A Review of Cardiovascular Risks Associated with Medications Used to Treat Type-2 Diabetes Mellitus

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TYPE-2 DIABETES MELLITUS AND CARDIOVASCULAR DISEASE

Patients with type-2 diabetes mellitus face up to a four times greater risk of developing cardiovascular disease compared with nondiabetic patients. Cardiovascular complications that are often associated with diabetes include heart failure, acute myocardial infarction (MI), peripheral vascular disease, and cerebrovascular disease. In one study, patients with diabetes had a slightly greater risk of experiencing a first MI than those without diabetes who had a history of MI. It was also discovered that patients with diabetes who had a previous MI were 45% more likely to experience a second MI. A previous MI is a significant risk factor for the subsequent development of heart failure. This can be one factor contributing to the increased risk of heart failure in diabetic patients. Even otherwise healthy diabetic individuals may present with systolic and diastolic myocardial dysfunction, which further potentiates their risk of heart failure.

In the Framingham Heart Study, men with type-2 diabetes were twice as likely to develop heart failure, whereas this risk was increased by five-fold in women. Another cardiovascular risk factor associated with diabetes is cerebrovascular accident (CVA), or stroke. Pooled data from epidemiological studies suggest that the risk of stroke may be reduced by 17% for every 1% decrease in glycosylated hemoglobin (HbA1c).

Cardiovascular complications are the leading cause of morbidity and mortality in patients with type-2 diabetes and are of great concern to practitioners caring for such patients. Management and prevention of cardiovascular disease may be complicated by the fact that cardiovascular damage is likely to be already present well before diabetes has been diagnosed. For this reason, it is essential that at-risk patients be regularly screened for fasting blood glucose levels, HbA1c, or both, and that they receive appropriate counseling and treatment based on their risk factors.

MECHANISMS OF INCREASED CARDIOVASCULAR RISK IN DIABETIC PATIENTS

For many years, the mechanisms behind the increase in cardiovascular risk in patients with type-2 diabetes were not well defined. Many thought that the elevation of blood glucose alone was the major contributing factor, whereas others believed that additional mechanisms were involved. Two pivotal studies—The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS)—demonstrated that microvascular (DCCT, UKPDS) and macrovascular (UKPDS) complications could be decreased with tight glycemic control. Controversy surrounding tight glucose control followed after the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) was stopped prematurely because of an increased mortality rate in the intensive-treatment group. ACCORD showed that cardiovascular risk associated with type-2 diabetes was not solely a result of elevated glucose levels. Several explanations have been proposed for the propensity toward cardiovascular complications.

Effects of Elevated Blood Glucose

Altered Coagulation

One mechanism behind a higher cardiovascular risk is attributed to altered effects on coagulation. Clotting factors IIa (thrombin) and VII are increased in patients with diabetes, whereas protein C, a natural anticoagulant, is decreased. Fibrinolysis is also reduced, further raising the risk of clot formation. Elevations in blood glucose levels can cause an increase in the number of vascular smooth muscle cells used in the formation of the fibrous cap found on the clot. The presence of excessive glucose may lead to inflammation at the artery wall through increased monocyte adhesion to endothelial cells and to alterations in the monocytes themselves, causing an accumulation of macrophages.

After a clot is formed, destabilization of the clot may lead to acute cardiac events. In studies of diabetic patients post mortem, the small coronary arteries appear to be hardened and thickened.

Insufficient Vasodilation

A deficiency in vascular vasodilation is another proposed mechanism attributed to an elevated risk of cardiovascular complications. Nitric oxide causes increased vasodilation in the endothelium. High blood glucose levels reduce as well as inactivate nitric oxide in the body, decreasing appropriate vasodilation. Patients with type-2 diabetes also appear to have an increase in endothelin, which may lead to vasoconstric-

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tion. This may further contribute to the development of cardiovascular complications.11

**Elevated Free Fatty Acids**

Free fatty acids (FFAs) are believed to be involved in the cardiovascular complications related to diabetes. Elevated blood glucose levels lead to higher levels of FFAs. An overabundance of FFAs may result in endothelial dysfunction, enhanced coagulation, insulin resistance, increased lipid deposits in various organs, and inflammation. FFAs also affect cholesterol components by causing an increase in triglycerides (TGs), low-density lipoproteins (LDLs), and very-low-density lipoproteins (VLDLs) and a decrease in high-density lipoproteins (HDLs).11

