# Cardiovascular Safety of Oral Antidiabetic Agents: The Insulin Secretagogues

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The prevalence of type 2 diabetes mellitus (T2DM) has increased rapidly over the past decade. In the Untied States, this increase has been greater than 40%. Obesity, which is closely linked to risk of developing T2DM, has likewise increased in prevalence by more than 60% during the same time period.

Cardiovascular disease is the major cause of mortality among patients with T2DM, accounting for 60–80% of deaths in these patients.[1] Blood glucose control has been shown to decrease the risk of microvascular complications of diabetes.[2] Whether blood glucose control decreases the risk of cardiovascular mortality in these patients has been more difficult to establish, but data such as those from the landmark United Kingdom Prospective Diabetes Study (UKPDS) suggest that good glycemic control probably does decrease cardiovascular risk in patients with T2DM.[3]

In the UKPDS, a regimen of more aggressive glycemic control was associated with a 16% reduction in risk for myocardial infarction (MI), including fatal and nonfatal MI and sudden death. While this reduction just missed statistical significance ($P = 0.052$), a more recent analysis of the UKPDS results showed that, for each 1% reduction in glycated hemoglobin, there was a 14% reduction in MI risk.[4]

Despite recent studies demonstrating the likely benefit of good glycemic control in decreasing cardiovascular risk in T2DM, there have been lingering concerns about potential adverse cardiovascular effects of insulin secretagogues, specifically sulfonylureas. Concern about sulfonylureas initially was raised by the results of the University Group Diabetes Program (UGDP).[5,6] In the UGDP, cardiovascular mortality was lower in the placebo group than in the group randomized to receive tolbutamide (Orinase). Subsequent publications have identified multiple methodological flaws in the UGDP, including failure of the randomization to control for differences in baseline characteristics, poor rates of patient follow-up, and controversy over whether the statistical analyses employed were appropriate.[7] However, the ultimate problem with the UGDP probably lay in its small size (~200 patients per arm), which increased the likelihood that the apparently lower placebo group mortality rate was simply a result of chance alone.

In this article, we seek to allay potential concerns of practitioners about the use of insulin secretagogues in patients with T2DM by reviewing more recent studies of this topic.

## Concerns About Insulin Secretagogues

Two general areas of concern have been raised about the potential adverse cardiovascular effects of insulin secretagogues. The first is the theoretical concern that high levels of insulin may promote atherosclerosis; however, recent human trials suggest that this concern is clinically unfounded. For example, the UKPDS has shown that lower glycated hemoglobin levels are associated with lower MI risk.[3,4] The second concern is that sulfonylureas might have cardiotoxic effects because they might, to a greater or lesser extent, inhibit sulfonylurea receptors in the heart, as well as in the pancreas. These concerns will be discussed in turn.

### *Concern 1: Supposed Atherogenicity of Insulin*

*In vitro*, insulin has been shown to have several potentially pro-atherogenic effects, including stimulation of cellular cholesterol accumulation and stimulation of vascular smooth muscle cell proliferation.[8] *In vivo*, hyperinsulinemia is associated with increased VLDL cholesterol levels, decreased HDL cholesterol levels, decreased LDL cholesterol particle size (so-called "small, dense LDL"), and hypertension. Insulin can also stimulate arterial smooth muscle cell proliferation. However, recent clinical trials suggest that raising circulating insulin levels with either sulfonylureas or intensive insulin therapy actually decreases, rather than increases, cardiovascular risk in patients with T2DM.[3,9,10]

The best data in this regard come from the UKPDS. It is the largest and longest study conducted in patients with T2DM. In the UKPDS, 3,867 patients with T2DM were randomized to either a

**IN BRIEF**

This article reviews and dispels concerns about the potential cardiotoxicity of insulin and oral diabetes drugs, specifically the insulin secretagogues, in patients with type 2 diabetes. The authors focus on insulin and the sulfonylurea drugs but also briefly discuss meglitinide analogs.

conservative or an intensive strategy of blood glucose control and followed for an average of 10 years. The intensive strategy was associated with a 16% decrease in risk of nonfatal and fatal MI and sudden death ($P = 0.052$). At the end of the study, the mean glycated hemoglobin level was 7.0% for the intensive group and 7.9% for the conservative group. Thus, the mean difference in glycated hemoglobin levels between the two groups was only 0.9% through the course of the study, raising the possibility that more aggressive glucose control may have demonstrated even greater cardiovascular benefit. A post-hoc analysis suggested that this was, in fact, the case, by showing a continuous decrease in MI risk of 14% for each 1% decrease in glycated hemoglobin.[4]

Additionally, despite having higher fasting insulin levels and more weight gain than patients treated with diet and exercise, UKPDS patients receiving either sulfonylureas or insulin had lower cardiovascular risk. Overall, these findings suggest that, rather than increasing cardiovascular risk, pharmacologically induced increases in insulin levels are associated with decreased cardiovascular risk in patients with T2DM.

