Non-Insulin Antidiabetic Therapy in Cardiac Patients: Current Problems and Future Prospects

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Abstract

Five types of oral antihyperglycemic drugs are currently approved for the treatment of diabetes: biguanides, sulfonylureas, meglitinides, glitazones and alpha-glucosidase inhibitors. We briefly review the cardiovascular effects of the most commonly used antidiabetic drugs in these groups in an attempt to improve knowledge and awareness regarding their influences and potential risks when treating patients with coronary artery disease (CAD). Regarding biguanides, gastrointestinal disturbances such as diarrhea are frequent, and the intestinal absorption of group B vitamins and folate is impaired during chronic therapy. This deficiency may lead to increased plasma homocysteine levels which, in turn, accelerate the progression of vascular disease due to adverse effects on platelets, clotting factors, and endothelium. The existence of a graded association between homocysteine levels and overall mortality in patients with CAD is well established. In addition, metformin may lead to lethal lactic acidosis, especially in patients with clinical conditions that predispose to this complication, such as heart failure or recent myocardial infarction. Sulfonylureas avoid ischemic preconditioning. During myocardial ischemia, they may prevent opening of the ATP-dependent potassium channels, impeding the necessary hyperpolarization that protects the cell by blocking calcium influx. Meglitinides may exert similar effects due to their analogous mechanism of action. During treatment with glitazones, edema has been reported in 5\% of patients, and these drugs are contraindicated in diabetics with NYHA class III or IV cardiac status. The long-term effects of alpha-glucosidase inhibitors on morbidity and mortality rates and on diabetic micro- and macrovascular complications is still unknown. Combined sulfonylurea/metformin therapy reveals additive effects on mortality. Four points should be mentioned: (1) the five oral antidiabetic drug groups present proven or potential cardiac hazards; (2) these hazards are not mere ‘side effects’ but are deeply rooted in the drugs’ mechanisms of action; (3) current data indicate that combined glibenclamide/metformin therapy seems to present a special risk and should be avoided in the long-term management of type 2 diabetics with proven CAD, and (4)
customized antihyperglycemic pharmacological approaches should be investigated for the optimal treatment of diabetic patients with heart disease. New possibilities are represented by incretin mimetic compounds, dipeptidyl peptidase (DPP)-4 inhibitors, inhaled insulin and eventually oral insulin.

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**Introduction**

Diabetes mellitus threatens to become a global health crisis, and treating diabetes and its complications is going to dominate future health care expenditure. Type 2 diabetes accounts for about 90% of the total diabetic population, and coronary artery disease (CAD) is the most common cause of morbidity and mortality. Cardiovascular deaths are increased up to 4-fold in diabetics compared with their nondiabetic counterparts [1]. More than two-thirds of diabetics are obese. They require drugs that stimulate beta cells to make more insulin and/or drugs that help insulin work better. When these no longer work, people require insulin. Unfortunately, this form of diabetes is growing at an alarming rate. Since these patients will receive antidiabetic therapy indefinitely, any undesirable cardiovascular effects from well-known and widely used oral antidiabetic drugs should be analyzed in depth. In 1970, the University Group Diabetes Program (UGDP) reported a higher frequency of major cardiovascular events in patients with type 2 diabetes treated with tolbutamide, a sulfonylurea [2]. Awareness of this issue has increased during recent years following detection of the harmful influences of sulfonylureas on the ischemic myocardial cell [3, 4]. On the other hand, cardiovascular derangement associated with the use of metformin has also been reported during both short- [5, 6] and long-term follow-up [7].

When oral antidiabetic monotherapy does not achieve the glycemic goal, combination treatment is implemented. A sulfonylurea – usually glibenclamide (known also as glyburide in the USA) – plus metformin constitutes the most widely used antihyperglycemic combination in clinical practice [8]. However, the safety of this therapeutic regimen in long-term treatment is questionable [9]. The use of insulin in type 2 diabetes is also controversial. Nonetheless, after 15 or 20 years of disease, the majority of patients receive insulin [10]. The issue whether the adverse cardiovascular effects of each of these medications may be additive and detrimental for the coronary patient is of paramount importance but has not yet been addressed specifically.

Insulin resistance represents the background of a series of common factors for the development of both diabetes and heart disease. These factors include genetics, hypertension, obesity, hyperglycemia, dyslipidemia, prothrombotic state, aging, and physical inactivity. Once both diseases are clinically established,
antidiabetic therapy per se may lead to a further derangement of cardiovascular status. Five types of oral antihyperglycemic drugs are currently approved for the treatment of diabetes: biguanides, sulfonylureas, meglitinides, glitazones and alpha-glucosidase inhibitors. We will briefly review the cardiovascular effects of the most commonly used antidiabetic drugs within these types in an attempt to improve the knowledge and awareness regarding their influences and potential risks when treating patients with CAD, and review the current and potential research paths.