**Cholesterol-Lowering Therapy**

Diabetic patients who are taking cholesterol-lowering treatment (e.g., statins) for elevated lipoprotein levels continue to have an increased risk of cardiovascular disease even when cholesterol goals have been reached. It has been speculated that this increased risk is associated with changes that occur to the lipoproteins themselves in diabetic patients. Not only are the atherogenic lipoproteins TGs and LDLs enhanced in patients with type-2 diabetes; the LDLs of diabetic patients are also denser. The size and composition of the HDLs are altered, making them less effective in scavenging and removing cholesterol.10

**Effects of Insulin Resistance**

In clinical trials, insulin resistance alone has contributed to cardiovascular complications.12 Insulin resistance is thought to have the potential to cause left ventricular hypertrophy (LVH) and diastolic dysfunction through alterations in cardiac contractility, endothelial dysfunction, and inflammation. Furthermore, calcification of the coronary arteries has been found in individuals with insulin resistance. This calcification may pose an increased risk of cardiovascular complications if it is left undetected and untreated.13

**TREATMENT OF TYPE-2 DIABETES**

Type-2 diabetes is believed to result from both genetic and lifestyle factors that produce a state of high insulin resistance. Despite the availability of a wide array of treatment options, choosing an appropriate therapy poses a challenge for health care professionals. A delicate balance exists between the efficacy of the chosen agent and the presence of cardiovascular risk. The American Diabetes Association (ADA) and the European Association for Study of Diabetes have developed an evidence-based algorithm to guide practitioners in the initial selection of a therapy.14

In addition to lifestyle modifications, metformin (e.g., Glucophage, Bristol-Myers Squibb) should be implemented as a first-line agent in patients when there are no contraindications. In UKPDS, metformin showed a cardiovascular benefit, probably a reason for its strong recommendation. Patients who are unable to attain glycemic control with maximum doses of metformin should receive an additional agent. The ADA lists three medication classes (insulin, sulfonylureas, and thiazolidinediones) that may be added to metformin with no preference among the agents. These medications have benefits, although variable, in lowering blood glucose levels. However, many concerns about non-glycemic effects remain. Some agents are cardioprotective, but others may pose a cardiovascular risk. More recently, the FDA raised concerns about the potential cardiovascular risk associated with rosiglitazone maleate (Avandia, GlaxoSmithKline).15

The following text highlights the literature regarding the use of insulin, sulfonylureas, metformin, and thiazolidinediones (TZDs) for the treatment of type-2 diabetes and their possible connection to cardiovascular disease.

**Insulin**

Insulin is believed to promote atherosclerosis in vitro through a variety of mechanisms. These include stimulation of smooth-muscle cell proliferation and migration, enhanced lipid synthesis, increased formation of lipid lesions, and improved LDL binding to smooth muscle cells and monocyte macrophages.16 Despite evidence of enhanced atherosclerosis from in vitro studies, several large trials have shown that insulin does not increase the risk of cardiovascular disease in patients with diabetes.8,17,18

**DCCT and EDIC8,17,19**

The DCCT investigators observed that in patients with type-1 diabetes mellitus, intensive insulin therapy (compared with conventional therapy) significantly reduced the incidence of microvascular and neurological complications of diabetes but not macrovascular events.8 However, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the DCCT’s long-term follow-up study, showed different results. Investigators evaluated carotid intima–media thickness as a measure of atherosclerosis six years after the completion of DCCT.19 They found that the progression of carotid artery intima–media thickness was significantly lower in patients who had originally been enrolled in the intensive-treatment arm compared with those in the conventional-treatment arm (P = 0.01). This finding encouraged the investigators to examine whether intensive insulin therapy also decreased clinical outcomes associated with cardiovascular disease. They found that by year 11 of the EDIC study, HbA1c levels were similar among patients who were originally enrolled in the intensive-treatment group and in the conventional-treatment group.

