CME SERIES: VOL. 7

article insights™

A nutshell analysis of medical journal articles for family physicians

volume 7

Implications of Insulin Resistance and Cardiovascular Risk to Primary Care

PCMG
Primary Care Metabolic Group

Primary Care Education Consortium

about article insights™

Article Insights™ CME Series are educational activities that provide practical pearls to the primary care physician (PCP) on various therapeutic areas treated and managed by PCPs. Each activity includes a reprint of an article that has recently been published in a specialty journal as well as a Question and Answer interview between two PCPs on the important "take-away" points of the article reprint.

In this edition of **Article Insights™ CME Series**, Dr. Brunton will interview Dr. Toth on how PCPs may apply the findings in the journal article, "Cardiovascular Manifestation of Insulin Resistance" by Veer Chawala, BS and Rohit Arora, MD, FACC, FACP, FAHA, FSCAL.

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learning objectives

After completing this activity, the primary care physician should be better able to:

1. State the relationship between insulin resistance and cardiovascular risk
2. Perform targeted screening of patients at risk for prediabetes
3. Assess strategies for preventing progression from prediabetes to type 2 diabetes mellitus
4. Prioritize intervention and patient education needs in the setting of brief office visits

target audience

Primary care physicians and clinicians who have an interest in treating patients with diabetes.

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The medical accuracy reviewer for this activity, Peter N. Weissman, MD, disclosed he is on the advisory boards and speakers' bureaus for Novo Nordisk Inc., Roche and GlaxoSmithKline. Dr. Weissman also disclosed he is on the advisory boards for Merck and Amylin.

The CME reviewer for this activity, Allan Wilke, MD has no real or apparent conflicts of interest to report.

Faculty Disclosure Statements

Dr. Brunton disclosed he is on the advisory boards for Amylin, Abbott Laboratories, Novo Nordisk Inc., and Takeda Pharmaceuticals North America.

Dr. Toth disclosed he is on the advisory boards and speakers' bureaus for Abbott Laboratories, AstraZeneca and Merck Shering-Plough. Dr. Toth also disclosed he is on the speakers' bureaus for Merck, Pfizer and Takeda Pharmaceuticals North America.

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- Content peer-review by an external topic expert
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- Content validation by internal PCEC clinical editorial staff

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The EB CME credit awarded for this activity was based on practice recommendations that were the most current with the strongest level of evidence available at the time this activity was approved. Since clinical research is ongoing, AAFP recommends that learners verify sources and review these and other recommendations prior to implementation into practice.

Clinical Practice Recommendations for AAFP EB CME Designation

Practice Recommendation #1: Testing to detect pre-diabetes and type 2 diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI 25 kg/m2) and who have one or more additional risk factors for diabetes.

Evidence based source: American Diabetes Association. Standards of medical care in diabetes—2009.

Supporting Evidence: *Diabetes Care* 2009;32 Suppl 1:S1-12. Page S6

Strength of Evidence: Practice Guideline, Strength of Recommendation: B

Practice Recommendation #2: Among individuals at high risk for developing type 2 diabetes, structured programs that emphasize lifestyle changes that include moderate weight loss (7% body weight) and regular physical activity (150 min/week), with dietary strategies including reduced calories and reduced intake of dietary fat, can reduce the risk for developing diabetes and are therefore recommended.

Evidence based source: American Diabetes Association. Standards of medical care in diabetes—2009.

Supporting Evidence: *Diabetes Care* 2009;32 Suppl 1:S1-12. Page S7

Strength of Evidence: Practice guideline, Strength of recommendation: A

Practice Recommendation #3: In asymptomatic patients with diabetes, evaluate risk factors to stratify patients by 10-year risk and treat risk factors accordingly.

Evidence based source: American Diabetes Association. Standards of medical care in diabetes—2009.

Supporting Evidence: *Diabetes Care* 2009;32 Suppl 1:S1-12. Page S9.

Strength of Evidence: Practice Guideline, Strength of Recommendation: B

Medium

Text publication in the form of a reprint article with a corresponding question and answer analysis by physicians.

Statement of Support

This program is sponsored by the Primary Care Education Consortium and Primary Care Metabolic Group and is supported by an educational grant from Takeda Pharmaceuticals North America.

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American Journal of Therapeutics 00, 000–000 (2009)

Cardiovascular Manifestations of Insulin Resistance

Veer Chahwala, BS and Rohit Arora MD, FACC, FACP, FAHA, FSCAL*

Data from the Centers for Disease Control and Prevention indicate that the prevalence of diabetes is increasing steadily and is coupled with a rise in obesity. Studies such as the Nurses' Health Study show that even slight glucose abnormalities, namely insulin resistance, increase the risk of myocardial infarctions, strokes, other cardiovascular disease, and mortality. Insulin resistance was found to accelerate atherosclerosis, inflammation, the onset of diabetes, cardiovascular disease, obesity, hypertension, chronic kidney disease, and dyslipidemia. Adiponectin was found to have potent antiinflammatory and antiatherosclerotic effects. Similarly, studies indicate that peroxisome proliferators-activated receptor agonists have the potential to treat obesity, diabetes, and atherosclerosis. From a preventive standpoint, it was shown that intensive glucose control reduces long-term cardiovascular risk. This intensive control approach included the use of thiazolidinediones (TZDs; troglitazone, pioglitazone, and rosiglitazone), which were demonstrated to have vascular and nonglycemic effects beyond glucose-lowering. A drawback of using TZDs is peripheral fluid retention. The DREAM study showed that participants with impaired fasting glucose or impaired glucose tolerance who are free from cardiovascular disease benefited significantly from taking 8 mg rosiglitazone per day. The ADOPT study provided evidence that rosiglitazone is more efficient at controlling glycemic loss and maintaining low glycosylated hemoglobin levels than metformin and glyburide. Data from the CHICAGO study indicate that the progression of carotid artery intima-media thickness, a marker of atherosclerosis and a surrogate end point for cardiovascular disease, was slowed more with pioglitazone than glimepiride in a racially diverse population of men and women with diabetes mellitus type 2. Overall, investigators have shifted from a focus on hyperglycemia to a multifactorial approach to risk management in diabetes. This multifactorial approach includes intensive glycemic control, lifestyle intervention, and intensive management of comorbid (dyslipidemia, hypertension, early renal disease) conditions. The implementation of a regular, rigorous exercise and diet program greatly decreased insulin resistance and allowed far more patients to reach their glycosylated hemoglobin goals. Studies with atrovastatin show significant improvement in cardiovascular risk factors in patients with diabetes and hypertension. Short-term studies provide support for the administration of a combination of TZD + sulfonylureas in patients with diabetes mellitus type 2. Likewise, studies have shown that a combination of TZDs + metformin reduced the risk of myocardial infarction. Finally, dipeptidyl peptidase-IV inhibitors and glycolipoprotein-1 analogs show potential for helping prevent the deterioration of glucose metabolism in early diabetes mellitus type 2.

Keywords: insulin resistance, diabetes, CV risk, TZDs, multifactorial

The 2005 statistics of the National Institute of Diabetes and Digestive and Kidney Diseases indicate that one-third or 6 million of the 20 million Americans with diabetes (aged 20 years or more) are undiagnosed. In addition, 26% of U.S. adults have impaired fasting glucose (IFG), defined as fasting glucose 100 to 125 mg/dL. For those aged 65 years or more, IFG incidence increases to 39%. Diabetes is defined as fasting plasma glucose (FPG) of 126 mg/dL or more.[1]

In the past 25 years, the rate of diagnosed diabetes has more than doubled. Since 1997, the rate has increased by greater than 40%. In New York City, this

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rising prevalence of diabetes has resulted in the mandatory electronic reporting of glycosylated hemoglobin (A1C) levels to the city's Department of Health and Mental Hygiene.[2]

The rise in diabetes has coincided with a rise in obesity throughout the United States. In 1994, all states had obesity rates of 20% or less. In 2004, 33 states reported obesity rates of 20% to 24%, and nine states had obesity rates of 25% or more. These data parallel diabetes rates in the United States. In 1994, only two states had diabetes rates 6% or more, but in 2004, 39 states had diabetes of 6% or more.

