Geus EJ, Lind L, Giedraitis V, Perola M, Evans A, Ferrières J, Virtamo J, Kee F, Tregouet DA, Arveiler D, Amouyel P, Gianfagna F, Brambilla P, Ripatti S, van Duijn CM, Metspalu A, Prokopenko I, McCarthy MI, Pedersen NL, Ingelsson E; European Network for Genetic and Genomic Epidemiology Consortium. Adiposity as a cause of cardiovascular disease: a Mendelian randomization study. *Int J Epidemiol*. 2015;**44**(2): 578–586.
212. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA*. 2013; **309**(1):71–82.
213. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, Wadden TA, Yanovski SZ, Kendall KA, Morgan LC, Trisolini MG, Velasco G, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;**129**(25 Suppl 2):S76–S99.
214. American Diabetes Association. 3. Foundations of care and comprehensive medical evaluation. *Diabetes Care*. 2016;**39**(Suppl 1):S23–S35.
215. Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, Coday M, Curtis JM, Egan C, Evans M, Foreyt J, Foster G, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jeffery RW, Johnson KC, Kitabchi AE, Knowler WC, Kriska A, Lang W, Lewis CE, Montez MG, Nathan DM, Neiberg RH, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Redmon B, Regensteiner J, Rejeski J, Ribisl PM, Safford M, Stewart K, Trence D, Wadden TA, Wing RR, Yanovski SZ; Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol*. 2016;**4**(11):913–921.
216. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland

MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ; Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;**369**(2):145–154.

217. Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM; Diabetes Prevention Program Research Group. 10-Year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009;**374**(9702):1677–1686.
218. Venditti EM, Bray GA, Carrion-Petersen ML, Delahanty LM, Edelstein SL, Hamman RF, Hoskin MA, Knowler WC, Ma Y; Diabetes Prevention Program Research Group. First versus repeat treatment with a lifestyle intervention program: attendance and weight loss outcomes (published correction appears in *Int J Obes (Lond)*. 2009;**33**(1):182). *Int J Obes*. 2008;**32**(10):1537–1544.
219. Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. *Am J Clin Nutr*. 2001;**74**(5):579–584.
220. Dansinger ML, Tatsioni A, Wong JB, Chung M, Balk EM. Meta-analysis: the effect of dietary counseling for weight loss. *Ann Intern Med*. 2007;**147**(1):41–50.
221. Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol*. 2011;**57**(11):1299–1313.
222. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med*. 2018;**378**(25):e34.
223. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;**351**(11):1106–1118.
224. Mayerson AB, Hundal RS, Dufour S, Lebon V, Befroy D, Cline GW, Enocksson S, Inzucchi SE, Shulman GI, Petersen KF. The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. *Diabetes*. 2002;**51**(3):797–802.
225. Natali A, Ferrannini E. Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review. *Diabetologia*. 2006;**49**(3):434–441.
226. Abdul-Ghani M, DeFronzo RA. Is it time to change the type 2 diabetes treatment paradigm? Yes! GLP-1 RAs should replace metformin in the type 2 diabetes algorithm. *Diabetes Care*. 2017;**40**(8):1121–1127.
227. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;**366**(9493):1279–1289.
228. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA*. 2007;**298**(10):1180–1188.
229. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R, Brass LM, Schwartz GG, Adams HP Jr, Berger L, Carolei A, Clark W, Coull B, Ford GA, Kleindorfer D, O'Leary JR, Parsons MW, Ringleb P, Sen S, Spence JD, Tanne D, Wang D, Winder TR; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med*. 2016;**374**(14):1321–1331.
230. Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT, D'Agostino RB Sr, Perez A, Provost JC, Haffner SM. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA*. 2006;**296**(21):2572–2581.
231. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, Jure H, De Larochellière R, Staniloae CS, Mavromatis K, Saw J, Hu B, Lincoff AM, Tuzcu EM; PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA*. 2008;**299**(13):1561–1573.