Despite this finding, an analysis of the cumulative incidence of a first cardiovascular event showed a 42% reduction in patients who were originally enrolled in the intensive-treatment arm compared with the conventional-treatment arm (P = 0.02). In addition, the risk of the first occurrence of nonfatal MI, stroke, or death from cardiovascular causes was reduced by 57% in the intensive-treatment arm (P = 0.02), compared with patients receiving conventional treatment.17

**UGDP18 and UKPDS9**

Two large trials examined whether insulin therapy decreased macrovascular events in patients with type-2 diabetes.9,18 The University Group Diabetes Program (UGDP) enrolled patients into a standard-therapy group, an intensive-therapy group, and a placebo group. The fourth treatment arm, which included a sulfonylurea, was terminated.18 After 13
years, neither insulin group differed from the placebo group in any cardiovascular endpoints evaluated. Further, there was no difference in cardiovascular endpoints between standard insulin and intensive insulin. This was the first large study to refute the hypothesis that exogenous insulin causes adverse cardiovascular outcomes.

UKPDS was also conducted to determine whether intensive insulin therapy would improve cardiovascular outcomes in type-2 diabetes. Patients were randomly assigned to receive intensive therapy with a sulfonylurea or insulin or conventional therapy with diet alone. Despite significantly reducing the incidence of microvascular complications, neither intensive-therapy group experienced reduced macrovascular complications. In addition, neither therapy (a sulfonylurea or insulin) adversely affected cardiovascular outcomes. Results of UKPDS further disprove the idea that exogenous insulin is a potentially harmful treatment despite its *in vitro* activity.

Sulfonylureas

**The Meinert, Meier, Johnsen, and Simpson Trials**

Cardiovascular risk associated with sulfonylureas became a concern when an interim analysis of UGDP, which had been conducted in 1969, showed a statistically significant increase in cardiovascular deaths associated with tolbutamide therapy. Because of this increased risk, the tolbutamide arm was discontinued.

Several hypotheses have been proposed in an attempt to explain these potentially detrimental effects of sulfonylureas. One proposed mechanism was that sulfonylureas are associated with elevated pro-insulin levels, which in turn are associated with elevated plasminogen-activating inhibitor-1 (PAI-1), a major inhibitor of fibrinolysis. In theory, elevated PAI-1 can lead to negative outcomes of atherothrombotic events.

Another hypothesis involves the inhibition of "ischemic pre-conditioning" caused by some sulfonylureas. In this phenomenon, the myocardium is exposed to brief periods of ischemia in order to minimize damage caused by a longer period of ischemia (such as in the event of an MI). Glipizide (Glucotrol, Pfizer), gliclazide (Diamicron, Servier) plus other drugs as required to decrease HbA1c levels to 6.5% or below, compared with standard glucose control, would reduce macrovascular events in patients with type-2 diabetes. The investigators found that there was no significant difference between the groups in terms of mortality rates. These results are in contrast to those of ACCORD, which was terminated early because of an increase in mortality in the intensive-therapy group. Although intensive therapy with a sulfonylurea did not improve cardiovascular outcomes in ADVANCE, it was not associated with an additional risk of mortality either. The results of this study, along with those from UKPDS, suggest that sulfonylureas do not increase mortality rates in patients with type-2 diabetes.

**Metformin**

**UKPDS** and Johnson et al.

Results from UKPDS provided the first evidence that intensive glucose control with metformin could improve cardiovascular outcomes. In this randomized study, a subset of 753 overweight patients with newly diagnosed type-2 diabetes were to receive intensive control with metformin or conventional therapy with diet alone. The investigators found that patients in the metformin group experienced risk reductions of 32% in any one diabetes-related endpoint (*P* = 0.002), 42% for diabetes-related death (*P* = 0.017), and 36% for all-cause mortality (*P* = 0.011). In addition, in contrast to intensive therapy with chlorpropamide (Diabinese, Pfizer), glibenclamide (glyburide), or insulin, metformin was associated with significant reductions in any one diabetes-related endpoint (*P* = 0.0034), all-cause mortality (*P* = 0.021), and stroke (*P* = 0.032).

