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Review Article

Safe Oral Antidiabetic Agents in Cardiac Patients: An Update

S M S Haque[1], F Pathan[2]

Abstract

Cardiovascular disease is the major cause of mortality among patients with type 2 diabetes mellitus, accounting for 60-80% of death in these patients. Despite recent studies demonstrating likely benefit of good glycaemic control in decreasing cardiovascular risk in type 2 DM, there have been lingering concerns about potential adverse cardiovascular effects of insulin secretagogues, specifically sulphonylureas. In this review article, we have tried to explore the issue of safe oral anti-diabetic agents in patients having different cardiovascular diseases.

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Introduction

The world wide prevalence of type-2 Diabetes mellitus (T2DM) is predicted to rise over the coming decades due to an aging population, urbanization, increasing obesity and reduced physical activity. In the United States, this increase has been greater than 40%. According to the international diabetes Federation ,the number of diabetic patients World wide was estimated at 150 million in 2000,a figure that is set to rise to 300 million in 2025[1] .The implications are enormous, both in terms of personal suffering and cost to health care systems, which are increasingly faced with treating the serious macro-vascular complications of diabetes

In the general population the prevalence of coronary artery disease lays at around 1%-4%, [2] but this may increase by as much as fourfold in older adult diabetic patients, compared with nondiabetic individuals of the same age. The risk of heart failure has been shown to increase two-fold for diabetic men and five-fold for diabetic women, relative to their nondiabetic counterparts,[3] and up to one third of patients with myocardial infarction also suffer from clinically diagnosed type 2 diabetes.[4] Monica project showed that the prevalence of type 2 diabetes mellitus is much higher in adult who suffer from acute myocardial infarction than in general population irrespective of age and sex. Type 2 diabetes mellitus now accounts for 90% of all diabetes[2] and that 80% of deaths in type 2 diabetic patients are cardiovascular(CV) related,[5] it is surprising that CV disease has replaced renal disease as the leading cause of death among diabetic patients.

Cardiovascular disease is the major cause of mortality among patients with T2DM, accounting for 60-80% of death in these patients.[6] Blood glucose control has been shown to decrease the risk of micro-vascular complications of diabetes.[7] 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 glycaemic control probably does decrease

[1] Assistant Professor, Department of Cardiology, Dinajpur Medical College, Dinajpur.
[2] Associate Professor, Department of Endocrinology, BIRDEM, Dhaka.

cardiovascular risk in patients with T2DM.[8] In the UKPDS, a regimen of more aggressive glycaemic 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.[9]

Despite recent studies demonstrating likely benefit of good glycaemic control in decreasing cardiovascular risk in T2DM, there have been lingering concerns about potential adverse cardiovascular effects of insulin secretagogues, specifically sulphonylureas. Concern about sulphonylureas initially was raised by the result of the University group Diabetes Program (UGDP).[10,11] In the UGDP, cardiovascular mortality was lower in the placebo group than in the group randomized to receive tolbutamide. 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 patients follow up, and controversy over whether the statistical analyses employed were appropriate.[12] 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.

Two Hypotheses of Insulin and Insulin Secretagogues in Cardiac patients:

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 trails suggest that this concern is clinically unfounded. For example, the UKPDS has shown that lower glycated hemoglobin levels are associated with lower MI risk[8, 9]. The second concern is that sulphonylureas might have cardio-toxic effect 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.

Hypothesis-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.[13] 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 trails suggest that raising circulating insulin levels with either sulphonylureas or intensive insulin therapy actually decreases, rather than increases, cardiovascular risk in patients with T2DM.[8,14,15]

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 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.[9]

Additionally, despite having higher fasting insulin levels and more weight gain than patients treated with diet and exercise, UKPDS patients receiving

either sulphonylureas 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) trail, has suggested that intensive insulin therapy confers cardiovascular benefit (rather than harm) in diabetic patients presenting with acute MI. DIGAMI, a multi-center Swedish study, randomized 620 T2DM patients presenting with acute MI to either usual care or an insulin/glucose infusion followed by a multi-dose 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. 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 Glycaemic control and complications in Type2 Diabetes (VACSDM), has suggested worse cardiovascular outcomes for more intensively treated patients.[16] In VACSDM, all patients were randomized to either "standard" or "intensive" glycaemic control. Standard therapy consisted of a single, evening dose of insulin. Intensive therapy consisted of the addition of either a morning of glipizide or a multi-dose 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 trail (VADT) is now underway to test the role of intensive insulin therapy in patients with T2DM.