232. American Diabetes Association. Peripheral arterial disease in people with diabetes. *Diabetes Care*. 2003;**26**(12):3333–3341.
233. Dormandy JA, Betteridge DJ, Schernthaner G, Pirags V, Norgren L; PROactive investigators. Impact of peripheral arterial disease in patients with diabetes—results from PROactive (PROactive 11). *Atherosclerosis*. 2009;**202**(1):272–281.
234. Ryder RE. Pioglitazone has a dubious bladder cancer risk but an undoubted cardiovascular benefit. *Diabet Med*. 2015;**32**(3):305–313.
235. Strongman H, Christopher S, Majak M, Williams R, Bahmanyar S, Linder M, Heintjes EM, Bennett D, Korhonen P, Hoti F. Pioglitazone and cause-specific risk of mortality in patients with type 2 diabetes: extended analysis from a European multidatabase cohort study. *BMJ Open Diabetes Res Care*. 2018;**6**(1):e000481.
236. Liao HW, Saver JL, Wu YL, Chen TH, Lee M, Ovbiagele B. Pioglitazone and cardiovascular outcomes in patients with insulin resistance, pre-diabetes and type 2 diabetes: a systematic review and meta-analysis. *BMJ Open*. 2017;**7**(1):e013927.
237. Miyazaki Y, Mahankali A, Matsuda M, Glass L, Mahankali S, Ferrannini E, Cusi K, Mandarino LJ, DeFronzo RA. Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care*. 2001;**24**(4):710–719.
238. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, Balas B, Gastaldelli A, Tio F, Pulcini J, Berria R, Ma JZ, Dwivedi S, Havranek R, Fincke C, DeFronzo R, Bannayan GA, Schenker S, Cusi K. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med*. 2006;**355**(22):2297–2307.
239. Miyazaki Y, Mahankali A, Matsuda M, Mahankali S, Hardies J, Cusi K, Mandarino LJ, DeFronzo RA. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2002;**87**(6):2784–2791.
240. de Alvaro C, Teruel T, Hernandez R, Lorenzo M. Tumor necrosis factor α produces insulin resistance in skeletal muscle by activation of inhibitor κB kinase in a p38 MAPK-dependent manner. *J Biol Chem*. 2004;**279**(17):17070–17078.
241. Coletta DK, Sriwijitkamol A, Wajcberg E, Tantiwong P, Li M, Prentki M, Madiraju M, Jenkinson CP, Cersosimo E, Musi N, Defronzo RA. Pioglitazone stimulates AMP-activated protein kinase signalling and increases the expression of genes involved in adiponectin signalling, mitochondrial function and fat oxidation in human skeletal muscle in vivo: a randomised trial. *Diabetologia*. 2009;**52**(4):723–732.
242. Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, Miyazaki Y, Kohane I, Costello M, Saccone R, Landaker EJ, Goldfine AB, Mun E, DeFronzo R, Finlayson J, Kahn CR, Mandarino LJ. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: potential role of *PGC1* and *NRF1*. *Proc Natl Acad Sci USA*. 2003;**100**(14):8466–8471.
243. Puigserver P, Spiegelman BM. Peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α): transcriptional coactivator and metabolic regulator. *Endocr Rev*. 2003;**24**(1):78–90.
244. Pérez-Girón JV, Palacios R, Martín A, Hernanz R, Aguado A, Martínez-Revelles S, Barrús MT, Salaices M, Alonso MJ. Pioglitazone reduces angiotensin II-induced COX-2 expression through inhibition of ROS production and ET-1 transcription in vascular cells from spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol*. 2014;**306**(11):H1582–H1593.
245. Pfützner A, Marx N, Lübben G, Langenfeld M, Walcher D, Konrad T, Forst T. Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. *J Am Coll Cardiol*. 2005;**45**(12):1925–1931.