Another landmark study, the Diabetes Insulin and Glucose in Acute Myocardial Infarction (DIGAMI) trial, has suggested that intensive insulin therapy confers cardiovascular benefit (rather than harm) in diabetic patients presenting with acute MI. DIGAMI, a multicenter, Swedish study, randomized 620 T2DM patients presenting with acute MI to either usual care or an insulin/glucose infusion followed by a multidose insulin regimen. Compared to the usual care group, patients randomized to the insulin/glucose infusion group had 30% lower mortality at 1 year and 28% lower mortality at 3.4 years.[10] Again, this study suggests substantial benefit, rather than harm, for insulin treatment in patients with T2DM.

One recent study, the Veterans' Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VACSDM), has suggested worse cardiovascular outcomes for more intensively treated patients.[11] In VACSDM, all patients were randomized to either "standard" or "intensive" glycemic control. Standard therapy consisted of a single, evening dose of insulin. Intensive therapy consisted of the addition of either a morning dose of glipizide (Glucotrol) or a multidose insulin regimen on top of a single, evening dose of insulin. However, VACSDM included only 153 patients, and the difference in cardiovascular events between the intensive and standard treatment arms was not statistically significant. In fact, the amount of insulin received was not a predictor of risk for new cardiovascular events. The Veterans' Affairs Diabetes Trial (VADT) is now underway to test the role of intensive insulin therapy in patients with T2DM.

### *Concern 2: Insulin Secretagogues May Have Unwanted Cardiovascular Effects*

Insulin secretagogues, including glucose, sulfonylureas, and meglitinides, stimulate insulin secretion by elevating the intracellular ratio of adenosinetriphosphate (ATP) to adenosinediphosphate (ADP) in the pancreatic β-cell.[12,13] This causes closure of ATP-sensitive potassium ($K_{ATP}$) channels, which results in membrane depolarization and influx of calcium ($Ca^{2+}$) into the β-cell. This increase in intracellular $Ca^{2+}$ causes release of insulin from β-cell secretory granules.

$K_{ATP}$ channels also are abundant in both cardiomyocytes[14] and arterial smooth muscle cells.[15] Thus, sulfonylureas, which stimulate insulin secretion by binding to pancreatic β-cell $K_{ATP}$ channels, may also bind to $K_{ATP}$ channels of cardiomyocytes and vascular smooth muscle cells. In cardiomyocytes, it has been shown that $K_{ATP}$ channels mediate ischemic preconditioning.[16,17] Ischemic preconditioning is the condition in which exposure of cardiomyocytes to episodes of ischemia induces cellular adaptations that make these cells resistant to damage during subsequent episodes of ischemia.[18]

Some data have raised the concern that impairment of ischemic preconditioning by older sulfonylureas may adversely affect clinical outcomes in humans. First, a post-hoc analysis of the DIGAMI study suggests that the group of patients who benefited most from randomization to the insulin/glucose infusion arm were those who were both *1*) not on insulin at trial entry, and *2*) thought to be at low risk of subsequent mortality, based on the absence of congestive heart failure, lack of treatment with digoxin, and age <70 years. Some have suggested that this benefit may have been because the low-risk/no-insulin patients randomized to insulin/glucose were withdrawn from sulfonylureas.[19] However, the DIGAMI study did not report the proportion of low-risk/no-insulin patients who had been receiving sulfonylureas before randomization. In addition, it is possible that the benefit actually resulted from administration of the insulin/glucose infusion and/or the subsequent multidose insulin regimen, rather than from the withdrawal of "toxic" sulfonylureas.

Another study raising the possibility of harm from sulfonylureas in the peri-MI period was published by Garratt et al.[20] This retrospective, non-randomized study included 185 patients with diabetes admitted to the hospital with acute MI and treated with angioplasty as their primary reperfusion strategy (i.e., "direct" angioplasty). Cardiovascular outcomes for patients treated with sulfonylureas were compared to those of patients treated with insulin or diet. Procedural success rates, late mortality, and late need for revascularization were similar in the sulfonylurea and no-sulfonylurea groups, but in-hospital mortality was twice as high in the sulfonylurea group. This difference persisted in a multivariate analysis, which demonstrated that, after decreased left ventricular function, sulfonylurea use was the second strongest predictor of in-hospital mortality.

***Newer sulfonylureas may not impair ischemic preconditioning***

Cardiomyocytes have $K_{ATP}$ channels in two sites: in sarcolemmal membranes and in mitochondrial membranes. Sulfonylureas differ in their relative affinities for sarcolemmal and mitochondrial $K_{ATP}$ channels. A recent study by Mocanu et al.[21] demonstrated that, while two commonly prescribed sulfonylureas, glyburide (Diabeta, Micronase) and glimepiride (Amaryl), both inhibit sarcolemmal $K_{ATP}$ channels, only glyburide inhibits mitochondrial $K_{ATP}$ channels. In addition, that study demonstrated quite convincingly that mitochondrial $K_{ATP}$ channels mediate ischemic preconditioning. The study further demonstrated that glyburide, which inhibited mitochondrial $K_{ATP}$ channels, impaired ischemic preconditioning and increased experimental infarct size, whereas glimepiride, which did not inhibit mitochondrial $K_{ATP}$ channels, had no adverse effect on ischemic preconditioning or infarct size.