Hypothesis- 2: Insulin secretagogues May Have Unwanted Cardiovascular effects

Insulin secretagogues, including glucose, sulphonylureas, and meglitinides, stimulate insulin secretion by elevating the intracellular ratio of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) in the pancreatic β-cell.[17,18] This causes closure of ATP-sensitive potassium (K_{ATP}) channel, which result in membrane depolarization and influx of calcium (Ca^2+)into the β-cell. This increases in intracellular Ca^2+ causes release of insulin from β-cell secretory granules.

K_{ATP} channels also are abundant in both cardiomyocytes,[19] and arterial smooth muscle cell.[20] Thus , sulphonylureas, 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 that K_{ATP} channels mediate ischemic preconditioning.[21,22] 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.[23]

Some data have raised the concern that impairment of ischemic preconditioning by older sulphonylureas may adversely affect clinical outcomes in humans. First a post-hoc analysis of the DIGAMI study suggest that group of patients who benefited most from randomization to the insulin/glucose infusion arm were those who were both; 1) not on insulin at trail 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 <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.[24] However; the DIGAMI study did not report the proportion of low- risk/no-insulin patients who had been receiving sulphonylureas before randomization. In addition, it is possible that the benefit actually resulted from administration of the insulin/glucose infusion and/or the subsequent multi-dose insulin regimen, rather than from the withdrawal of "toxic" sulphonylureas.

Another study raising the possibility of harm from sulphonylureas in the peri-MI period was

published by Garrat et al.[25] 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 sulphonylureas 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 sulphonylureas may not impair ischemic preconditioning:

Cardiomyocytes have K_{ATP} channels in two sites: in sarcolemmal membranes and in mitochondrial membranes. Sulphonylureas differ in their relative affinities for sarcolemmal and mitochondrial K_{ATP} channels. A recent study by Mocanu et al.[26] demonstrated that, while two commonly prescribed sulphonylureas, glyburide and glimepiride, both inhibit sarcolemmal K_{ATP} channels, only glyburide inhibits mitochondrial K_{ATP} channels. In addition, that study demonstrated quite convincingly that mitochondrial K_{ATP} channel mediate ischemic preconditioning. The study further demonstrated that glyburide, which inhibited mitochondrial K_{ATP} channels, impaired preconditioning and increases 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 sulphonylureas on ischemic preconditioning demonstrated in vitro may translate into clinically measurable differences in humans. The first study[27] employed serial exercise tolerance tests (ETT) to examine the effect of sulphonylureas 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 ETT separated by a 15-min recovery period. Haemodynamics, 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 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.

The second study [28] ischemic preconditioning was modeled in the cardiac catheterization laboratory by repeated inflation of an angioplasty balloon. In patients receiving a placebo infusion, the magnitude of ST segment depression decreased progressively with subsequent balloon inflation, indicating that the balloon inflations induced ischemic preconditioning. Following a glimepiride infusion, patients had similar, progressive decreases in ST segment depression with subsequent balloon inflation, 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 sulphonylureas do have the potential to impair ischemic preconditioning, this does not appear to be a concern with newer-generation sulphonylureas, such as glimepiride.