246. Deeg MA, Buse JB, Goldberg RB, Kendall DM, Zagar AJ, Jacober SJ, Khan MA, Perez AT, Tan MH; GLAI Study Investigators. Pioglitazone and rosiglitazone have different effects on serum lipoprotein particle concentrations and sizes in patients with type 2 diabetes and dyslipidemia. *Diabetes Care*. 2007;**30**(10):2458–2464.
247. Chiquette E, Ramirez G, Defronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. *Arch Intern Med*. 2004;**164**(19):2097–2104.
248. Bajaj M, Suraamornkul S, Pratipanawatr T, Hardies LJ, Pratipanawatr W, Glass L, Cersosimo E, Miyazaki Y, DeFronzo RA. Pioglitazone reduces hepatic fat content and augments splanchnic glucose uptake in patients with type 2 diabetes. *Diabetes*. 2003;**52**(6):1364–1370.
249. Natali A, Baldeweg S, Toschi E, Capaldo B, Barbaro D, Gastaldelli A, Yudkin JS, Ferrannini E. Vascular effects of improving metabolic control with metformin or rosiglitazone in type 2 diabetes. *Diabetes Care*. 2004;**27**(6):1349–1357.
250. Pistrosch F, Passauer J, Fischer S, Fuecker K, Hanefeld M, Gross P. In type 2 diabetes, rosiglitazone therapy for insulin resistance ameliorates endothelial dysfunction independent of glucose control. *Diabetes Care*. 2004;**27**(2):484–490.
251. Vinik AI, Stansberry KB, Barlow PM. Rosiglitazone treatment increases nitric oxide production in human peripheral skin: a controlled clinical trial in patients with type 2 diabetes mellitus. *J Diabetes Complications*. 2003;**17**(5):279–285.

252. Yamauchi T, Kadowaki T. Physiological and pathophysiological roles of adiponectin and adiponectin receptors in the integrated regulation of metabolic and cardiovascular diseases. *Int J Obes*. 2008; **32**(Suppl 7):S13–S18.
253. Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, Eto K, Yamashita T, Kamon J, Satoh H, Yano W, Froguel P, Nagai R, Kimura S, Kadowaki T, Noda T. Disruption of adiponectin causes insulin resistance and neointimal formation. *J Biol Chem*. 2002;**277**(29):25863–25866.
254. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, Kuriyama H, Hotta K, Nakamura T, Shimomura I, Matsuzawa Y. PPARγ ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes*. 2001;**50**(9):2094–2099.
255. Ghanim H, Garg R, Aljada A, Mohanty P, Kumbkarni Y, Assian E, Hamouda W, Dandona P. Suppression of nuclear factor-κB and stimulation of inhibitor κB by troglitazone: evidence for an anti-inflammatory effect and a potential antiatherosclerotic effect in the obese. *J Clin Endocrinol Metab*. 2001;**86**(3): 1306–1312.
256. Cersosimo E, Xu X, Musi N. Potential role of insulin signaling on vascular smooth muscle cell migration, proliferation, and inflammation pathways. *Am J Physiol Cell Physiol*. 2012;**302**(4):C652–C657.
257. Mudaliar S, Chang AR, Henry RR. Thiazolidinediones, peripheral edema, and type 2 diabetes: incidence, pathophysiology, and clinical implications. *Endocr Pract*. 2003;**9**(5):406–416.
258. Erdmann E, Charbonnel B, Wilcox RG, Skene AM, Massi-Benedetti M, Yates J, Tan M, Spanheimer R, Standl E, Dormandy JA; PROactive Investigators. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). *Diabetes Care*. 2007;**30**(11):2773–2778.
259. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care*. 2004;**27**(3):699–703.
260. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA. Thiazolidinediones improve β-cell function in type 2 diabetic patients. *Am J Physiol Endocrinol Metab*. 2007;**292**(3): E871–E883.
261. Lewis JD, Habel LA, Quesenberry CP, Strom BL, Peng T, Hedderson MM, Ehrlich SF, Mamtani R, Bilker W, Vaughn DJ, Nessel L, Van Den Eeden SK, Ferrara A. Pioglitazone use and risk of bladder cancer and other common cancers in persons with diabetes. *JAMA*. 2015;**314**(3):265–277.