In adults aged 18 to 79 years, self-reported diagnosed diabetes increased 41% from 1997 to 2003. National Health Interview Survey data reveal that 90% of adults with newly diagnosed diabetes are obese or overweight, 60% of these are obese, and 30% are overweight. Within the self-reported cases of diabetes, the occurrence of obesity increased from 52% in 1997 to 60% in 2003. Moreover, this increase in obesity was the only noteworthy change in patient characteristics over the observed time.[3]

Government statistics estimate that a total of 41 million adults aged 40 to 74 have impaired glucose tolerance (IGT) and/or IFG. Of these, 35 million have IFG and 16 million have IGT, defined as a plasma glucose of 140 to 199 mg/dL after a 2-hour glucose tolerance test. Patients with IGT and/or IFG are at higher risk for developing type 2 diabetes, heart diseases, and stroke.[4,5]

Compared with women who did not develop diabetes, women who did eventually develop diabetes were shown to be at greater risk for myocardial infarction (MI) and stroke before diagnosis of their diabetes. Hu et al found that of the 117,629 female nurses free of cardiovascular (CV) disease at baseline, 1508 had diabetes at baseline and 5894 developed diabetes during 20 years of follow up. Those women who developed type 2 diabetes during the follow-up period had an adjusted relative risk of MI or stroke of 2.8 before diabetes diagnosis and 3.7 after the diagnosis. The ''ticking clock'' hypothesis refers to the fact that increased risk of CV disease began at least 15 years before the diagnosis of diabetes.[6]

The DECODE study assessed mortality associated with diabetes and IGT based on World Health Organization and American Diabetes Association diagnostic criteria. The data demonstrate a stepwise progression of worsening risk. Other studies have also shown that people with IGT are at increased risk of CV disease. IGT is merely a substitute for the core problem, insulin resistance. The highest number of excess deaths was among persons with IGT. World Health Organization criteria define IGT and diabetes with plasma glucose of 140 to 199 mg/dL and greater than or equal to 200 mg/dL, respectively.[7]

Recent data suggest that risk of heart disease begins at normal blood glucose levels (<96 mg/dL). Bruner et al's examination of the relationship between 2-hour postload glucose levels and coronary heart disease mortality demonstrated a linear correlation between rising glucose levels and coronary heart disease mortality. Recent meta-analyses also show a correlation between CV risk and glucose levels below diabetic threshold. This evidence supports the idea that diabetes-associated CV risk occurs within the normal range.[8]

The Cardiovascular Health Study showed that risk of CV events increased by 42% at levels of 112 mg/dL or more compared with reference levels of 92 mg/dL or less. The risk of CV events was increased at every quintile above 103 mg/dL. These data suggest that both IFG and IGT are linked with an increased risk of CV disease and cause for early intervention.[9]

In a group of 1612 patients (mean age, 62 years) undergoing percutaneous coronary intervention, more than 62% had fasting glucose anomalies that were linked with a higher than expected mortality risk. In addition, patients with fasting glucose abnormalities had significantly higher mortality rates. The mortality rates for patients with IFG, undiagnosed type 2 diabetes, and type 2 diabetes are 6.6%, 9.5%, and 11.2%, respectively. Hence, this study shows that a normal fasting glucose is associated with greater mortality in patients with advanced CV disease.[10]

Data from Norhammar et al suggest that in 181 consecutive patients hospitalized with MI and no diagnosed diabetes, 66% had undiagnosed glucose abnormalities, including undiagnosed diabetes or IGT.[11]

Matz et al, in a study of 238 consecutive patients hospitalized with stroke, found that 39% had either IGT or undiagnosed diabetes in addition to 20% with known diabetes.[12]

The Northern Manhattan Study found that flow-mediated dilation, a direct measure of endothelial function, was significantly reduced with in patients with impaired versus normal fasting glucose levels. These data support the role of IFG as a risk factor for macrovascular disease.[13]

Cabellero et al studied changes in vascular reactivity in persons at risk for type 2 diabetes. Ultrasound was used to measure brachial artery diameter, an indicator of macrovascular reactivity. It was found that the percent increase in blood flow over baseline was dramatically reduced for relatives, IGT, and diabetes groups versus the control groups. These results indicate that abnormalities in macrovascular reactivity are present in persons at risk for development of diabetes.[14]

Both genetic and environmental factors play a role in the development of insulin resistance, which is generally defined as a reduced sensitivity to the metabolic actions of insulin that promote glucose disposal. Insulin resistance is an important feature of diabetes, obesity, glucose tolerance, dyslipidemia, hypertension, coronary artery disease, and atherosclerosis. It contributes to atherosclerosis before the clinical appearance of diabetes.[15]

Insulin resistance leads to vasoconstriction, inflammation, and thrombosis. Inflammation and insulin resistance are reciprocally reinforced. This relationship results in a cycle of atherosclerosis and increased insulin resistance.[16]

Insulin resistance is quite common in clinical practice. Most patients with diabetes also have insulin resistance. Insulin resistance is highly prevalent in patients with low high-density lipoprotein cholesterol and high triglyceride levels. Approximately 50% of all patients referred to a cardiologist are insulin-resistant. Approximately 40% of patients aged 40 to 74 years and 50% of patients with hypertension are insulin-resistant.[17–20]

Ingelsson et al extended the correlation among diabetes, obesity, and heart failure (HF) and demonstrated that impaired glucose regulation independently predicted HF in elderly (age 70 years or more) patients. HF risk was found to decrease 34% with each standard deviation increase in insulin sensitivity. These data suggest the link between obesity and HF may be mediated by insulin resistance.[21]

In patients without diabetes, insulin resistance and compensatory hyperinsulinemia are strong predictors of chronic kidney disease. NHANES, a national sample of U.S. adults, identified a significant positive dose–response relationship among insulin resistance, insulin level, and risk of chronic kidney disease among participants without diabetes.[22] Obesity causes the metabolic stretching of adipose tissue, which in turn activates inflammatory responses and macrophage recruitment. Localized insulin resistance is caused by inflammation within adipose tissue. Inflammation is amplified by the release of cytokines, adipokines, and free fatty acids by adipocytes. Insulin resistance in muscles and the liver may arise from adipose tissue serving as an endocrine organ and transmitting inflammatory signals. Systemic insulin resistance may result from metabolic stress in both the liver and muscle.[23]

Visceral or abdominal fat is a major factor in CV risk. It is the fat around the viscera, within the peritoneum, the dorsal border of the intestines, and the ventral surface of the kidneys. Body mass index does not predict intraabdominal fat accumulation.[24]

Kuk et al evaluated the relationship among three measures of adiposity with all-cause mortality in white professionals and executives. Computed tomography examinations were used to quantify abdominal and liver fat. Visceral fat was the only important independent predictor of mortality. The relationship between visceral fat and mortality risk is curvilinear with the risk increasing substantially at the highest levels of visceral fat. When adjusted for age alone, visceral, abdominal subcutaneous, liver fat, and waist circumference were all significant predictors of mortality. In the clinical setting, waist circumference provides an acceptable approximation of visceral fat.[25]

C-reactive protein (CRP) is a systemic marker for low-grade inflammation and has been shown to predict CV events in patients without CV disease. CRP strongly correlated with measures of obesity, waist circumference, body mass index, and fat mass in 159 healthy men ranging from lean to obese. Visceral obesity was directly related to elevated CRP levels, and patients with high levels of both had the highest CRP levels.[26]

Metabolic and CV disease progression are cumulative degenerative processes that involve interdependent risk factors. Atherogenic risk factors are reduced by modest weight loss with the initial weight loss preferentially reducing visceral fat.[27]

Adipose tissue secretes active adipokines. Most adipokines have proinflammatory and atherogenic effects. Some examples include CRP, interleukin-6, plasminogen activator inhibitor-1, angiotensinogen, leptin, resistin, tumor necrosis factor-alpha, and monocytes chemotactic protein-1. In contrast, adiponectin has a number of antiatherogenic effects and is involved in the regulation of insulin sensitivity and lipid oxidation. The expression of adiponectin is reduced in obesity, insulin resistance, and type 2 diabetes. Adipokine levels inversely correlate with CV risk.[28,29]

Adiponectin not only exhibits strong antiinflammatory and antiatherosclerotic effects, but also shows insulin-sensitizing effects in tissues involved in glucose and lipid metabolism. Accordingly, adiponectin plays a role in the complex signaling network connecting adipocytes and insulin-sensitive tissues. The many effects of adiponectin serve as protection from macrovascular disease. As visceral adipose mass increases, adiponectin secretion is markedly reduced. However, secretion of other adipokines that reduce insulin sensitivity and contribute to endothelial dysfunction is increased. This helps promote the CV risk like with obesity and type 2 diabetes.[30]

Adiponectin has been shown to inhibit vascular inflammation. A study by Manigrasso et al that assessed adiponectin levels in healthy women showed that adiponectin levels were lower in obese versus nonobese women. Moreover, women with visceral

obesity had markedly lower levels of adiponectin than those with nonvisceral obesity.[31] Pischon et al used data from the Health Professionals Follow-up Study to perform a case–control study to evaluate the relationship between adiponectin and risk of MI in men (aged 40–75 years) without diagnosed CV disease. The highest adiponectin levels correlated with a significantly lower risk of MI.[32]

Glucotoxicity, lipotoxicity, and inflammation all contribute to the development of both insulin resistance and endothelial dysfunction as a result of shared causal factors. Insulin resistance and endothelial dysfunction manifest as diabetes, obesity, and CV disease.