Meglitinide analogs:

The meglitinide analogs, including nateglinide and repaglinide are non-sulfonylurea secretagogues that also bind to K_{ATP} channels, albeit at a different site than traditional sulphonylureas. In general, meglitinide analogs have much shorter half-lives

than do sulphonylureas. The meglitinide analogs affect both sarcolemmal and mitochondrial K_{ATP} channels, and the different agents may vary in their relative selectivity for K_{ATP} channels at these different intracellular sites.[29]

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[18]. 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.[30]

Metformin

Significant decreases in LDL cholesterol and triglycerides occur.[31, 32] The incidence of lactic acidosis with metformin is 9 per 100,000 person-year. Contraindications to its use include an elevated creatinine (>1.4 in women, >1.5 in men), congestive heart failure, severe pulmonary disease, or any hypoxic state.[33]

Use of Thiazolidinediones:

TZDs, by reducing insulin resistance, reduce the cardiac risk factors of endothelial dysfunction, inflammation, microalbuminuria, plasminogen activator inhibitor, increased adhesion molecule levels, decreased LDL and HDL particle sizes, and accelerated vascular smooth muscle cell proliferation. In addition, it has been conclusively shown in both animal and human studies that TZDs have no adverse effect on the myocardium. In fact, animal studies have shown that TZDs may have a positive effect on remodeling.[34]

However, there is some concern regarding TZDs use in patients with or at high risk of HF because of the potential of this drug to induce edema. Edema with TZDs occurs for three reasons. First, with the return of insulin sensitivity, the ability of insulin to act on distal tubule of the kidney to retain sodium is increased, an effect that may be relieved with diuretics[35]. Second with the return of insulin sensitivity, the ability of insulin to vasodilate the microcirculation leads to activation of RAS. This effect may be reversed utilization angiotensin-converting enzyme (ACE) inhibitors, ARBs, spironolactone, or eperolone[36]. Finally with all TZDs; there is an increase in vascular endothelial growth factor, which increases capillary permeability. This causes an edema that is similar in etiology to the edema that occurs with the dihydropyridine calcium channel blockers. The edema does not respond to diuretics, ACE inhibitors, ARBs, or aldosterone receptor blockers.[37]

Overall the plasma volume increases by as much as 6% in TZD-utilizing diabetic patients. This increase may cause a dilutional anemia that is potentially advantageous because there is retention of red cell mass and oxygen-carrying capacity and, with the higher plasma volume, a decrease in blood viscosity and improved blood flow.[38] However in diabetic subjects with diastolic dysfunction who are destined to develop HF, this increase in plasma volume can prematurely precipitate the development of HF.[8] In the situation of an “ill wind” this may be beneficial, because earlier therapy with ACE inhibitors and β-blockers will result in earlier and better remodeling of the ventricle. This is particularly important because undiagnosed left ventricular dysfunction, even in asymptomatic patients, is associated with an increased incidence of sudden death caused by arrhythmias.[39]

When a patient has been diagnosed with HF, the question of whether TZDs should be used or continued to be used is unanswered. Based on their package inserts, both rosiglitazone and pioglitazone TZDs can be used in both class 1 and class 2 New York Heart Association HF (i.e. patients who can walk 200 yards without dyspnoea). Until ongoing studies of TZDs in HF are presented or published, TZDs should be used with caution in HF. This is particularly true when TZDs are being utilized with insulin. Starting with a lower-than recommended dose and slowly increasing the dose in prudent. Patients should be informed that a weight gain of> 7 lb should trigger a call to the physician. Withdrawal of TZDs will, within 3 days, reverse the fluid overload, and

restarting the \TZDs at half the original dose should then be considered.[40]

Alpha-Glucosidase Inhibitors:

Which of the drug has any adverse or beneficial effect on cardiac patients is still not known. Acarbose and miglitol work in the intestine to reversibly inhibit brush border alpha-glucosidases, resulting in a delay in carbohydrate absorption. Only about 1 percent of the drug is absorbed from the gastrointestinal tract. These drugs cause a 30 percent decrease in postprandial glucose in contrast to a 10 percent decrease in fasting glucose levels. They are adjuncts to other oral agents and rarely are potent enough to be used as monotherapy. The beneficial effect of this drug in cardiac patients yet not established.

Conclusions

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

Further, while some in vitro and in vivo evidence suggests that older sulphonylureas 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 sulfonylurea 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 pre-conditioning. 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,[41] treating LDL cholesterol to <100mg/dl,[42] and identifying and treating microalbuminuria.[43] 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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All correspondence to:
Shaikh Md. Shahidul Haque
Assistant Professor
Department of Cardiology
Dinajpur Medical College, Dinajpur.