Abstract

We’ve been treating diabetes for 70 or 80 years, and despite the fact that 70% of people with diabetes die from heart disease. Our therapies for treating diabetes have not been shown to reduce the very high rate of CV death. Our mainstays of therapy is to get sugars down but that don’t seem to reduce heart attack and stroke and cardiac death. Better control of diabetes mellitus reduces microvascular complications, but has limited effect on macrovascular complications including cardiovascular mortality. It has shown that some new oral antidiabetic agents can paradoxically increase cardiovascular events and mortality. Literature search showed that some sulfonylureas increase cardiovascular risk presumably by preventing protective ischemic cardiac preconditioning. Rosiglitazone increases risk of myocardial infarction and death possibly by increasing serum triglycerides and LDL-cholesterol levels. Muraglitazar increased risk of cardiovascular death, myocardial infarction, or stroke due to unidentified reasons. Only insulin sensitizing drugs like metformin and pioglitazone have been well established nowadays that the cardiovascular risk of diabetes is of great importance.

Key Words

• Glitazone
• Metformin
• DPP4 inhibitors
• Cardiovascular events
• Ischemic preconditioning

Introduction

Patients with type 2 diabetes have cardiovascular morbidity and mortality at least four times higher compared to patients without diabetes. Moreover, it is well established nowadays that the cardiovascular risk of diabetic patients without a history of a prior myocardial infarction is similar to the risk of nondiabetic patients who have already had one. Hence, the reduction of cardiovascular risk in type 2 diabetic patients using antidepressant medication is of great importance.

Address for correspondence
Ms. Shraddha Chauhan
Email: Shraddha.phd11@gmail.com
Clinical experience with long term use of oral agents has revealed that many of these agents have nonglycemic effects that affect the development or progression of cardiovascular disease. A spate of reports in the past few years has shown that new antidiabetic drugs reduced HbA1c levels, but paradoxically increased cardiovascular events or mortality. Very little is known about the cardiovascular (CV) effects of newer agents proposed for the treatment of diabetes, and there is concern about harmful effects that may be associated with new drugs. As a result, experts and regulatory authorities have suggested that new drugs for diabetes will need to demonstrate CV safety prior to approval either by not showing a signal for CV risk or through long term clinical trials.

Sulfonylureas and heart

The mechanism responsible for the insulin secretagogue effects of sulfonylureas is associated with the opening of adenosine 5'-triphosphate (ATP)-sensitive potassium (K+)-channels (KATP) in pancreatic tissue. In addition to elicits effects in pancreatic tissue, however, sulfonylureas also interact with KATP channels in myocardial tissue. This interaction results in inhibition of ischemic preconditioning, a protective mechanism that allows the heart to be more resistant to ischemic insult (Figure 1), there is a potential for increasing the consequences of ischemia in the heart of a patient using several agents in the sulfonylurea class.9,10

Another study also evaluated myocardial ischemia after coronary angioplasty in both non-diabetic and diabetic patients who were receiving either glimepiride or glibenclamide.11 Analogous to the first study, the authors of this study observed impairment of preconditioning in glimepiride-treated patients after balloon inflation. Patients treated with glimepiride exhibited ST-segment changes compared to those patients treated with placebos. In addition, there is evidence that long-term use of glimepiride has beneficial effects on elevated cholesterol levels as well as nontraditional risk factors for cardiovascular disease, such as elevated homocysteine and plasma lipoprotein(a) levels, which have been shown to be independently associated with atherothrombotic events and ischemic stroke, respectively. Specifically, after 12 months of treatment, glimepiride-treated patients exhibited statistically significant decreases in homocysteinaemia and lipoprotein(a) levels compared with baseline values (p < 0.05) and with a rosiglitazone treatment group (p < 0.05). Multivariable and propensity-matched analyses revealed a consistent increase in all-cause deaths associated with Glimepiride. Glimepiride, and tolbutamide compared with metformin in patients with and without previous myocardial infarction. Glimepiride was associated with a significantly lower risk than other sulfonylureas.

Meglitinides and heart

Similar to the sulfonylureas, meglitinides, such as repaglinide and nateglinide, stimulate insulin secretion through their action of potassium channels on pancreatic β-cells. They are distinct from sulfonylureas in that they have shorter metabolic half-lives, and they may have a more complex mechanism of action owing to the fact that there are three meglitinide receptor-binding sites on β-cells.12 Repaglinide has been shown to have near-equivalent binding affinities for the KATP channels in pancreatic and myocardial tissue; nateglinide exhibits greater affinity for KATP channels in pancreatic tissue than myocardial tissue.13 Although it may be hypothesized that meglitinides may have effects similar to those of sulfonylureas on ischemic preconditioning because of their analogous mechanism of action, appropriate assessment of the cardiovascular impact of these agents requires further study.