The metabolic and antiinflammatory effects of peroxisome proliferators-activated receptor (PPAR) activation are thought to be a new approach to blunting atherosclerosis. PPARs are ligand-activated transcription factors belonging to the nuclear receptor superfamily. One of the metabolic benefits of PPAR activation is the direct effect of downregulation of cytokines, chemokines, and adhesion molecules in vascular and inflammatory cells within the arterial wall. Another possible benefit is the indirect effect of improving glucose and lipid metabolism through adipocytes, hepatocytes, and skeletal myocytes.[33]

PPARs are central metabolic regulators with widespread influence on lipid and glucose metabolism. The three PPAR isoforms (alpha, gamma, delta) share 60% to 80% homology in their ligand and DNA-binding domains. PPARs can limit the expression of proinflammatory genes by antagonizing the activity of other transcription factors such as nuclear factor-kappa B and activator protein-1.[34,35]

The three PPAR isoforms have distinct yet complex and overlapping biologic activities and expression patterns. The alpha isoform is expressed mainly in the liver where it regulates lipid metabolism. The gamma isoform is present mainly in fat tissue, where it controls glucose balance and participates in inflammation, atherosclerotic plaque development, and adipocyte differentiation. The delta isoform has a global tissue distribution and has been implicated in adipose homeostasis and inflammation.[36] PPAR-gamma is expressed specifically in cell types associated with CV disease, including vascular endothelial cells, vascular smooth muscle cells, T-lymphocytes, monocytes/macrophages, cardiac myocytes, and renal tubule cells. These data support the hypothesis that PPAR-gamma agonists may potentially have direct antiatherosclerotic effects in the vasculature.[37]

Obesity is associated with a chronic low-grade inflammation. Macrophages are thought to play a major role in the molecular changes that occur in adipose tissue. An increase in adiposity changes adipose paracrine function. In particular, adipocytes begin to secrete tumor necrosis factor-alpha, an inflammatory cytokine. Obesity also increases the secretion of leptin (and/or decreases the production of adiponectin) by adipocytes. These changes promote macrophage accumulation. Damage to endothelium may also promote macrophage recruitment. Macrophage activity and presence in adipose tissue promotes a vicious cycle of increased macrophage recruitment, inflammatory cytokine production, and impaired adipocyte production. Adipocytes and macrophages have common metabolic and inflammatory pathways. Normally, adipocytes regulate metabolic balance, whereas macrophages function in inflammation. However, each cell type has the ability to perform both functions. In the obese state, each cell type gains additional functions. Macrophages accumulate lipids and become foam cells. Fat tissue becomes inflamed as a result of both macrophage infiltration and cytokine secretion by adipocytes.[38]

PPAR-alpha and gamma activation in macrophages increases LXR-alpha expression and promotes expression of ABCA1, thereby mediating cholesterol efflux to apolipoprotein A1. PPAR-gamma activation may directly regulate ABCG1 and promote cholesterol release through high-density lipoprotein. PPAR agonists are hypothesized to exert antiatherosclerotic effects through many mechanisms, including improvement of system lipid levels and insulin resistance and inhibition of foam cell formation.[39] A previous study by Pistrosch et al showed that PPAR-gamma activation improved endothelial function independent of its role in glucose control in patients with type 2 diabetes. Campia et al demonstrated that PPAR-gamma activation and thiazolidinedione (TZD) treatment improved endothelial function in nondiabetic patients with hypertension or hypercholesterolemia relative to placebo treatment. Pioglitazone treatment improved endothelium-dependent dilation after bradykinin infusion without affecting endothelium-independent dilation. In the subgroup of insulin-resistant patients, pioglitazone significantly lowered CRP, the inflammatory marker. Pioglitazone also markedly lowered plasma insulin (22.9%) and triglycerides (15.1%) and increased high-density lipoprotein cholesterol (8.2%).[40]

Samaha et al assessed the effects of 12 weeks of TZD treatment on inflammatory markers and adiponectin values in patients with metabolic syndrome and without diabetes. Rosiglitazone (8 mg per day) versus placebo caused a significant reduction in inflammatory marker levels (CRP, −32%; interleukin-6, −22%) and had a favorable effect on adiponectin levels (+168%) in obese, highly insulin-resistant individuals.[41]

Derosa et al assessed TZD treatment for subjects with diabetes who were unable to control glucose levels despite taking the maximum dose oral glucose-lowering treatment. Patients received either rosiglitazone or pioglitazone added to the sulfonylurea glimepiride. Both drugs produced significant reductions in systolic and diastolic blood pressure. Blood pressure reductions seen with TZDs may be related to the concurrent reduction in insulin resistance.[42]

Atherosclerotic plaques are destabilized by enzymes that break down collagen and elastin at the fibrous cap. Meisner et al demonstrated that PPAR-gamma agonists may provide stability to these lesions by increasing the mean collagen content. Rosiglitazone not only significantly increased collagen content (7% in the plaque area), but was also found to reduce serum levels of two inflammatory markers, CRP and serum amyloid A.[43] Both synthetic and natural PPAR agonists are antiatherogenic through various mechanisms. Insulin-sensitizing PPAR-gamma agonists are used to both to treat type 2 diabetes and improve lipid profiles. Fibrates activate PPAR-alpha and limit hypertriglyceridemia.[44]

The United Kingdom Prospective Diabetes Study 34 randomized overweight patients with newly diagnosed type 2 diabetes to metformin or other intensive glycemic control medication or usual care. Metformin was linked with a 36% relative risk reduction (RRR) in all-cause mortality versus usual care. The other intensive treatments produced an 8% RRR versus usual care. There was no difference between the two intensive treatment groups in the RRR in MI, but the trend did favor metformin. These data indicate that insulin-sensitizing medication may be associated with greater reductions in CV outcomes than other glucose-lowering therapies.[45]

The Diabetes Control and Complications Trial compared the effect of intensive therapy versus conventional therapy on the long-term incidence of CV disease events in 1441 patients with type 1 diabetes (aged 13–40 years). At 6.5 years, the A1C levels were 7.4% in the treatment group and 9% in the conventional group. The small number of CV events prevented determination of whether intensive therapy prevented CV risk. Ninety-seven percent of the Diabetes Control and Complications Trial patients joined the Epidemiology of Diabetes Interventions and Complications study for 11 additional years. The primary outcome was to the first CV event (MI, stroke, angina, revascularization). Intensive treatment was correlated with a 42% reduction in the incidence of a first CV event as compared with conventional treatment. The risk of the first occurrence of nonfatal MI, stroke, or death from CV disease was reduced 57% with intensive treatment. These data support the idea that patients with type 1 diabetes should be treated with intensive therapy as early as possible.

Microalbuminuria is a prognostic marker for CV risk for both diabetic and nondiabetic patients. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications results showed that albuminuria was significantly lower among patients receiving intensive therapy. Albuminuria is strongly linked with an increased risk of CV disease.[46]

TZDs have vascular and nonglycemic benefits that extend beyond glucose-lowering. TZD treatment reduces carotid intima-media thickness (IMT), a surrogate of atherosclerotic disease, in patients with type 2 diabetes or coronary artery disease. Minamikawa et al demonstrated that troglitazone versus usual care lowered IMT incidence within 3 months in a study of 135 Japanese subjects. Koshiyama et al showed strong reductions in IMT with pioglitazone versus usual care in 106 Japanese patients with type 2 diabetes. Sidhu et al demonstrated IMT reductions with rosiglitazone in 92 patients with coronary artery disease without diabetes. Langenfield et al showed that treatment with pioglitazone substantially reduced IMT versus glimepiride in 173 patients with type 2 diabetes. Hence, TZD treatments have been shown to reduce a surrogate of atherosclerotic disease progression.[47–50]

Restenosis in stented patients is related to neointimal hyperplasia. Impaired insulin sensitivity and the inflammatory response are important factors in the development of restenosis after coronary stenting. Choi et al found that rosiglitazone substantially reduced the rate of restenosis 17.6% versus 38% in the control group. The rosiglitazone group also had a lower degree of diameter of stenosis, 23% versus 40.4% for the control group.[51]

Studies performed by Takagi et al showed that TZDs consistently and significantly lowered the rate of restenosis in stented patients with type 2 diabetes. Treatment with troglitazone resulted in a 43% decrease in neointimal reductions. A 50% reduction was seen with troglitazone treatment added to conventional diabetes therapy. A 39% reduction was observed with pioglitazone treatment added to conventional diabetes therapy.[52–54]

Choi et al observed a 54% reduction in restenosis with rosiglitazone added to conventional diabetes therapy versus other diabetes therapies.

Surrogate outcome studies with TZDs provide indirect evidence for CV event reduction. The CV risk factor reductions observed with TZDs may also reduce CV morbidity and mortality.[55]

Several large, multicenter trials are evaluating the effects of TZDs in the reduction of complications from type 2 diabetes (DM2) and insulin resistance.

PROactive, ADOPT, CHICAGO, and DREAM are discussed in detail.

PROactive assessed whether pioglitazone treatment could reduce CV morbidity and mortality in patients with DM2 and evidence of CV disease. Inclusion criteria included an A1C $>$ 6.5% with diet alone or oral glucose-lowering agents. Patients treated with insulin alone were excluded. Patients were randomized to pioglitazone or placebo in addition to their existing medications. The pioglitazone dosage was increased from 15 mg to 30 mg for the second month and 45 mg thereafter. The patients in the study had a high risk status. Most participants were male (66%), white (99%), and had a history of hypertension (75%). The vast majority of the patients were taking medications to reduce CV risk in addition to diabetes medications as needed. Approximately 55% of the patients were taking metformin, sulphonylurea, or both. Approximately 30% were taking insulin along with metformin, sulphonylurea, or both. Twelve percent of patients were taking another combination of glucose-lowering medications, and only 4% of patients controlled their glucose levels with diet alone. The primary outcome (death, nonfatal MI, stroke, acute coronary syndromes [ACS], leg amputation, revascularization) was reduced an insignificant 10% over 3 years with pioglitazone versus placebo. However, the confirmed survival curve indicates that a greater risk reduction may have been achieved with longer treatment.[56]