Two recent studies have suggested that differential effects of sulfonylureas on ischemic preconditioning demonstrated *in vitro* may translate into clinically measurable differences in humans. The first study[22] employed serial exercise tolerance tests (ETTs) to examine the effect of sulfonylureas on the "warm-up" phenomenon, which may be a clinical marker of ischemic preconditioning. The warm-up phenomenon refers to the observation that when a second ETT is performed shortly after a first ETT, the time to onset of angina, time to onset of ST depression, and total exercise duration are longer on the second ETT. In the Ovunc study, patients with T2DM and chronic stable angina underwent two ETTs separated by a 15-min recovery period. Hemodynamics, time to 1.5 mm ST depression, and exercise duration were recorded. The following day, patients received an intravenous glyburide infusion and repeated the serial ETT protocol. In the absence of glyburide pre-treatment, time to 1.5 mm ST depression, time to onset of pain, and duration of exercise were significantly longer on the second ETT as compared to the first. In contrast, pre-treatment with glyburide abolished these exercise-induced changes, suggesting that glyburide treatment abolishes these clinical markers of ischemic preconditioning.

In the second study,[23] ischemic preconditioning was modeled in the cardiac catheterization laboratory by repeated inflations of an angioplasty balloon. In patients receiving a placebo infusion, the magnitude of ST segment depression decreased progressively with subsequent balloon inflations, indicating that the balloon inflations induced ischemic preconditioning. Following a glimepiride infusion, patients had similar, progressive decreases in ST segment depression with subsequent balloon inflations, suggesting no adverse effect of glimepiride on ischemic preconditioning. In contrast, patients pre-treated with glyburide had no change in the magnitude of ST segment depression with subsequent balloon inflations, suggesting that glyburide, but not glimepiride, impaired ischemic preconditioning.

Thus, while older sulfonylureas do have the potential to impair ischemic preconditioning, this does not appear to be a concern with newer-generation sulfonylureas, such as glimepiride.

***Meglitinide analogs***

The meglitinide analogs, including nateglinide (Starlix) and repaglinide (Prandin), are nonsulfonylurea secretagogues that also bind to $K_{ATP}$ channels, albeit at a different site than traditional sulfonylureas. In general, meglitinide analogs have much shorter half-lives than do sulfonylureas. The meglitinide analogs affect both sarcolemmal and mitochondrial $K_{ATP}$ channels, and the different agents may vary in their relative selectivities for $K_{ATP}$ channels at these different intracellular sites.[24]

Whether the meglitinide analogs have adverse effects on ischemic preconditioning is not known. However, both nateglinide and repaglinide have plasma half-lives of <2 h, and plasma insulin decreases to basal levels within 2 h after an oral dose.[13] Thus, even if one or both of these agents was found to have an adverse effect on ischemic preconditioning, their short half-lives would tend to minimize this effect. In addition, studies are on-going to determine the net effect (i.e., positive, negative, or neutral) of these agents on cardiovascular outcomes in patients with T2DM.[25]

**Conclusions**

Some authors have raised concerns about potential adverse cardiac and vascular effects of insulin and of insulin secretagogues. However, the majority of experimental evidence in humans suggests that, in patients with T2DM, tighter glycemic control decreases cardiovascular events, even though patients' intensive treatment results in higher plasma insulin levels. In addition, tighter glycemic control *clearly* has been shown to decrease risk of microvascular complications of retinopathy and nephropathy, as well as risk of neuropathy. Thus, the beneficial effect on microvascular endpoints alone is sufficient justification to recommend tight glycemic control in patients with T2DM.

Further, while some *in vitro* and *in vivo* evidence suggests that older sulfonylureas may impair the phenomenon of ischemic preconditioning, the extent to which ischemic preconditioning is a real phenomenon in humans is unresolved. Further, *in vitro* and *in vivo* data suggest that newer sulfonylureas, such as glimepiride, may not impair ischemic preconditioning. In addition, because of their short plasma half-lives, the meglitinide analogs may also be less likely to adversely affect ischemic preconditioning. Thus, to the extent that ischemic preconditioning may be a clinically relevant phenomenon, there should be little concern about the use of newer insulin secretagogues in patients with T2DM.

Finally, while attaining good glycemic control is a key factor in improving morbidity and mortality in patients with T2DM, practitioners also should remember the importance of

treating patients with T2DM to a blood pressure of <130/80 mmHg,[26] treating LDL cholesterol to <100 mg/dl,[27] and identifying and treating microalbuminuria.[28] Only with proper attention to controlling hyperglycemia, hypertension, dyslipidemia, and microalbuminuria can we expect to achieve the best possible clinical outcomes for our patients with T2DM.

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