It is debatable whether the combination of metformin and sulfonylurea increases cardiovascular mortality in patients with type-2 diabetes compared with either agent alone. In a sub-study analysis, the UKPDS authors noted that adding metformin to ongoing sulfonylurea therapy was associated with an increase in diabetes-related deaths and all-cause mortality rates compared with a sulfonylurea alone. However, a retrospective analysis of a Canadian health database by Johnson and coworkers, examining whether there was a relationship...
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between the new use of metformin and sulfonylureas and mortality, showed different results. The Johnson investigators identified 12,272 new users of metformin, sulfonylureas, or both. They concluded that metformin, with or without sulfonylurea therapy, was associated with reduced all-cause and cardiovascular mortality compared with a sulfonylurea alone.

Abbasi et al.29

In a small study involving 31 patients with type-2 diabetes, Abbasi and associates sought to determine whether metformin, either alone or added to ongoing sulfonylurea therapy, would have different effects on cardiovascular risk factors (total cholesterol, TGs, HDLs, LDLs, and LDL particle size). These researchers found that the effect of metformin mono-therapy or combination therapy on several cardiovascular disease risk factors was similar for both groups. These results further refuted the idea that combining metformin with a sulfonylurea could be harmful to patients with type-2 diabetes.

Metformin Product Information30 and Masoudi et al.31

Until recently, heart failure requiring pharmacological therapy was a contraindication to metformin therapy because of the increased risk of lactic acidosis in these patients. Despite this prior contraindication, a retrospective analysis by Masoudi and colleagues found that a significant number of elderly patients hospitalized with heart failure were taking concomitant metformin.31 Examining two national samples of Medicare beneficiaries hospitalized for heart failure (from 1998 to 1999 and from 2000 to 2001), they found that 7.1% of patients in the first sample and 11.2% in the second sample were being discharged with a prescription for metformin. The investigators concluded that elderly patients hospitalized for heart failure were being commonly treated with medications (like metformin) that are not recommended. More studies are needed to determine whether these drugs can be used safely in such patient populations.

Fisman et al.32 and Mayer et al.33

Although metformin does not cause weight gain and is recommended as a first-line therapy for type-2 diabetes, it can have a negative influence on the cardiovascular system. A common adverse effect associated with metformin is transient diarrhea, which usually resolves after patients are stabilized with an appropriate dose. In patients receiving chronic therapy who experience diarrhea, folate absorption can be impaired; this in turn can increase homocysteine levels. Increased homocysteine levels are known to accelerate the progression of vascular disease.31 Metformin also undergoes renal excretion and may have pharmacokinetic interactions with drugs used to treat cardiovascular conditions. These drugs include nifedipine (Procardia, Pfizer) and furosemide (Lasix, Sanofi-Aventis), which can increase metformin levels, as well as digoxin (Lanoxin, GlaxoSmithKline), quinidine, and triamterene (Dyrenium, Wyeth), which compete with metformin for proximal renal tubular transport.32

Thiazolidinediones

In 2007, TZDs came under fire because of the controversy surrounding the cardiovascular effects of rosiglitazone. Before we present the evidence available regarding rosiglitazone and pioglitazone (Actos, Takeda/Lilly), it would be practical to discuss the TZD class as a whole.

Package inserts for the TZDs contain a boxed warning recommending against their use in patients with heart failure. In fact, the use of TZDs is contraindicated in patients with New York Heart Association (NYHA) Class III or IV heart failure.

Masoudi et al.31

Despite these warnings, a retrospective analysis conducted by Masoudi et al. found that a significant number of elderly patients hospitalized with heart failure were taking concomitant TZDs. These researchers evaluated two national samples of Medicare beneficiaries hospitalized for heart failure (from 1998 to 1999 and from 2000 to 2001) to see how many patients with type-2 diabetes were discharged with prescriptions for TZDs. The investigators found that 7.2% of patients in the first sample and 16.1% in the second sample were discharged with a prescription for TZDs. They concluded that it was common for elderly patients hospitalized for heart failure to be treated with medications (like TZDs) that are not recommended.