The main secondary outcome (death, stroke, first nonfatal MI) was significantly lowered by 16% with pioglitazone versus placebo. Analysis of the data indicates that for 48 patients were treated with pioglitazone, a first major CV event could be prevented in 3 years. All three secondary components saw improvement with pioglitazone versus control. Furthermore, the benefit occurred in subjects already receiving comprehensive medical therapy. Analysis of the subgroup of patients who had a previous MI revealed that pioglitazone significantly reduced the risk of ACS by 37% and recurrent MI by 28%. The addition of pioglitazone to the medication of 1000 patients would prevent approximately 22 recurrent MIs and 23 ACS events over 3 years.[57]

Although HF rates were higher for the pioglitazone versus the control group, HF death frequency was similar between both groups. The higher occurrence of HF may be the result of a diagnostic bias in the pioglitazone group attributable to the increase in TZD-related edema. TZDs do not appear to have any direct adverse effects on myocytes.[58]

The cardioprotective benefits of pioglitazone in the PROactive study were similar to the benefits seen in subgroups of patients with diabetes in other clinical trials. A comparison of benefits in year 3 of each trial revealed that the observed benefits were greater in PROactive. The Heart Protection Study demonstrated that simvastatin reduced CV death, MI, stroke, or revascularization by 22% in patients with diabetes.[59]

The Cholesterol and Recurrent Events Study found that pravastatin reduced coronary heart disease death or MI by 20% in patients with a previous MI.[60]

The MICRO-HOPE study showed that ramipril reduced CV death, MI, and stroke by 235% in patients with diabetes.[61]

The PROactive study, in the subgroup of patients with prior MI, demonstrated that pioglitazone at 15 to 45 mg per day reduced cardiac death, nonfatal MI, coronary revascularization, and ACS by 19%.[62]

Pioglitazone reduced CV events in high-risk patients with diabetes when added to baseline medications for glycemic control and CV risk reduction. Pioglitazone provided additional glycemic control, which reduced the need for insulin therapy.

TZD-linked edema was assessed in patients with DM2 plus chronic systolic HF and left ventricular ejection fraction less than 45%. Seventeen percent of TZD users exhibited edema, which was most often seen as peripheral edema. Pulmonary edema was infrequently observed in TZD versus non-TZD-treated patients with HF with edema. Edema development in the TZD-treated patients did not correlate with HF severity.[63]

Karalliedde et al evaluated edema management strategies in 381 TZD-treated patients with DM2 and found that patients initially treated with 4 mg rosiglitazone twice daily gained an average of 4 lbs and observed a 2.9% reduction in hematocrit.[64]

PPAR-gamma expression in the kidney is largely restricted to the inner medulla and the inner medullary collecting duct. Zhang et al found that in mice lacking the PPAR-gamma receptors in the collecting ducts, plasma volume increased 20% less with rosiglitazone than the control group. Mice with CD-specific knockout of PPAR-gamma were resistant to rosiglitazone-induced effects of increased body weight and plasma volume expansion. Rosiglitazone reduced sodium excretion in the control group, but not the knockout mice. These data illustrate the PPAR-gamma dependent pathway in controlling sodium transport in the collecting duct that underlies TZD-induced edema.[65]

In a cohort study of 16,417 Medicare beneficiaries with diabetes discharged after hospitalization for HF, Masoudi et al found that TZDs were associated with reduced mortality. Mortality among those receiving TZD therapy was substantially lower than in patients receiving no insulin-sensitizing therapy.[66]

Patients with diabetes and coexisting HF were cautioned about TZD therapy because of the potential for fluid retention.[67]

The following trials—ADOPT, CHICAGO, DREAM—are anticipated in 2006. Ramipril, an angiotensin-converting enzyme inhibitor, is known to reduce CV and renal disease in subjects with diabetes and in patients with vascular disease without diabetes. The DREAM trial analyzed whether rosiglitazone or ramipril, alone or in combination, can prevent or delay new-onset diabetes in high-risk individuals. The STARR substudy will assess the treatment effects on carotid atherosclerosis as measured by ultrasound.

Agents that block the renin–angiotensin–aldosterone system cause a reduction in new-onset diabetes. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers resulted in a lower incidence of diabetes than beta-blockers and diuretics. Whereas ACE inhibitors and angiotensin-receptor blockers improve insulin sensitivity and glucose metabolism, thiazide diuretics and beta-blockers may cause metabolic disturbances and increased insulin resistance.[68–70]

The TRIPOD study tested the role of insulin resistance in pancreatic beta-cell failure and DM2. Young Hispanic women with a history of gestational diabetes received troglitazone or placebo. The troglitazone groups showed a 55% reduction in the risk of diabetes. Preserved beta-cell function was also observed.[71]

The Diabetes Protection Program (DPP) assessed four treatments to prevent diabetes in individuals at high risk. A total of 2343 patients were randomized to receive troglitazone, metformin, placebo, or aggressive lifestyle modification. Troglitazone reduced the development of diabetes by 75% compared with placebo.[72]

The primary outcome for the DREAM study was new-onset diabetes or all-cause mortality. The secondary outcome was a composite of CV events and renal events. There was a washout period subsequent to the outcome assessments, which allowed investigators to distinguish transitory glucose-lowering from a more fundamental effect on diabetes development.[74] The DREAM study had a 2×2 factorial design and compared daily doses of 8 mg rosiglitazone plus 15 mg ramipril, 8 mg rosiglitazone plus placebo, 15 mg ramipril plus placebo, and placebo plus placebo. Rosiglitazone was initiated at 4 mg per day and uptitrated. Ramipril was initiated at 5 mg per day and uptitrated. IFG for the DREAM trial was a fasting glucose between 100 and 125 mg/dL. IGT was defined as a plasma glucose level after a 2-hour 75-mg oral glucose tolerance test (OGTT) that was $<$200 mg/dL. Individuals with known CV disease, congestive heart failure, previous MI or stroke, or uncontrolled hypertension were excluded from the DREAM study. The study included both sexes with the mean age at 54.7 years. Participants were generally overweight or obese and had hypertension (43.5%) and hyperlipidemia (35.5%). Approximately half of the participants had both IFG and IGT, whereas 35% and 14% had isolated IGT and IFG, respectively. The average FPG and 2-hour plasma glucose after OGTT were 104 mg/dL and 157 mg/dL, respectively. The STARR substudy will assess the effects of treatment on carotid atherosclerosis as measured by B-mode ultrasound. The EpiDREAM study will evaluate other determinants (dietary, lifestyle-related, demographic, clinical) of diabetes, IFG, IGT, and other metabolic and clinical outcomes.[73]

The primary outcome in the DREAM study occurred in 11.6% and 26.0% of the rosiglitazone and placebo groups with a RRR of 60%. Diabetes occurred in 10.6% and 25% of participants, respectively, with a 62% RRR. Death occurred in 1.1% and 1.3%, respectively, demonstrating a 9% RRR. In addition, there were no cases of fatal HF and no renal events were reported. The primary outcome occurred in 18.1% and 19.5% of the ramipril and placebo groups, respectively, a 9% RRR. Diabetes occurred in 17.1% and 18.5% of participants, respectively, with a 9% RRR. Death occurred in 1.2% of each group. The CV composite occurred in 2.6% and 2.4% of participants, respectively. Regression to normoglycemia was observed in 42.5% and 38.2%, respectively, with a 16% increase in this outcome. Overall, then, in participants with IFG or IGT who are free from CVD, 8 mg rosiglitazone per day significantly reduced the risk of diabetes or death, whereas 15 mg ramipril had no significant effect. The DREAM investigators forecast that for every 7 patients with IFG or IGT who receive 8 mg rosiglitazone for 3 years, one would be prevented from developing diabetes. They also predict that treatment of 1000 individuals with rosiglitazone would prevent 144 cases of new-onset diabetes with an excess of four to five cases of HF.

The ADOPT study directly compared the impact of metformin, glyburide, and rosiglitazone on metabolic and clinical outcomes in patients with recently diagnosed type 2 diabetes. Although metformin and sulfonylureas (glyburide) improve glycemic control in the short term, they are unable to prevent progressive beta-cell failure or deterioration in glycemia in the long term. ADOPT is a randomized, blind, controlled, international study that tested whether improving glycemic control in drug-naïve patients with newly diagnosed DM2 altered disease progression. Patients diagnosed with diabetes were randomized to rosiglitazone, metformin, or glyburide, each titrated to the maximum effective daily dose to reach

a plasma fasting glucose less than 140 mg/dL. The primary outcome is time to monotherapy failure, when plasma glucose exceeds 180 mg/dL despite maximum treatment. Secondary outcomes evaluated the effects of treatments on glycemic control, beta-cell function, insulin sensitivity, CV risk markers, and renal function.[74]

The results of the ADOPT study showed that at 5 years, the cumulative incidence of monotherapy failure was 15%, 21%, and 34% in the rosiglitazone, metformin, and glyburide groups, respectively. Also, risk reduction for rosiglitazone was 32% versus metformin and 63% versus glyburide. Furthermore, at the time of treatment failure, 99% of patients were receiving the maximum study drug dose. At the 4-year evaluation, 40% of patients in the rosiglitazone group had a glycated hemoglobin of <7% versus 36% of the metformin group ($P = 0.03$) and 26% of the glyburide group. The ADOPT data document the glycemic durability and risks associated with rosiglitazone, metformin, and glyburide in the initial management of type 2 diabetes. The potential risks and benefits, the profile of adverse events, and the costs of these three drugs are all factors that should be taken into account when deciding which pharmacotherapy to use for patients with type 2 diabetes. The ADOPT study provides long-term evidence that progressive loss of glycemic control can be delayed and a mean level of glycated hemoglobin maintained at less than 7% for a longer period with rosiglitazone (60 months) than with either metformin (45 months) or glyburide (33 months).