### Biguanides

Metformin is the only drug belonging to the biguanide class currently available in most parts of the world. It reduces blood glucose levels through suppression of gluconeogenesis, stimulation of peripheral glucose uptake by tissue (mainly skeletal muscles) in the presence of insulin, and decreased absorption of glucose from the gastrointestinal tract. It has no direct effects on beta cells, does not produce hypoglycemia, reduces glycohemoglobin and improves both blood lipid profile and fibrinolytic activity. In contrast to other antidiabetic medications, metformin does not cause weight gain and appears to be the drug of choice in obese patients.

Despite these beneficial effects, metformin presents disadvantages that may influence the cardiovascular system. Gastrointestinal disturbances such as diarrhea are frequent, and the intestinal absorption of group B vitamins and folate is impaired during chronic therapy [15]. This deficiency may lead to increased plasma homocysteine levels which, in turn, accelerate the progression of vascular disease due to adverse effects on platelets, clotting factors, and endothelium [16]. The existence of a graded association between homocysteine levels and overall mortality in patients with CAD is well established [16]. In addition, metformin may lead to lethal lactic acidosis, especially in patients with clinical conditions that predispose to this complication, such as heart failure or recent myocardial infarction [6]. It should be remembered that another drug of the biguanide group, phenformin, was withdrawn in many countries during the 1970s due to its link to lactic acidosis. A possible association of phenformin with increased cardiovascular mortality has also been suggested [17]. Finally, metformin undergoes renal excretion, presenting undesirable pharmacologic interactions with several widely used cardiovascular drugs. The coadministration of nifedipine or furosemide leads to increased metformin plasma levels. Furthermore, digoxin, quinidine, and triamterene – which are eliminated by renal tubular secretion – may interact with metformin by competing for proximal renal tubular transport systems [18]. Metformin was introduced in
the USA in 1995, and serious controversies regarding cardiovascular safety followed its approval for use [5]. We have found increased mortality in CAD patients receiving metformin after a 5-year follow-up [7]. However, it should be stressed that this finding ought be treated with caution since it arose from a nonrandomized study in which information on drug doses and severity and duration of diabetes was incomplete or unavailable. In addition, metformin was found to be associated with less morbidity than sulfonylurea therapy in patients with diabetes and heart failure [19].

Sulfonylureas

These compounds have been available for nearly half a century. Today, sulfonylureas continue to represent a mainstay of therapy in patients with type 2 diabetes; their hypoglycemic potency is directly related to baseline plasma glucose values [20]. At the cellular level, they exert their action by closing the ATP-dependent potassium channels; this feature is responsible for both the insulinotropic effect and the adverse effects on the heart [3, 4]. Namely, sulfonylureas bind with high affinity to a subunit of these channels leading to depolarization of the cell. Under physiologic conditions, the channels remain closed. During ischemia, sulfonylureas may prevent their opening, avoiding the necessary hyperpolarization that protects the cell by impeding calcium influx [4]. In this context, it should be stressed that cardiac and vascular sulfonylurea receptors are structurally different from their pancreatic analog [4]. In fact, sulfonylureas have been reported to reduce resting myocardial blood flow [21], impair the recovery of contractile function after experimental ischemia [22], increase the ultimate infarct size [23], elicit proarrhythmic effects [24], abolish ischemic preconditioning in animal models [25], and increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction [26]. Prevention of myocardial preconditioning by glibenclamide has also been demonstrated in clinical trials [27].

It is important to stress that not all the undesirable effects on cardiovascular outcome reported for the first-generation sulfonylureas such as tolbutamide [2] can be automatically extrapolated to the more modern second-generation compounds such as glibenclamide, which is short-acting and possesses antiarrhythmic properties [3]. In our experience, cardiovascular mortality rates in CAD patients on sulfonylureas (mainly glibenclamide) were lower than those on combined sulfonylurea-metformin therapy, and similar to the rates in patients on diet alone [7]. Another new second-generation sulfonylurea, glimepiride, is more pancreas-specific and does not show interaction with cardiovascular ATP-dependent potassium channels [3, 27].
Meglitinides

Meglitinides stimulate insulin secretion. The first drug of this group, repaglinide, a benzoic acid derivative, was introduced in the USA in 1998. The second, nateglinide, is a \( d \)-phenylalanine derivative. Like sulfonylureas, these compounds act by closing the ATP-dependent potassium channels. However, its mechanism of action seem to be more complex since possibly three meglitinide receptor-binding sites have been found on the beta cells [28].