262. DeFronzo RA, Triplitt C, Qu Y, Lewis MS, Maggs D, Glass LC. Effects of exenatide plus rosiglitazone on β-cell function and insulin sensitivity in subjects with type 2 diabetes on metformin. *Diabetes Care*. 2010;**33**(5):951–957.
263. Viberti G, Kahn SE, Greene DA, Herman WH, Zinman B, Holman RR, Haffner SM, Levy D, Lachin JM, Berry RA, Heise MA, Jones NP, Freed MI. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. *Diabetes Care*. 2002;**25**(10):1737–1743.
264. Lupi R, Del Guerra S, Marselli L, Bugliani M, Boggi U, Mosca F, Marchetti P, Del Prato S. Rosiglitazone prevents the impairment of human islet function induced by fatty acids: evidence for a role of PPARγ$_2$ in the modulation of insulin secretion. *Am J Physiol Endocrinol Metab*. 2004;**286**(4): E560–E567.
265. Miyazaki Y, Glass L, Triplitt C, Matsuda M, Cusi K, Mahankali A, Mahankali S, Mandarino LJ, DeFronzo RA. Effect of rosiglitazone on glucose and non-esterified fatty acid metabolism in type II diabetic patients. *Diabetologia*. 2001;**44**(12):2210–2219.
266. Miyazaki Y, DeFronzo RA. Rosiglitazone and pioglitazone similarly improve insulin sensitivity and secretion, glucose tolerance and adipocytokines in type 2 diabetic patients. *Diabetes Obes Metab*. 2008; **10**(12):1204–1211.
267. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;**356**(24): 2457–2471.
268. GlaxoSmithKline. GlaxoSmithKline clinical trial register: study no. ZM2005/00181/01, Vandia Cardiovascular Event Modeling Project, and study no. HM2006/00497/00/WEUS-RTP866, Coronary heart disease outcomes in patients receiving antidiabetic agents. Available at: www.gsk-clinicalstudyregister.com/tiles2/3104.pdf. Accessed 19 March 2016.
269. US Food and Drug Administration. Division of Metabolism and Endocrine Products and Office of Surveillance and Epidemiology, US Food and Drug Administration. FDA briefing document: joint meeting of the Endocrinologic and Metabolic Drugs advisory committee. 30 July 2017. Available at: www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf. Accessed 19 March 2016.
270. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes–an interim analysis. *N Engl J Med*. 2007;**357**(1):25–38.
271. Florez H, Reaven PD, Bahn G, Moritz T, Warren S, Marks J, Reda D, Duckworth W, Abraira C, Hayward R, Emanuele N; VADT Research Group. Rosiglitazone treatment and cardiovascular disease in the Veterans Affairs Diabetes Trial. *Diabetes Obes Metab*. 2015;**17**(10):949–955.
272. Bertrand OF, Poirier P, Rodés-Cabau J, Rinfret S, Title LM, Dzavik V, Natarajan M, Angel J, Batalla N, Alméras N, Costerousse O, De Larochellière R, Roy L, Després JP; VICTORY Trial Investigators. Cardiometabolic effects of rosiglitazone in patients with type 2 diabetes and coronary artery bypass grafts: a randomized placebo-controlled clinical trial. *Atherosclerosis*. 2010;**211**(2):565–573.
273. Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet*. 2006;**368**(9541): 1096–1105.
274. Lu Y, Ma D, Xu W, Shao S, Yu X. Effect and cardiovascular safety of adding rosiglitazone to insulin therapy in type 2 diabetes: A meta-analysis. *J Diabetes Investig*. 2015;**6**(1):78–86.
275. European Medicines Agency. European Medicines Agency recommends suspension of Avandia, Advandamet and Avaglim. Available at: www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001119.jsp&mid=WC0b01ac058004d5c1. Accessed 24 April 24 2018.