The CHICAGO trial compared the effects of pioglitazone versus sulfonylurea glimepiride in patients with type 2 diabetes on progression of atherosclerosis. The CHICAGO trial is a double-blind, randomized, active control, parallel efficacy study being conducted on approximately 462 subjects with DM2 who are asymptomatic for coronary artery disease. Patients were randomized to treatment with pioglitazone or glimepiride for 18 months. The primary outcome is the effect of pioglitazone on absolute changes in carotid IMT. Secondary outcomes include coronary artery calcium as measured by electron-beam computed tomography as well as fat distribution, markers of lipoprotein metabolism and inflammation, and coagulation factors. Glimepiride was used as an active comparator, so any effect of pioglitazone on carotid IMT was independent of glycemic changes.[75,76]

The results of the CHICAGO study showed that at baseline, the majority of participants (mean age, 60 years) were taking oral antidiabetic medication (78%) and the mean A1C was 7.4%. Patients were also receiving renin–angiotensin–aldosterone system modulators (57%), other antihypertensive drug(s), and/or statins (55%). Pioglitazone reduced the primary end point of progression of mean carotid artery intima-media thickness (CIMT). At week 72, the mean CIMT with pioglitazone was −0.001 mm versus +0.012 mm with glimepiride. The absolute treatment group difference in mean CIMT was −0.013 mm. Regardless of the time point, the absolute mean change in CIMT was lower with pioglitazone. Maximum CIMT was also lower with pioglitazone versus glimepiride (0.002 mm vs. 0.026 mm, respectively; the difference was −0.024 mm). Finally, the treatment effects on mean CIMT were similar across the prespecified subgroups (age, gender, systolic blood pressure, duration of type 2 diabetes mellitus, body mass index, AIC, and statin use). These data indicate that the progression of CIMT, a marker of atherosclerosis and a surrogate end point for CV disease, was slowed with pioglitazone in a racially diverse population of men and women with DM2 at 18 months compared with glimepiride. CHICAGO investigators will need additional data to determine the clinical significance of these findings. More particularly, they need more data to determine whether a strategy of routine use of pioglitazone instead of glimepiride substantially reduces major cardiovascular events.

There are several criteria for the diagnosis of diabetes. One criterion is a patient showing symptoms of diabetes plus a casual plasma glucose concentration greater than 200 mg/dL. An FGP >126 mg/dL or a 2-hour postload glucose >200 mg/dL during an OGTT is also indicative of diabetes. Patients with IFG and/or IGT are referred to as having "prediabetes," indicating that they are at high risk for developing diabetes.[77,78]

The management of diabetes has shifted to a multifactorial approach to risk management. Target levels have been set for A1C, blood pressure, and lipid levels. Ideally, A1C levels should be <7%, blood pressure should be controlled with ACE inhibitors or angiotensin-receptor blockers, and low-density lipoprotein cholesterol levels should be maintained with statins. Aspirin is advised as a prophylactic measure. ACE inhibitors are recommended to high-risk patients to help reduce the risk of CV events and because they have positive renal effects.[79–82]

The American Heart Association supports the importance of aggressive comprehensive risk factor management. An A1C goal of <7% is recommended and is part of a multifactorial intervention.[83]

The DPP study showed that both metformin and lifestyle intervention groups had a lower incidence of diabetes than the placebo group. The incidence of diabetes was reduced by 58% with diet and exercise and by 31% with metformin as compared with placebo.

The DPP results showed that metformin and lifestyle modifications reduced diabetes independently of race and ethnicity. Lifestyle intervention was particularly effective at reducing the risk of developing diabetes. In fact, diet and exercise was more effective than metformin at reducing new-onset diabetes in every racial and ethnic group.[84]

Roberts et al demonstrated significant benefits of an intensive 3-week program combining diet and exercise 31 overweight or obese men with metabolic risk factors. The diet consisted of high-fiber, low-fat, and moderate protein meals with no caloric restrictions. The exercise program consisted of treadmill walking for 45 to 60 minutes per day at 70% to 85% of maximum heart rate. The number of individuals who were obese decreased from 22 to 18. Lipid profiles and insulin resistance showed significant improvements. Total cholesterol, low-density lipoprotein cholesterol, and triglyceride reductions were 21%, 26%, and 28%, respectively. Insulin use was reduced by 30% and homeostasis model assessment insulin resistance was reduced by 33%. The short-term diet and exercise intervention produced reductions in oxidative stress, vascular endothelial cell activation (20%), platelet activation (8%), and inflammation (CRP reduced by 39%).[85]

These factors are all predictors of early risk for CV disease or MI. Medical therapy for each metabolic dysfunction is required to reduce atherogenesis in patients with diabetes.[86]

Steno-2 compared the effects of multifactorial intervention versus usual care in patients with DM2 and microalbuminuria. A total of 80 patients received either conventional treatment or lifestyle and multifactorial pharmacologic therapy with specific target goals. The primary outcome was a composite of CV death, nonfatal MI or stroke, revascularization, and amputation. In Steno-2, multifactorial intervention reduced CV outcomes in patients with DM2 and albuminuria. In addition, substantially more patients in the intensive treatment group reached their target levels. Intensive treatment was associated with a 53% reduction in the composite primary outcome compared with usual care. Therapy for longer periods of time might achieve an even better prognosis. Results also showed that intensive therapy significantly improved systolic and diastolic blood pressure, FPG, A1C, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and urinary albumin excretion rate.[86] The results of Steno-2 showed reduction in neuropathy (61%), retinopathy (58%), and autonomic neuropathy (63%). Reductions in these complications were maintained at 8 years.[87]

Four randomized, controlled trials of statin therapy provide evidence that aggressive low-density lipoprotein cholesterol-lowering reduces CV risk in persons with diabetes, irrespective of their cholesterol levels. The TNT study demonstrated that atorvastatin at 80 mg per day reduced CV events by 25%. The ASCOT study revealed that in patients with diabetes, atorvastatin reduced major CV events by 23% versus placebo. The CARDS study showed that atorvastatin resulted in a 37% reduction in the occurrence of major CV events. The Heart Protection Study results demonstrated that simvastatin reduced major vascular events by 22% for all patients and 335 in those patients with diabetes but without CV disease.[88,89]

In the lipid-lowering arm of the ASCOT study, atorvastatin at 10 mg showed substantial improvement in CV parameters in patients with diabetes and hypertension.[90]

Findings in two substudies, MICRO-HOPE and PERSUADE, suggest the use of ACE inhibitors for the treatment of patients with diabetes. In MICRO-HOPE, 10 mg per day of ramipril on top of standard therapy was shown to give high-risk patients with diabetes a 25% RRR in the primary outcome of MI, stroke, or CV death. In PERSUADE, treatment with 8 mg perindopril per day for 5 years reduced the primary outcomes by 19%.[91]

Insulin resistance and dyslipidemia commonly coexist in DM2. The combination of rosiglitazone plus atorvastatin had previously been shown to improve glycemic control and lipid profiles. Chu et al compared effects of the combination of the drugs versus rosiglitazone monotherapy on markers of vascular inflammation in patients with DM2. Rosiglitazone at 4 mg per day was given to all patients for 3 months. This resulted in a decreased high-sensitivity CRP (26%) and an increased adiponectin level (192%). Then, atorvastatin at 10 mg per day was added to the 4-mg per day rosiglitazone dose and given for another 3 months. Inflammatory markers were much further improved, with high-sensitivity CRP levels decreasing another 16% and adiponectin levels increasing another 124%.[92]

Five types of oral agents are available to treat diabetes, each with a unique mechanism of action. Sulfonylureas and meglitinides sensitize pancreatic beta cells to glucose and directly stimulate pancreatic secretion of insulin. The alpha-glucosidase inhibitors inhibit enzymes in the small intestines and pancreas, thus delaying glucose absorption and decreasing the rise in postprandial glucose levels. Biguanides decrease hepatic glucose output and intestinal absorption of glucose and increase peripheral glucose uptake and sensitivity. Thiazolidinediones and PPAR-gamma activators work directly by enhancing insulin action in the liver, skeletal muscle, and adipose tissue. Thiazolidinediones reduce insulin resistance at the sites of insulin action and increase glucose disposal rates and decrease

both hepatic glucose output and plasma insulin concentrations.[93]

Type 2 diabetes is characterized by insulin deficiency, insulin resistance, and increased hepatic glucose output. Medications used to treat DM2 are designed to correct one ore more of these problems. TZDs and biguanides increase insulin sensitivity. Insulin secretagogues (sulfonlylureas and meglitinides) increase insulin secretion. Alpha-glucosidase inhibitors inhibit breakdown and absorption of carbohydrates. Thus, they impact mainly postprandial hyperglycemia. Combinations of these oral agents may have additive therapeutic effects and result in better glycemic control.[94,95]

Oral antidiabetic agents may also change CV risk factors linked with insulin resistance. TZDs and metformin enhance insulin sensitivity and attenuate inflammation. Both rosiglitazone and pioglitazone substantially lower blood pressure. TZDs increase low-density lipoprotein particle size, reduce plasminogen activator inhibitor-1, and increase levels of tissue plasminogen activator. Metformin and TZDs also have beneficial effects on flow-mediated dilation and oxidative stress.[96]