Thiazolidinediones and heart

In the last few years thiazolidinediones (glitazones), a new class of antidiabetic drugs, have been developed. These drugs are potent and highly selective agonists for peroxisome proliferator-activated receptors (PPARs), directly improving insulin sensitivity at the sites of insulin action in type 2 diabetes patients.14,15 Furthermore, thiazolidinediones seem to have pleiotropic vascular protective effects, as they appear to improve diabetic dyslipidaemia, hypertension and abnormalities of the coagulation–fibrinolysis system, thus reducing the overall cardiovascular risk in patients with the metabolic syndrome (Figure 2).16 There is substantial evidence to suggest that glitazones not only ameliorate insulin resistance at the level of adipocytes, skeletal muscles and liver, but also may play a beneficial role in other underlying pathophysiological mechanisms of vascular impairment, such as atherosclerosis and inflammation.17,18 Troglitazone, which became available in practice in 1997, was the first thiazolidinedione; it was subsequently withdrawn from the market in 2000 because of hepatotoxicity. The two currently available

Image 1. Blunting of ischemic preconditioning with sulfonylurea

It has been proposed that the increased cardiovascular mortality rates observed in the University Group Diabetes Program and a retrospective study on postmyocardial infarction mortality in patients with diabetes were the result of inhibition of ischemic preconditioning by treatment with sulfonylureas.12 Two retrospective studies using health care system data have provided further evidence suggesting a causal link to adverse cardiac events.12 Results from one of these studies, which evaluated the risk for adverse cardiovascular outcomes in patients with diabetes treated with sulfonylureas and metformin, showed that those treated with sulfonylureas alone had an increased relative risk (RR) for all-cause mortality (1.43, 95% confidence interval [CI]: 1.15-1.77) and cardiovascular-related mortality (1.70, 95% CI: 1.18-2.45) compared with those treated with metformin alone. The mortality rate was shown to increase in a dose-dependent manner with sulfonylurea use, particularly with first-generation sulfonylureas, in a study of 579 subjects using oral antidiabetic drugs as recorded in the Saskatchewan Health Database.14 The exception to the sulfonylurea class effect on ischemic preconditioning is glimepiride, which interacts with a different subunit of KATP protein complex from other sulfonylureas and has been shown not to abolish ischemic preconditioning in animal studies.15 Similar results have been observed in clinical trials with humans. One study in patients with coronary heart disease undergoing elective coronary angioplasty found that glimepiride maintained myocardial preconditioning as measured by ST-segment depression after repeated balloon occlusion (p = 0.01 for change between dilations).16 In contrast, patients in the glibenclamide treatment group did not exhibit any change in ST-segment depression after balloon occlusion (p = NS), which is consistent with impairment of ischemic preconditioning.

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members of the thiazolidinedione family, rosiglitazone and pioglitazone, have entered clinical practice since 1999.6

Gliazones: Vascular Effects

- Reduce carotid intimal medial thickness
- Reduce neointimal/VSMC proliferation
- Microphage migration and foam-cell formation
- Improve vascular reactivity and endothelial function
- Decrease vascular inflammation, CRP, and MMP-9 levels
- Increase thrombolyis and decrease PAI-1
- Decrease blood pressure and microalbuminuria

Figure 2. Glitazones and its vascular effects

In contrast to these proposed benefits, the thiazolidinedione class of agents has also been known to cause edema. Furthermore, edema resulting from thiazolidinedione use may indicate incipient CHF. Patients with type 2 diabetes frequently have existing risk factors for CHF, such as coronary artery disease or hypertension, which can act synergistically to increase the risk of CHF.6-11 In monotherapy with thiazolidinediones, pedal edema was seen in 3–5% of patients, although the percentage increased when thiazolidinediones were administered in combination with other oral agents.12 Moreover, when thiazolidinediones are used in combination with insulin, the rate of edema increases, ranging from 13.1% to 16.2%.13,14 The potential of thiazolidinediones to worsen advanced CHF and cause weight gain may therefore limit their clinical relevance as a preventive measure for cardiovascular disease. Although no formal guidelines exist for the use of thiazolidinediones in patients with diabetes and overt risk factors for CHF, a joint consensus statement from the American Heart Association and ADA is being prepared. At lower doses, with gradual upward titration to obtain glycomic control.15 In addition to previously existing concerns regarding edema and CHF, a recent meta-analysis has generated a whirlwind of controversy regarding the risk of myocardial infarction and cardiovascular-related mortality associated with rosiglitazone treatment.16 The meta-analysis, which included 42 clinical trials involving 27,847 patients, reported a significant increase in the risk of myocardial infarction (odds ratio [OR] 1.43, 95% CI: 1.03–1.98, p = 0.03) and a substantial increase in the risk of mortality due to cardiovascular causes that bordered on statistical significance (OR 1.64, 95% CI: 0.98–2.74, p = 0.06). In response to these findings, another group reported on the cardiovascular outcomes from an unscheduled interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial.17

Overall, the recent flurry of publications regarding the cardiovascular risk associated with rosiglitazone therapy presents a mixed bag of conflicting studies and opposing viewpoints. Although the U.S. Food and Drug Administration (FDA) required the addition of a new boxed warning and revised warnings, precautions, and contraindications in rosiglitazone’s labeling to address the risk of heart failure. It has not requested that any ongoing studies be halted or that the drug no longer be prescribed. Results of ongoing and additional prospective clinical trials with cardiovascular outcomes among the prespecified end points are necessary to properly ascertain the effects of thiazolidinedione treatment. Ironically, since the May 21, 2007, publication of the meta-analysis, and after the widespread controversy that it ignited, patient withdrawal from the RECORD trial (one of only a handful of ongoing trials designed to capture cardiovascular outcomes) has increased dramatically, and the study may no longer be sufficiently powered to evaluate its end points.18 The clinical significance of any such study must be evaluated by weighing the results and conclusions against the morbidity and possible mortality associated with these conditions. In the absence of such scrutiny, meaningful interpretation of the data is not possible.

