Insulin Resistance and Atherosclerosis: Implications for Insulin-Sensitizing Agents

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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)

ultiple 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 metaanalysis 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.

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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 (PI3K) (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 I κ B/nuclear factor κ B (NF- κ B), 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/PI3K/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 shortterm 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 \pm 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 longstanding 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





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 (TNF α , 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). Intraabdominal 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 I κ B/NF- κ B 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

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

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).

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 insulinresistant 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 doubleblind, 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 (\leq 6 months) stroke or transient ischemic attack were treated with pioglitazone or placebo for 4.8 years. Pioglitazonetreated 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/m²·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



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.]

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 (I κ B/NF- κ B, TLR-4, TNF α) 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 (PPAR γ) (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).

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 metaanalysis 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 PPAR α (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 insulinsensitizing effect might have resulted in a decrease in adverse CV events.

Metformin

Metformin is commonly referred to as an insulinsensitizing 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 m², 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 reductionrepresent 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 highrisk individuals (323).

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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 steatohepatiti; NF- κ B, nuclear factor κ B; 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.