This study compared the effect of rosiglitazone versus glyburide on glycemic control in 203 patients with type 2 diabetes. Patients were randomized to the aforementioned drugs and the treatment period lasted 52 weeks. Although both treatments succeeded in lowering A1C and FPG levels by week 52, the patter of glycemic decreases differed. Glyburide resulted in a rapid, initial reduction of A1C levels, but then glycemic control progressively deteriorated. In contrast, progressive reductions in A1C were sustained with rosiglitazone. By week 52, 28% of the patients randomized to rosiglitazone achieved an A1C $<7\%$ versus only 13% in the glyburide group. FPG decreased rapidly for the patients on rosiglitazone during weeks 0 through 8 and then continued to decrease to week 52. In the patients on glyburide, FGP levels saw a rapid initial decrease, then stabilization, and finally a gradual increase in the later weeks of the trial.[97]

This study assessed the addition of rosiglitazone added to an underlying sulfonylurea treatment for 4 months. It resulted in beta-cell-protective and anti-inflammatory effects and an overall improvement in long-term glycemic control. Patients were randomized to glimepiride monotherapy, glimepiride plus 4 mg rosiglitazone, or glimepiride plus 8 mg rosiglitazone. The favorable effects of rosiglitazone on glucose control, insulin resistance, and beta-cell function were found to be dose-related or more pronounced for the 8 mg versus 4-mg dose of rosiglitazone. This study provides reinforcement for the rationale of combining TZDs with sulfonylurea drugs to treat patients with DM2.[98]

The PROactive study demonstrated that treatment with pioglitazone significantly reduced the needs to start insulin use by 53% in patients with DM2. At the start of the study, 66% of the subjects were not using insulin. Of these, 11% in the pioglitazone group and 21% in the placebo group began permanent use of insulin during the course of the study. Hanefeld et al compared the safety and efficacy of adding pioglitazone or metformin to existing sulfonylurea therapy in patients with poorly controlled type 2 diabetes. Patients were randomized to receive either >15 mg pioglitazone or >850 mg metformin. Both treatments had similar effects at the end of 52 weeks. Compared with metformin/sulfonylurea, the addition of pioglitazone to sulfonylurea was associated with a reduction in urinary albumin-to-creatinine ratio and substantial improvements in high-density lipoprotein cholesterol and triglyceride levels. Therefore, the combination of sulfonylurea plus pioglitazone may be effective for patients insufficiently treated with sulfonylurea monotherapy and may also positively effect CV risk factors.[99]

A case-controlled study evaluated the effect of insulin-sensitizing therapy for prevention of MI in patients with DM2. The study was conducted in Philadelphia for 56 months. Inclusion criteria included current use of sulfonylureas, metformin, or TZDs. Compared with sulfonylurea monotherapy, the risk of MI was reduced significantly with TZDs or metformin. Combination therapy with TZD plus sulfonylurea was also found to be more favorable than sulfonylurea alone for MI reduction. These findings suggest that prevention of MI in patients with diabetes may be related to improved insulin sensitivity rather than improved glycemic control alone.[100]

This study showed that rosiglitazone added to submaximal does of metformin provides at least as good glycemic control as uptitration of metformin to its maximal dose. Seven hundred sixty-six subjects were involved and given randomized treatments. It was found that a higher percentage of patients in the rosiglitazone + metformin group than the group receiving metformin alone achieve the American Diabetes Association target level of A1C $<7\%$. The combination of rosiglitazone + metformin also provided greater reductions from baseline FPG than metformin alone. The patients receiving the combination also experienced fewer gastrointestinal complications than those subjects receiving metformin monotherapy. These data suggest that the actions of metformin and rosiglitazone are complimentary and help maintain optimal glycemic control in patients with type 2 diabetes.[101]

Dipeptidyl peptidase-IV (DPP-IV) inhibitors are currently under development in clinical studies for the treatment of patients with type 2 diabetes. DPP-IV inhibitors are potentially important early in preventing the deterioration of glucose metabolism. They also reduce the rate of glucagons-like peptide-1 (GLP-1) degradation, restore impaired insulin secretion, and protect beta cells. Two oral DPP-IV inhibitors, vildagliptin (Novartis) and sitagliptin, are currently in phase 3 trials.[102]

GLP is one of the incretin hormones known to induce insulin secretion from beta cells in a glucose-dependent manner. It is released by the gut in response to meals and potentiates glucose-mediated insulin release. Levels of GLP-1 are decreased in type 2 diabetes and obesity and DPP-IV quickly inactivates GLP-1. GLP-1 analogs (resistant to DPP-IV degradation) and DPP-IV inhibitors (prevent degradation of endogenous GLP-1) stimulate insulin secretion in a glucose-dependent manner and have related yet distinct modes of action. Interest in these chemicals lays in their potential to protect beta cells, which would delay the onset of type 2 diabetes or prevent its progression.[103]

Exenatide was the first GLP-1 analog to be approved by the U.S. Food and Drug Administration. It is administered subcutaneously by injection. Studies found that the addition of exenatide at 5 μg and 10 μg twice daily resulted in significant reductions in A1C for patients who had failed to achieve adequate glycemic levels with maximal doses of sulfonylureas, metformin, or metformin/sulfonylurea combinations. Treatment with exenatide was also associated with progressive weight loss.[104–106]

Evidence from randomized trails supports the use of four classes of therapies for CV risk reduction. These include antiplatelet agents (aspirin), ACE inhibitors, A1C, beta-blockers, blood pressure control, cholesterol management, diet, and exercise.[107]

CONCLUSION

Insulin resistance is linked to disorders and abnormalities that lead to endothelial dysfunction, atherosclerosis, and thrombosis. Hypertension, hyperinsulinemia, increased inflammation, and diabetes are also associated with insulin resistance. Finally, dyslipidemia (hypertriglyceridemia, high low-density lipoprotein, low high-density lipoprotein) has also been linked with insulin resistance. The epidemics of diabetes and obesity are major contributors to CV disease. Current guidelines recommend diet and exercise and intensive reduction of CV risk factors along with appropriate pharmacologic therapy to lower the risk of insulin resistance and reduce the risk of diabetes and CV events. TZDs target insulin resistance and potentially improve CV risk factors. DDP-IV inhibitors and GLP-1 agonists provide a future hope for the treatment of insulin resistance and diabetes mellitus type 2.

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CME Series: volume 7

Implications of Insulin Resistance and Cardiovascular Risk to Primary Care

In this seventh issue of Article Insights, Peter P. Toth, MD, PhD, FAAFP expands on the article by Chahwala et al (2009) on the cardiovascular manifestations of insulin resistance and their implications for primary care.

Question 1

Dr. Brunton: 2007 data from the Centers for Disease Control and Prevention reveal that nearly 24 million Americans now have type 2 diabetes mellitus,[1] an increase of more than 4 million from the 2005 data cited by Chahwala.[2] Because they have impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), an additional fifty-seven million people in the US have prediabetes.[3] Will you provide us some insight on the interplay of different factors and the implications of this epidemic?

Dr. Toth: In large part, the diabetes epidemic in the United States stems directly from a parallel epidemic of obesity. Today, more than a third of adult Americans are considered obese.[4] Visceral obesity induces insulin resistance and both diabetes and insulin resistance increase the risk of cardiovascular disease (CVD). As we know, CVD is the major cause of death for patients with type 2 diabetes. Metabolic syndrome, a constellation of risk factors that includes elevated triglycerides, low high-density lipoprotein cholesterol, elevated blood pressure, elevated fasting glucose, and abdominal obesity, also predicts the development of CVD and diabetes.[5] The insulin resistance observed in patients who are obese and/or who have type 2 diabetes leads to abnormalities in free fatty acid metabolism and alterations in insulin signaling, which impairs glucose sensing at the cellular level.

Question 2

Dr. Brunton: Just how common is insulin resistance in clinical practice?

Dr. Toth: In the US, the frequency of insulin resistance has been cited at ~3% of the general population.[6] Insulin resistance is clearly a feature of type 2 diabetes[2] and of prediabetes, is highly prevalent in persons with dyslipidemia characterized by low HDL and high triglycerides, and with the numbers we've described who have, or are at risk for, type 2 diabetes, insulin resistance is highly prevalent in our society.

Question 3

Dr. Brunton: How can we identify patients in our practice who are insulin resistant?

Dr. Toth: Clues for the identification of insulin-resistant patients include abdominal obesity and the presence of hypertriglyceridemia and low HDL cholesterol. Other characteristics of insulin-resistant individuals are hypertension and hyperglycemia.

Question 4

Dr. Brunton: Besides these clinical presentations is there an opportunity to screen patients for insulin resistance?

Dr. Toth: Screening for insulin resistance per se is not routinely done in practice. As you know, the test that most accurately measures insulin resistance, called the euglycemic clamp, is too costly and complicated to be used in most doctors' offices – it's really a research tool. However, if tests indicate that a patient has prediabetes or the metabolic syndrome, insulin resistance most likely is present. Therefore, it is more appropriate to consider screening those patients at risk for prediabetes or with features of the metabolic syndrome to determine whether insulin resistance is clinically evident and whether these patients will benefit from some form of intervention.