Despite a common basic mechanism of action, the insulinitropic effects of the two approved agents can be influenced differently by ambient glucose, leading to dissimilar responsiveness. Nateglinide may exert a more physiologic effect on insulin secretion, i.e. a glycemia-dependent response, than repaglinide, presenting less propensity to elicit hypoglycemia in vivo [29]. On the other hand, nateglinide presents a relatively lesser influence on glycohemoglobin levels. When used as monotherapy, these drugs reduce both fasting plasma glucose and glycohemoglobin, and have no significant effects on the lipid profile. They present some specific characteristics that differentiate them from sulfonylureas: pills are taken before meals (the medication should not be administered if a meal is skipped), exhibit a short onset of action and a short pharmacologic half-life, and act mainly on postprandial glucose.

The cardiovascular safety of these insulin secretagogues is still uncertain. Increased morbidity, particularly acute ischemic events, was observed for repaglinide after 1 year compared with glibenclamide. Nevertheless, patients on repaglinide appeared to have had more severe CAD at baseline than those in the glibenclamide group, and when adjustments were made the relative risk declined [30]. Thus, while definite assertions regarding cardiovascular safety cannot be made at this stage, caution should be implemented in view of the strong involvement of the ATP-dependent potassium channels in the mechanism of action.

Glitazones

This group of drugs was introduced in 1997 and includes antidiabetic medications such as troglitazone, pioglitazone, and rosiglitazone, the chemical structure and mechanisms of action of which are very different from those of the other groups. Chemically, they are thiazolidinediones having chroman moieties; some of the analogues may present an aminoalkyl group as a linker between the chroman ring and the 4-[5-(2,4-dioxo-1, 3-thiazolidinyl)methyl] phenoxy moiety. Troglitazone, which was the first agent in this class to receive labeling approval, was withdrawn from clinical use in the US due to hepatotoxicity [31].
These recently developed drugs are insulin sensitizers, and they bind to a novel receptor called peroxisome proliferator-activated receptor (PPAR)-gamma, leading to increased glucose transporter expression. Sensitivity to insulin – especially in adipocytes, muscle and liver – is improved, and an additional major effect is the inhibition of hepatic gluconeogenesis [32]. It should be pointed out that no increment in insulin secretion is documented. PPARs are transcription factors belonging to the superfamily of nuclear receptors; nowadays, three isoforms (alpha, beta/delta, gamma) are known, which regulate glucose homeostasis, lipoprotein metabolism, local immune responses, local inflammation, tumor development and thrombosis and also present potential antiatherogenic effects [33].

Glitazone monotherapy is only modestly effective in reducing glucose and glycohemoglobin levels. Plasma triglycerides are reduced by 10–20%, and HDL cholesterol levels increase by 5–10%, since glitazones also stimulates the isoform PPAR-alpha that regulates lipid metabolism. These favorable effects are counterbalanced by a 10–15% increase in LDL cholesterol [11]. Edema has been reported in 5% of patients, and these drugs are contraindicated in diabetics with NYHA class III or IV cardiac status [11]. Regarding hepatotoxicity, studies with rosiglitazone and pioglitazone indicate that it is not a class effect. Further differences in the safety profiles of these agents arise because the oxidative metabolism for each agent occurs by distinct cytochrome pathways: pioglitazone involves CYP 3A4 and CYP 2C8 whereas rosiglitazone is principally metabolized by CYP 2C8. CYP 3A4 is involved in the metabolism of over 150 drugs, hence the potential for drug interactions with pioglitazone is much greater than with rosiglitazone. Class effects include slight reductions in hemoglobin and hematocrit (due to hemodilution) [31].

It was stressed that rosiglitazone reduces urinary albumin excretion in type 2 diabetes and may even mildly reduce blood pressure [34]. Nontraditional markers of cardiovascular disease – such as matrix metalloproteinase-9 – may also be reduced [35]. In addition, another notorious characteristic of glitazones is their capability of lowering leptin levels, leading to several degrees of weight gain, usually proportional to the administered dose [34]. This feature has obvious harmful clinical implications and was documented in both experimental [36, 37] and human studies [35]. In addition, it was recently suggested that rosiglitazone may be associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance [38].

Thus, glitazones exhibit a broad landscape of complex clinical effects, in part favorable and in part detrimental for the cardiovascular system. The concluding balance between these effects requires further elucidation.