AHA and ADA Consensus (Nathan et al.)34

In 2003, the American Heart Association (AHA) and the American Diabetes Association (ADA) developed a consensus statement regarding TZDs in patients with fluid retention and congestive heart failure. Their joint statement recommended that before prescribing therapy with a TZD, health care professionals should take a multistep approach, including obtaining a patient’s medical history, conducting a physical examination and electrocardiogram (ECG), and providing patient education (Table 1).

Before initiating therapy in patients without heart disease, prescribers should first determine the patient’s risk factors for heart failure. These risk factors consist of a history of heart failure, a prior MI or symptomatic coronary artery disease, and from 2000 to 2001), they found that 7.1% of patients in the first sample and 11.2% in the second sample were being discharged with a prescription for metformin. The investigators concluded that elderly patients hospitalized for heart failure were being commonly treated with medications (like metformin) that are not recommended. More studies are needed to determine whether these drugs can be used safely in such patient populations.

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<table>
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<tr>
<th>Table 1 Multistep Approach to Evaluating Patients Prior to Prescribing Thiazolidinedione (TZD) Therapy</th>
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<tbody>
<tr>
<td><strong>Patient history:</strong></td>
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<tr>
<td>• Does the patient have underlying cardiovascular disease?</td>
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<tr>
<td>• Is the patient taking any drugs that can cause fluid retention or pedal edema?</td>
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<tr>
<td>• If edema is present, what is the suspected cause?</td>
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<tr>
<td>• Does the patient experience shortness of breath, especially with exertion?</td>
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<tr>
<td><strong>Electrocardiography:</strong></td>
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<tr>
<td>• Silent myocardial infarction or left ventricular hypertrophy is a risk factor for heart failure.</td>
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<tr>
<td><strong>Patient education:</strong> Report any of the following:</td>
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<tr>
<td>• weight gain over 6.5 pounds</td>
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<td>• pedal edema</td>
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<tr>
<td>• shortness of breath</td>
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<td>• fatigue with unknown cause</td>
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hypertension, LVH, aortic or mitral valve disease, age older than 70 years, having had diabetes for more than 10 years, edema or treatment with loop diuretics, concomitant insulin therapy, and renal failure (a serum creatinine level above 2 mg/dL).

In patients with one or more of these risk factors or with a depressed ejection fraction of less than 40%, TZDs should be initiated at a low dose and should be titrated gradually while the physician monitors for weight gain, peripheral edema, or heart failure. Patients with NYHA Class I or II heart failure can begin therapy, but at the lowest possible dose with appropriate monitoring, as described. Patients with NYHA Class III or IV heart failure should not receive TZDs.

Lincoff et al. and Richter et al.

In clinical trials, pioglitazone decreased TG levels and increased HDL levels. A 15% increase in HDL, like that seen with pioglitazone, has been associated with regression of coronary atheroma and a reduction in coronary heart disease in trials with lipid-modifying agents. This suggests that pioglitazone might have beneficial effects on cardiovascular outcomes.

The authors of a Cochrane Database Systematic Review, published in 2006, concluded that based on findings of published studies with 24 weeks or more of pioglitazone therapy, the drug did not positively influence morbidity, mortality, adverse effects, or health-related quality of life. The authors also stated that significantly more patients treated with pioglitazone developed heart failure. At the time of that publication, several large trials involving pioglitazone were ongoing.

The Lincoff meta-analysis, published in 2007, included many of these large trials and evaluated the effect of pioglitazone on ischemic cardiovascular events. In this meta-analysis, 19 trials that enrolled more than 16,000 patients, pioglitazone was associated with a significant decrease in the risk of death, MI, or stroke. The drug was also linked to a significantly higher rate of serious heart failure, although there was no associated increased risk of death. Results of this meta-analysis refute the theory that pioglitazone is associated with adverse outcomes of ischemic cardiovascular events such as MI.

PERISCOPE (Nissen et al.)

A more recent study—PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation)—aimed to compare the effect of pioglitazone with glimepiride, a sulfonylurea, on the progression of coronary atherosclerosis. In this randomized trial by Nissen and coworkers, 543 patients received glimepiride 1 to 4 mg or pioglitazone 15 to 45 mg for 18 months. The primary outcome was the change in percentage of atheroma volume from the baseline measurement.