The diagnosis of prediabetes can be made by any of 3 criteria:[3]

1. IFG with glucose levels of 100 to 125 mg/dL. IFG should be determined after an overnight fast (8 hours minimum).
2. IGT with 2-hour post-challenge glucose levels of 140 to 199 mg/dL after a 75-g oral glucose load given in the morning (after an appropriate overnight fast). In patients with IFG, a 2-hour glucose tolerance test may further clarify the level of risk while also detecting undiagnosed diabetes.

Screening and Diagnosing Pre-Diabetes

Testing by	Normal	Pre-Diabetes	Diabetes
Impaired fasting glucose	<100 mg/dL	100-125 mg/dL	≥125 mg/dL
Impaired glucose tolerance	<140 mg/dL	140-200 mg/dL	≥200 mg/dL

3. Metabolic syndrome diagnosed by the NCEP criteria should be considered a prediabetes equivalent.[3] It predicts future diabetes better than IFG. Three of the metabolic syndrome criteria are sufficient to make the diagnosis. They include:
    - Central obesity (excessive fat tissue in and around the abdomen)
    - Atherogenic dyslipidemia (mainly high triglycerides and low HDL cholesterol)
    - Insulin resistance or glucose intolerance
    - Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor-1 in the blood)
    - Elevated blood pressure (130/85 mmHg or higher, can be either systolic or diastolic blood pressure elevation, or both)
    - Proinflammatory state (e.g., elevated high-sensitivity C-reactive protein in the blood)

In addition to identifying patients with prediabetes, screening of at-risk patients may also help us identify the 6 million patients with type 2 diabetes who are as yet undiagnosed but who will benefit from interventions designed to reduce the risk of diabetes-related complications. Fortunately, the most recent estimates show that the number of undiagnosed patients has dropped from 30% to 25% in just 2 years, suggesting that efforts to identify patients with diabetes are having some success.[7]

Question 5

Dr. Brunton: Should we be screening all overweight patients for insulin resistance and prediabetes?

Dr. Toth: It is certainly something to consider, given the implications for the patient. A recent consensus panel recommends targeted screening at any age for populations at high risk for the development of diabetes. These risk factors include any of the following: overweight or obese or sedentary lifestyle to which we've alluded, a family history of diabetes, those of non-Caucasian ancestry, presence of CVD or hypertension; increased levels of triglycerides, low concentrations of HDL (or both lipid abnormalities), previously identified impaired glucose tolerance (IGT), or impaired fasting glucose (IFG), and/or metabolic syndrome. Finally, women with a history of gestational diabetes, delivery of a baby weighing more than 9 pounds, or polycystic ovarian syndrome are at risk for prediabetes, just as they are at risk for type 2 diabetes.[3] So there are several populations that we should screen.

Question 6

Dr. Brunton: What is the likelihood that patients with impaired glucose tolerance or impaired fasting glucose (i.e., those who meet the criteria for prediabetes) will go on to develop diabetes?

Dr. Toth: Well, in the San Antonio Heart Study, IGT increased future diabetes risk by approximately 6-7 fold, as did a diagnosis of the metabolic syndrome.[5] In other studies, the progression to diabetes for persons with IGT, in which insulin resistance was a feature, was about 6% to 10% per year. For persons with both impaired fasting glucose IFG and IGT, the cumulative incidence of diabetes by 6 years may be as high as 65% (compared with levels on the order of 5% for those with normal glucose levels at baseline).[8] So you can see that having prediabetes has important implications for the future health of such patients.

Question 7

Dr. Brunton: You've stated that CVD accounts for a great majority of deaths in patients with type 2 diabetes. What are the CV risks of insulin resistance and prediabetes and the implications for not intervening?

Dr. Toth: Chahwala referred to the "ticking clock" hypothesis – wherein an increased risk of CVD is present at least 15 years before the diagnosis of diabetes.[2] He cited the Nurses' Health Study, which demonstrated that women destined to convert to type 2 diabetes (a "true" prediabetes population) have nearly 3 times the risk of a CV event prior to diagnosis of diabetes compared with those who remained nondiabetic over an exyended follow-up period. For those who were not initially diabetic, but converted, the relative risk was nearly 4 fold after the diagnosis was made; the risk was 5 fold for those known to be diabetic at baseline.[9] These data highlight a continuum of risk associated with severity and duration of hyerglycemia.

The CVD event rate in epidemiologic studies, such as the Australian Diabetes, Obesity, and Lifestyle Study[10] and the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study,[11] suggest a doubling of CV risk in prediabetes compared with what would be expected for individuals without IFG or IGT. Regardless of whether or not persons subsequently developed overt diabetes, baseline IGT has been shown to be an independent risk predictor for CV morbidity and mortality as well as for total mortality.[12] Conversely, as shown in the STOP-NIDDM Trial, treating patients with IGT with acarbose (an agent that lowers postprandial hyperglycemia) was associated with a 49% relative risk reduction in the occurrence of CV events and a 34% risk reduction in the incidence of new cases of hypertension (defined in the study as 140/90 mm Hg).[13]

Question 8

Dr. Brunton: There are several factors that account for the increased CV risk in persons with insulin resistance. Would you describe for us the mechanisms for this increased CV risk?

Dr. Toth: Epidemiologic data suggests that the effect of hyperglycemia is independent of other known CV risk factors. Hyperinsulinemia, elevated blood pressure, dyslipidemia, and low-grade inflammation are all factors that may result from insulin resistance and central adiposity. Glucotoxicity appears to play a pathogenic role in the blood vessel wall in the early stages of glucose intolerance. This may include damaging effects on heart function and the vasculature via different mechanisms including oxidative stress and other aspects of intravascular inflammation. There is evidence that hyperglycemia can lead to accelerated formation of advanced glycation end-products (AGEs), protein kinase-C activation, upregulated inflammatory signaling and oxidative stress. Studies have shown that increased glucose levels may trigger multiple mechanisms increasing susceptibility to atherosclerosis.[14]

Insulin resistance also is associated with the development of hypertension and dyslipidemia. This topic brings us back to obesity. When patients develop central or visceral adiposity (in contrast to peripheral fat in the subcutaneous layers), fat accumulates in mesenteric, perinephric, and omental depots, promoting insulin resistance. This adipose tissue becomes an endocrinologically active "organ" that produces a variety of cytokines and interleukins and becomes a source of free fatty acids that drive systemic inflammation.[2] This tissue also becomes a source of angiotensinogen (a precursor of angiotensin II, a driver of hypertension). In the setting of insulin resistance, there is an increase in both renal sodium reabsorption and expansion of intravascular volume. In the insulin resistant state, patients also have increased sympathetic outflow, increasing both blood pressure and heart rate. In addition, insulin resistance is highly correlated with endothelial cell dysfunction which results in reduced nitric oxide and prostacyclin production and net vasoconstriction. Dysfunctional endothelial cells are also characterized by reduced tissue plasminogen activator expression and increased production of plasminogen activator inhibitor-1, changes associated with an increased prothrombotic state.

Adipocyte metabolism is significantly altered in insulin resistance. Hormone sensitive lipase is an enzyme that hydrolyzes triglycerides to free fatty acids and glycerol. Under normal circumstances, insulin inhibits hormone sensitive lipase. In insulin resistant adipose tissue, the insulin brake on hormone sensitive lipase is lost. Free fatty acids begin to flood the portal circulation. The free fatty acids can undergo multiple fates. First, they can be reassimilated into triglycerides and packaged into very low-density lipoproteins (VLDL). The VLDL is secreted into blood. High serum levels of VLDL are associated with hypertriglyceridemia. Triglycerides from VLDL particles can be transferred into HDL particles via the activity of cholesterol ester transfer protein. As HDL particles become progressively more enriched with triglyceride, they become better substrates for lipolysis by hepatic lipase, an enzyme that breaks HDL particles down, resulting in lower serum levels of HDL. Excess fatty acids can also be deposited in the hepatic parenchyma, leading to nonalcoholic hepatic steatosis, a significant marker of insulin resistance. Fatty acids can also be burned as fuel by mitochondria during beta-oxidation or shunted toward gluconeogenesis, which can exacerbate a patient's hyperglycemia.

I'd summarize by saying insulin resistance leads to vasoconstriction, inflammation, dyslipidemia and increased thrombotic risk, and thus an increased risk for adverse CV outcomes.

Question 9

Dr. Brunton: With regard to glucotoxicity, is there a relative importance of fasting glucose levels, postprandial glucose levels, or overall A1C levels?

Dr. Toth: Most epidemiological data implicate postprandial hyperglycemia in the development of CVD, whereas the link between fasting glycemia and diabetes complications is not as clear. Moreover, in many studies, postprandial hyperglycemia is a better predictor of CV risk than A1C level. Postprandial hyperglycemia may exert its effects through its substantial contribution to total systemic glycemic exposure. Postprandial glucose also may have a direct toxic effect on the vascular endothelium, mediated by oxidative stress that is independent of other CV risk factors.[15] Just recently, adults with post-challenge hyperglycemia were shown to be more insulin resistant and have more pro-atherosclerotic and pro-thrombotic vascular profiles.[16]

Question 10

Dr. Brunton: Can insulin resistance and prediabetes be reversed?