276. US Food and Drug Administration. FDA requires removal of certain restrictions on the diabetes drug Avandia. Available at: www.fda.gov/NewsEvents/News-room/PressAnnouncements/ucm376516.htm. Accessed 19 March 2016.
277. Rizos CV, Liberopoulos EN, Mikhailidis DP, Elisaf MS. Pleiotropic effects of thiazolidinediones. *Expert Opin Pharmacother*. 2008;**9**(7):1087–1108.
278. Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, Tan MH, Khan MA, Perez AT, Jacober SJ; GLAI Study Investigators. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care*. 2005;**28**(7): 1547–1554.
279. Derosa G, D'Angelo A, Ragonesi PD, Ciccarelli L, Piccinni MN, Pricolo F, Salvadeo SA, Montagna L, Gravina A, Ferrari I, Paniga S, Cicero AF. Metformin-pioglitazone and metformin-rosiglitazone effects on non-conventional cardiovascular risk factors plasma level in type 2 diabetic patients with metabolic syndrome. *J Clin Pharm Ther*. 2006;**31**(4): 375–383.
280. Qin S, Liu T, Kamanna VS, Kashyap ML. Pioglitazone stimulates apolipoprotein A-I production without affecting HDL removal in HepG2 cells: involvement of PPAR-α. *Arterioscler Thromb Vasc Biol*. 2007; **27**(11):2428–2434.
281. Sakamoto J, Kimura H, Moriyama S, Odaka H, Momose Y, Sugiyama Y, Sawada H. Activation of human peroxisome proliferator-activated receptor (PPAR) subtypes by pioglitazone. *Biochem Biophys Res Commun*. 2000;**278**(3):704–711.
282. Stojanović M, Prostran M, Radenković M. Thiazolidinediones improve flow-mediated dilation: a meta-analysis of randomized clinical trials. *Eur J Clin Pharmacol*. 2016;**72**(4):385–398.
283. DeFronzo RA, Goodman AM; The Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1995;**333**(9):541–549.
284. Cusi K, DeFronzo RA. Metformin: a review of its metabolic effects. *Diabetes Rev*. 1998;**6**:89–131.
285. Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, Shulman GI. Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med*. 1998;**338**(13): 867–873.
286. Jensen JB, Gormsen LC, Sundelin E, Jakobsen S, Munk OL, Vendelbo MH, Christensen MM, Brosen K, Frokiaer J, Jessen N. Organ-specific uptake and elimination of metformin can be determined in vivo in mice and humans by PET-imaging using a novel 11c-metformin tracer. In: Proceedings of American Diabetes Associaton Scientific Sessions; 5–9 June 2015; Atlanta, GA. Abstract 128-LB. Available at: http://diabetes.diabetesjournals.org/content/diabetes/suppl/2015/06/03/64.Supplement_1.DC1/2015_ADA_LB_Abstracts.pdf. Accessed 15 August 2019.
287. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998; **352**(9131):854–865.
288. Eriksson JW, Bodegard J, Nathanson D, Thuresson M, Nyström T, Norhammar A. Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality. *Diabetes Res Clin Pract*. 2016; **117**:39–47.
289. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of

randomised trials among people with type 2 diabetes. *Diabetologia*. 2017;**60**(9):1620–1629.
290. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;**373**(22):2117–2128.
291. Abdul-Ghani M, Del Prato S, Chilton R, DeFronzo RA. SGLT2 inhibitors and cardiovascular risk: lessons learned from the EMPA-REG OUTCOME Study. *Diabetes Care*. 2016;**39**(5):717–725.
292. Abdul-Ghani M, DeFronzo RA, Del Prato S, Chilton R, Singh R, Ryder RE. Cardiovascular disease and type 2 diabetes: has the dawn of a new era arrived (published correction appears in *Diabetes Care*. 2017;**40**(11):1606)? *Diabetes Care*. 2017;**40**(7):813–820.