Pioglitazone significantly lowered the progression of coronary atherosclerosis compared with glimepiride. The results provide further support that pioglitazone might have favorable effects on cardiovascular outcomes.

Nissen et al.

In the meta-analysis published by Nissen et al. in 2007, 42 trials involving 15,560 patients were evaluated to determine whether rosiglitazone had a significant effect on cardiovascular morbidity and mortality. Rosiglitazone was found to be associated with a significant increase in the risk of MI. The risk of death from cardiovascular causes was also increased, although not significantly, in patients taking rosiglitazone. This work has been criticized by others for being a meta-analysis (instead of a randomized, controlled trial) and for including large trials that did not investigate cardiovascular risk as a primary outcome.

Singh et al. and Lipscombe et al.

A follow-up meta-analysis was performed to examine the long-term effects of rosiglitazone on MI, heart failure, and cardiovascular mortality. This meta-analysis included four trials involving 14,291 patients. Only randomized, controlled trials that utilized rosiglitazone for 12 months or more for treating or preventing type-2 diabetes were involved. Cardiovascular events also had to be monitored, and numerical data had to be included. The results showed that rosiglitazone was associated with a significantly elevated risk of MI and heart failure, even though its use was not observed to be related to increased cardiovascular mortality.

A retrospective analysis by Lipscombe et al. that evaluated the association between TZDs and MI, heart failure, and mortality in people older than 65 years of age produced similar results. Although this study looked at TZDs as a class, the investigators noted that the increased risk of heart failure, acute MI, and mortality affected only patients taking rosiglitazone.

RECORD (Home et al.)

After the meta-analysis by Nissen and colleagues was released, investigators involved in the RECORD trial (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) released results from an interim analysis, concerned that new information regarding rosiglitazone could cause significant patient dropout. The trial, by Home et al., enrolled 4,447 patients with type-2 diabetes who were currently receiving metformin or a sulfonylurea. Patients were randomly assigned to receive add-on rosiglitazone therapy or add-on therapy with metformin or a sulfonylurea, whichever agent they were not then taking. After 3.75 years, rosiglitazone was not associated with an increased risk of MI or death from cardiovascular causes, but the authors noted that the data were insufficient to make a final determination.

VADT

In 2009, the results of the Veterans Affairs Diabetes Trial (VADT) were published. This trial had also examined intensive control versus standard control. Rosiglitazone was used as a primary therapy in both groups, and extra therapies were added based on body mass index, glucose control, or both. The primary outcome was defined as time to first occurrence of a composite of cardiovascular events (documented MI, stroke, death from cardiovascular causes, new or worsening heart failure, surgical intervention for cardiovascular, cerebrovascular, or peripheral vascular disease, and amputation). After 5.6 years, the investigators found no significant difference
between groups in the primary outcome or in the rate of death from any cause. The findings of this study further complicate the debate surrounding the cardiovascular risk associated with rosiglitazone use.

CONCLUSION

Patients with type-2 diabetes mellitus represent a unique population with a high lifetime risk of cardiovascular disease. Glycemic control is a crucial element in reducing this risk. However, the same agents used to lower glucose may also increase a patient’s risk of a cardiovascular event. The American Diabetes Association guides practitioners in choosing adjunctive therapy if target HbA1c levels are not reached with metformin. The American Heart Association and the American College of Cardiology recommend the use of aspirin for adults 60 years of age or older with diabetes. The Framingham Offspring Study showed that an increase in cardiovascular mortality may be evident with sulfonylureas, and TZDs on body weight appear equal between classes, cardiovascular effects may guide health care professionals in selecting the appropriate product.

Insulin has been studied extensively and appears to be essential for diabetic patients with or without cardiovascular disease. An increase in cardiovascular mortality may be evident with sulfonylureas. However, large prospective trials evaluating differences within this class have not been performed and would shed light on this controversy.

The intense debate linking TZDs to cardiovascular events is far from over. Greater caution should be used when TZDs are prescribed for patients with existing cardiovascular disease. With the large arsenal of antidiabetic agents available, physicians must carefully weigh the cardiovascular risks and benefits associated with these agents when designing a treatment approach.

REFERENCES

28. Johnson JA, Simpson SH, Majumdar SR, Toth EL. Decreased
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