Dr. Toth: Yes. Physical activity and weight loss help the body respond better to insulin. By losing weight through nutritional efforts and being more physically active, people with insulin resistance or pre-diabetes may avoid developing type 2 diabetes. The Diabetes Prevention Program (DPP)[17,18] and other large studies have shown that people with prediabetes and/or the metabolic syndrome can often prevent or delay diabetes if they lose a modest amount of weight by cutting fat and calorie intake and increasing physical activity—for example, walking 30 minutes a day 5 days a week. Many participants in the lifestyle intervention group returned to normal blood glucose levels and lowered their risk for developing heart disease and other problems associated with diabetes. Although less effective than lifestyle intervention, the use of metformin[17,18] and acarbose[19] have also been shown to reduce the risk of converting to diabetes. Additionally, acarbose may be associated with a reduced risk of coronary heart disease as shown in the STOP-NIDDM trial.[20] There is also clinical trial evidence showing that TZDs decrease the likelihood of progressing from prediabetes to diabetes[11,21,22] showing an approximately 50-80% risk reduction with the use of different TZDs. The effect of TZDs is greater than that of lifestyle intervention but of course, a risk: benefit assessment should be made when considering pharmacologic intervention and this use is off-label.

Question 11

Dr. Brunton: What are the main treatment recommendations for prediabetes?

Dr. Toth: We know that early identification and treatment of persons with prediabetes has the potential to reduce or delay the progression to diabetes and related cardiovascular and microvascular disease. The management of prediabetes involves multifactorial risk reduction efforts designed to address cardiometabolic disease abnormalities. Given its safety and the strength of evidence for its effectiveness in improving glycemia and reducing CV risk factors, the initial treatment approach for risk reduction across the board is intensive lifestyle management.[3] Lifestyle modification should be discussed with patients at each visit, as should inquiries about smoking. Smoking cessation has been shown to improve insulin resistance in otherwise healthy men.[23]

As prediabetes progresses, drug therapies directed towards hyperglycemia and the individual coronary heart disease risk factors might be required, although no drugs are approved for prediabetes per se.

Question 12

Dr. Brunton: Are there any blood pressure, and lipid goals recommended for persons with insulin resistance or prediabetes?

Dr. Toth: There are no formal recommendations for patients with insulin resistance. However, in the recent prediabetes consensus conference statement from the American Association of Clinical Endocrinologists, the same blood pressure and lipid goals were suggested for both prediabetes and diabetes[3] (low-density lipoprotein cholesterol levels goals are ≤100 mg/dL; non–high-density lipoprotein cholesterol ≤130 mg/dL and/or apolipoprotein B ≤90 mg/dL). I think it is best to determine CV risk in patients with features of insulin resistance using a Framingham risk score calculation and set goals based on the results of this for individual patients. This simple calculator can be found at:

http://hp2010.nhlbihin.net/atpiii/calculator.asp

Question 13

Dr. Brunton: Several large, multicenter trials have evaluated the effects of TZDs in the reduction of complications from type 2 diabetes and insulin resistance, and as you described earlier, the conversion from prediabetes to diabetes. Can you briefly review these for us and provide your perspective on what they collectively tell us?

Dr. Toth: The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) is the only positive completed CV outcomes study with a TZD. It provides valuable information on the impact of pioglitazone on CV outcomes in a high-risk population of patients with type 2 diabetes and established macrovascular disease. The investigators in PROactive chose a challenging primary composite endpoint that included events in multiple vascular beds (cerebral, cardiac, and peripheral), as well as both disease-related and procedural endpoints. They also chose for a pre-specified endpoint a more conventional secondary composite endpoint of all-cause mortality, myocardial infarction, and stroke. In PROactive, pioglitazone was associated with a reduction in a secondary composite endpoint of clinical cardiovascular events in high-risk patients with existing macrovascular disease who were already receiving other antihyperglycemic and cardiovascular medications.[24] Since the results of PROactive were first presented, there has been debate on the relative merits of the statistically non-significant 10% decrease in the primary endpoint vs. the statistically significant 16% decrease in the main secondary endpoint seen with pioglitazone. PROactive incorporated several pre-specified analyses in two pre-defined patient subgroups—those with previous MI and those with previous stroke. Among patients with a previous MI, there was a statistically significant 28% relative risk reduction (RRR) for recurrent fatal/non-fatal MI in those treated with pioglitazone.[25] Effects on two pre-specified CV composite endpoints (i) CV mortality and MI and (ii) CV mortality, MI, and

stroke were not statistically significant, but trended in the same direction. Similarly, among patients with a previous stroke (secondary prevention), there was a statistically significant 47% RRR for recurrent fatal/non-fatal stroke with pioglitazone,[26] as well as a decrease in the composite of CV mortality, MI, and stroke (38% reduction). However, there was no decrease in risk among those patients without previous history of stroke (primary prevention). In contrast, the DREAM investigators[27] showed that while rosiglitazone therapy decreased the development of renal disease, it did not improve cardiorenal outcomes and it did increase the risk of heart failure.

There also are some interesting mechanistic studies that have recently been reported. As we know, carotid artery intima-media thickness (CIMT) is a marker of coronary atherosclerosis. The CHICAGO study was a randomized double-blind active comparator trial done in a multiracial population of patients with type 2 diabetes. In the CHICAGO study, treatment with pioglitazone was shown to slow progression of CIMT compared with glimepiride over an 18-month treatment period in patients with type 2 diabetes.[28] Further evidence supporting an antiatherogenic effect of pioglitazone has also been gained from the PERISCOPE study which used intravascular ultrasonography to evaluate changes in coronary atherosclerotic disease.[29] This was another large multicenter study of patients with type 2 diabetes. In this case, patients had a known history of CAD. Treatment with pioglitazone, but not glimepiride, was associated with a reduced progression rate of atherosclerosis. Recent data from other investigators suggest that the reduced rate of atherosclerosis associated with this TZD correlates with improved (increased) HDL levels.[30]

Question 14

Dr. Brunton: Certainly, there has been a lot of discussion recently on the cardiovascular effects of TZDs. Would you expand on that for us please?

Dr. Toth: As we know, TZDs should not be used in people with pre-existing NYHA Class III or IV heart failure. The recent boxed warning now advises physicians to look carefully for heart-failure signs and symptoms, including edema, shortness of breath, and rapid weight gain in patients for whom TZDs are being considered. A recent meta-analysis has linked the use of rosiglitazone with an increased risk of ischemic events[31]; there is now a black box warning specifically regarding this for rosiglitazone. Conversely, another meta-analysis showed that pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. However, serious but not fatal heart failure was increased by pioglitazone.[32]

TZDs also have vascular and nonglycemic benefits that extend beyond glucose-lowering effects. Clinical data suggest that use of TZDs in patients with type 2 diabetes may also result in lower blood pressure, improvements in dyslipidemia, improvements in vascular structure and function, decreased inflammation, improvements in the adipokine profile, and reduced systemic oxidative stress.[33] One study that I find quite compelling is a head-to-head comparison of pioglitazone and rosiglitazone comparing lipid and glycemic effects in patients with both type 2 diabetes and dyslipidemia.[34] The two agents had significantly different effects on plasma lipids, independent of glucose control. Treatment with pioglitazone reduced triglyceride levels by ~52 mg/dL compared to an increase in triglyceride levels of ~13 mg/dL that was observed with rosiglitazone ($p<0.001$). Pioglitazone also increased HDL levels to a greater extent ($P<0.001$) than rosiglitazone, and increased LDL levels to a significantly lesser extent ($P<0.001$). LDL particle size increased more with pioglitazone ($P = 0.005$). Another very recent study has shown that TZDs reduce restenosis rates in stented patients with type 2 diabetes.[35]

Question 15

Dr. Brunton: There has also been some interesting discussion on the "durability" of different antihyperglycemic agents, that is, "how long does the efficacy last for a given class of agents?" Can you tell us where TZDs fare with regard to durability?

Dr. Toth: ADOPT unequivocally demonstrated that TZDs have a durable effect on the ability to maintain A1C levels over time. This has never been shown before – in all other studies, there has always been an inexorable rise in A1C levels, with the need to add additional glucose-lowering agents to maintain glycemic control with other agents. In ADOPT, monotherapy failure rates at 5 years were 15% with rosiglitazone, 21% with metformin, and 34% with glyburide.[36] This finding was echoed in the CHICAGO trial,[28] with pioglitazone therapy associated with a stable reduction in A1C levels, while glimepiride therapy induced an initial reduction in A1C followed by a linear increase in this parameter during the following 18 months of follow-up.

Question 16

Dr. Brunton: What are the key points that primary care clinicians should remember about insulin resistance and cardiovascular disease?

Dr. Toth: My main thoughts are as follows:

1. Insulin resistance has a very complex pathophysiology.
2. Insulin resistance is associated with an increased risk of CVD secondary to disturbances in glucose and lipid metabolism, increased blood pressure, and induction of endothelial dysfunction.
    a. These effects occur in both men and women and in people of all racial/ethnic groups.
3. Insulin resistance, especially if caught early, is reversible through lifestyle modification.

a. Insulin resistance can also be reversed through pharmacologic therapy, with metformin, TZDs, and acarbose, as demonstrated in large clinical trials.

i. This can reduce the risk of conversion from a prediabetic state to type 2 diabetes as shown in several studies and most recently in ACT NOW.

4. Among DM patients treated with TZDs, there is evidence for durability of effect for maintaining glycemic indices over time with this treatment option.

a. TZDs also have some favorable effects on markers of CV risk that should be considered.

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