293. Kern M, Klöting N, Mark M, Mayoux E, Klein T, Blüher M. The SGLT2 inhibitor empagliflozin improves insulin sensitivity in *db/db* mice both as monotherapy and in combination with linagliptin. *Metabolism*. 2016;**65**(2):114–123.
294. Rossetti L, Smith D, Shulman GI, Papachristou D, DeFronzo RA. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. *J Clin Invest*. 1987;**79**(5):1510–1515.
295. Merovci A, Solis-Herrera C, Daniele G, Eldor R, Fiorentino TV, Tripathy D, Xiong J, Perez Z, Norton L, Abdul-Ghani MA, DeFronzo RA. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest*. 2014;**124**(2):509–514.
296. Abdul-Ghani MA, Norton L, DeFronzo RA. Renal sodium-glucose cotransporter inhibition in the management of type 2 diabetes mellitus. *Am J Physiol Renal Physiol*. 2015;**309**(11):F889–F900.
297. Verma S, Garg A, Yan AT, Gupta AK, Al-Omran M, Sabongui A, Teoh H, Mazer CD, Connelly KA. Effect of empagliflozin on left ventricular mass and diastolic function in individuals with diabetes: an important clue to the EMPA-REG OUTCOME trial? *Diabetes Care*. 2016;**39**(12):e212–e213.
298. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;**377**(7):644–657.
299. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;**380**(24):2295–2306.
300. Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, Broedl UC, Woerle HJ. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest*. 2014;**124**(2):499–508.
301. Ferrannini E, Mark M, Mayoux E. CV protection in the EMPA-REG OUTCOME trial: a "thrifty substrate" hypothesis. *Diabetes Care*. 2016;**39**(7):1108–1114.
302. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Sliverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;**380**(4):347–357.
303. Furtado RHM, Bonaca MP, Raz I, Zelniker TA, Mosenzon O, Cahn A, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Nicolau JC, Gause-Nilsson IAM, Fredriksson M, Langkilde AM, Sabatine MS, Wiviott SD. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction. *Circulation*. 2019;**139**(22):2516–2527.
304. Sonesson C, Johansson PA, Johnsson E, Gause-Nilsson I. Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis. *Cardiovasc Diabetol*. 2016;**15**(1):37.
305. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, Norhammar A, Birkeland KI, Jørgensen ME, Thuresson M, Arya N, Bodegård J, Hammar N, Fenici P; CVD-REAL Investigators and Study Group. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL Study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). *Circulation*. 2017;**136**(3):249–259.
306. Kosiborod M, Lam CSP, Kohsaka S, Kim DJ, Karasik A, Shaw J, Tangri N, Goh SY, Thuresson M, Chen H, Surmont F, Hammar N, Fenici P; CVD-REAL Investigators and Study Group. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 Study. *J Am Coll Cardiol*. 2018;**71**(23):2628–2639.
307. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;**375**(4):311–322.
308. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;**375**(19):1834–1844.
309. Cervera A, Wajcberg E, Sriwijitkamol A, Fernandez M, Zuo P, Triplitt C, Musi N, DeFronzo RA, Cersosimo E. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. *Am J Physiol Endocrinol Metab*. 2008;**294**(5):E846–E852.
310. Sandoval DA, D'Alessio DA. Physiology of proglucagon peptides: role of glucagon and GLP-1 in health and disease. *Physiol Rev*. 2015;**95**(2):513–548.
311. le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DC, Van Gaal L, Ortiz RV, Wilding JP, Skjøth TV, Manning LS, Pi-Sunyer X; SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 Years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. 2017;**389**(10077):1399–1409.
312. Drucker DJ. The biology of incretin hormones. *Cell Metab*. 2006;**3**(3):153–165.
313. Baggio LL, Yusta B, Mulvihill EE, Cao X, Streutker CJ, Butany J, Cappola TP, Margulies KB, Drucker DJ. GLP-1 receptor expression within the human heart. *Endocrinology*. 2018;**159**(4):1570–1584.
314. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. *Cell Metab*. 2016;**24**(1):15–30.
315. Nathanson D, Frick M, Ullman B, Nyström T. Exenatide infusion decreases atrial natriuretic peptide levels by reducing cardiac filling pressures in type 2 diabetes patients with decompensated congestive heart failure. *Diabetol Metab Syndr*. 2016;**8**(1):5.
316. Liu L, Liu J, Huang Y. Protective effects of glucagon-like peptide 1 on endothelial function in hypertension. *J Cardiovasc Pharmacol*. 2015;**65**(5):399–405.
317. Kumarathurai P, Anholm C, Larsen BS, Olsen RH, Madsbad S, Kristiansen O, Nielsen OW, Haugaard SB, Sajadieh A. Effects of liraglutide on heart rate and heart rate variability: a randomized, double-blind, placebo-controlled crossover study. *Diabetes Care*. 2017;**40**(1):117–124.
318. Lønborg J, Vejlstrup N, Kelbæk H, Bøtker HE, Kim WY, Mathiasen AB, Jørgensen E, Helqvist S, Saunamäki K, Clemmensen P, Holmvang L, Thuesen L, Krusell LR, Jensen JS, Køber L, Treiman M, Holst JJ, Engstrøm T. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J*. 2012;**33**(12):1491–1499.
319. Ussher JR, Baggio LL, Campbell JE, Mulvihill EE, Kim M, Kabir MG, Cao X, Baranek BM, Stoffers DA, Seeley RJ, Drucker DJ. Inactivation of the cardiomyocyte glucagon-like peptide-1 receptor (GLP-1R) unmasks cardiomyocyte-independent GLP-1R-mediated cardioprotection. *Mol Metab*. 2014;**3**(5):507–517.
320. Smits MM, Muskiet MH, Tonneijck L, Kramer MH, Diamant M, van Raalte DH, Serné EH. GLP-1 receptor agonist exenatide increases capillary perfusion independent of nitric oxide in healthy overweight men. *Arterioscler Thromb Vasc Biol*. 2015;**35**(6):1538–1543.
321. Arturi F, Succurro E, Miceli S, Cloro C, Ruffo M, Maio R, Perticone M, Sesti G, Perticone F. Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure. *Endocrine*. 2017;**57**(3):464–473.
322. Nikolaidis LA, Mankad S, Sokos GG, Miske G, Shah A, Elahi D, Shannon RP. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation*. 2004;**109**(8):962–965.
323. DeFronzo RA. Combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor. *Diabetes Obes Metab*. 2017;**19**(10):1353–1362.
324. Eriksson L, Saxelin R, Röhl S, Roy J, Caidahl K, Nyström T, Hedin U, Razuvaev A. Glucagon-like peptide-1 receptor activation does not affect re-endothelialization but reduces intimal hyperplasia via direct effects on smooth muscle cells in a nondiabetic nodel of arterial injury. *J Vasc Res*. 2015;**52**(1):41–52.
325. Gaspari T, Welungoda I, Widdop RE, Simpson RW, Dear AE. The GLP-1 receptor agonist liraglutide inhibits progression of vascular disease via effects on atherogenesis, plaque stability and endothelial function in an ApoE$^{-/-}$ mouse model. *Diab Vasc Dis Res*. 2013;**10**(4):353–360.
326. Hirano T, Mori Y. Anti-atherogenic and anti-inflammatory properties of glucagon-like peptide-1, glucose-dependent insulinotropic polypepide, and dipeptidyl peptidase-4 inhibitors in experimental animals. *J Diabetes Investig*. 2016;**7**(Suppl 1):80–86.
327. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson

SM, Iqbal N, Maggioni AP, Marso SP, Öhman P, Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;**377**(13):1228–1239.

328. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Botros FT, Riffle MC, Rydén L, Xavier D, Atisso CM, Dyal L, Hall S, Rao-Melacini P, Wong G, Avezum A, Basile J, Chung N, Conget I, Cushman WC, Franek E, Hancu N, Hanefeld M, Holt S, Jansky P, Keltai M. Lanas F, Leiter LA, Lopez-Jaramillo P, Cardona Munoz EG, Pirags V, Pogosova N, Raubenheimer PJ, Shaw JE, Sheu WH, Temelkov-Kurkstschieve T; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomized placebo-controlled trial. *Lancet*. 2019;**394**(10193):131–138.
329. Intarcia. Intarcia presents FREEDOM-2 trial results in type 2 diabetes demonstrating clinically meaningful superiority and sustained glucose control and weight reduction for ITCA 650 vs. Januvia®: oral presentation at ADA 76th Scientific Sessions. Available at: www.intarcia.com/media/press-releases/2016-june-12-freedom-2-trial-results-in-type-2-diabetes.html. Accessed 15 August 2019.
330. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med*. 2015;**373**(23):2247–2257.
331. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riddle MC, Rydén L, Xavier D, Atisso CM, Avezum A, Basile J, Chung N, Conget I, Cushman WC, Franek E, Hancu N, Hanefeld M, Holt S, Jansky P, Keltai M, Lanas F, Leiter LA, Lopez-Jaramillo P, Cardona-Munoz EG, Pirags V, Pogosova N, Raubenheimer PJ, Shaw J, Sheu WH, Temelkova-Kurktschiev T; REWIND Trial Investigators. Design and baseline characteristics of participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial on the cardiovascular effects of dulaglutide. *Diabetes Obes Metab*. 2018;**20**(1):42–49.
332. Ahrén B, Landin-Olsson M, Jansson PA, Svensson M, Holmes D, Schweizer A. Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. *J Clin Endocrinol Metab*. 2004;**89**(5):2078–2084.
333. DeFronzo RA, Okerson T, Viswanathan P, Guan X, Holcombe JH, MacConell L. Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. *Curr Med Res Opin*. 2008;**24**(10):2943–2952.
334. DeFronzo RA, Burant CF, Fleck P, Wilson C, Mekki Q, Pratley RE. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2012;**97**(5):1615–1622.
335. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care*. 2014;**37**(8):2149–2158.
336. Solis-Herrera C, Triplitt C, Garduno-Garcia JJ, Adams J, DeFronzo RA, Cersosimo E. Mechanisms of Glucose lowering of dipeptidyl peptidase-4 inhibitor sitagliptin when used alone or with metformin in type 2 diabetes: a double tracer study. *Diabetes Care*. 2013;**36**:2756–2762.
337. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;**369**(14):1317–1326.
338. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;**369**(14):1327–1335.
339. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;**373**(3):232–242.
340. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, Alexander JH, Pencina M, Toto RD, Wanner C, Zinman B, Woerle HJ, Baanstra D, Pfarr E, Schnaidt S, Meinicke T, George JT, von Eynatten M, McGuire DK; CARMELINA Investigators. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: The CARMELINA randomized clinical trial. *JAMA*. 2019;**321**(1):9–79.

Acknowledgments

Financial Support: This work was supported in part by National Institutes of Health Grant DK-24092-38 (to R.A.D.).

Correspondence and Reprint Requests: Ralph A. DeFronzo, MD, Diabetes Division, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, Medicine/Diabetes, San Antonio, Texas 78229. E-mail: albarado@uthscsa.edu.

Disclosure Summary: The authors have nothing to disclose.

Abbreviations

ARIC, Atherosclerosis Risk in Communities; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; FDA, Food and Drug Administration; FFA, free fatty acid; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; IMT, intima–media thickness; IRS, insulin resistance syndrome; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor κB; NGT, normal glucose-tolerant; PI3K, phosphatidylinositol 3-kinase; PPAR, peroxisome proliferator–activated receptor; RA, receptor agonist; ROS, reactive oxygen species; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.