Effect of DPP-4 Inhibitors on selected markers of cardiovascular risk

Since GLP-1 is known to have many effects beyond glucose lowering, there is interest in determining whether DPP-4 inhibitors will also have similar effects, albeit with perhaps a smaller absolute magnitude. On the other hand, inhibition, the level of GLP-1 is only moderately increased. On the other hand, DPP-4 inhibition raises levels of GIP and may affect the breakdown of other incretins that could have vascular effects. In addition to incretins, DPP-4 cleaves various neuropeptides. These include pituitary adenylate cyclase activation polypeptide (PACAP), a vasoactive intestinal polypeptide (VIP), gastrin-releasing peptide (GRP), neuropeptide Y (NPY), growth hormone-releasing hormone (GHRH), GLP-2 and peptide YY. The clinical significance of these roles of the DPP family of enzymes and DPP-4 in cardiovascular function, and had modestly improved survival after myocardial infarction. In diabetic mice, the DPP-4 inhibitor sitagliptin also reduced mortality following myocardial infarction. Sitagliptin improved functional recovery following reperfusion injury in vivo in mice with similar protection from injury also manifest in hearts from DPP-4 knockout mice. These studies suggest that genetic disruption or chemical inhibition of DPP-4 does not impair cardiovascular function in the normoglycemic mouse heart and may be modestly beneficial. Read et al. assessed the hypothesis that increasing the plasma concentration of GLP-1 by DPP-4 inhibition would protect the heart from ischemic left ventricular (LV) dysfunction during dobutamine stress echocardiography in patients with coronary artery disease. Following administration of sitagliptin, plasma GLP-1 was increased at peak stress and during recovery, and the LV response to stress was enhanced. DPP-4 inhibition also improved LV regional functional in the 12 paired-apical segments assessed by peak systolic tissue Doppler. This was predominantly due to a cardioprotective effect on ischemic segments. In recovery, sitagliptin saturated the post ischemic stunning seen after the control study. Thus, the augmentation of GLP-1 by inhibition of DPP-4 improves global and regional LV performance in response to stress and mitigates post ischemic stunning in humans with coronary artery disease. Since insulin resistance is an important risk associated with cardiovascular disease, an improvement in insulin sensitivity may be beneficial. Vildagliptin has been shown to enhance insulin sensitivity. On the other hand, its effect on fasting lipid levels is essentially neutral, as is the case with most other DPP-4 inhibitors. However, in one study, postprandial lipid levels, particularly triglycerides and chylomicrons, were significantly decreased by vildagliptin.19 Importantly, in contrast to some other antidiabetic agents, DPP-4 inhibitors are generally neutral on body weight and blood pressure. An analysis of data from several pooled clinical trials with sitagliptin has shown no difference in adverse events between sitagliptin and control groups, including serious adverse events such as myocardial infarction.20 Similarly, vildagliptin was shown to have no major effect on cardiovascular events in a pooled analysis (EASD Congress 2008). However, an analysis of several trials shows that major adverse cardiovascular events were significantly reduced, with a relative risk of 0.44 (confidence interval 0.24 to 0.82) (ADA Scientific Sessions, 2009). Possibly because of this reduced risk and a confidence interval that was less than 1.3, saxagliptin may have been approved for use in the United States without doing a long-term outcome safety trial. Incretins have been reported to have some relationship, not yet fully understood, to hypertension. GLP-1 and GLP-1 receptor agonists have been reported to affect blood pressure and heart rate in animal models, and cause a mild decrease in blood pressure in patients with type 2 diabetes.21 Since sitagliptin increases GLP-1, its effect on hypertension was studied by Mistry et al. who found no significant effect on blood pressure.22 Figure 3 outlines the cardiovascular effects of DPP inhibitors.

Figure 3. Cardiovascular effects of DPP-4 inhibitors

Clinical trials with DPP-4 inhibitors

Despite some encouraging preclinical and small clinical study data with DPP-4 inhibitors, ultimately, long-term clinical trials are needed to determine whether DPP-4 inhibitors are clearly safe in terms of cardiovascular risk, or whether they have a significant cardiovascular benefit. SAVOR TIMI 53 recently been presented in ESC-2013, showed that when added to the standard care in patients with T2DM with high cardiovascular risk saxagliptin neither reduced nor increased the risk of primary composite endpoints of cardiovascular death, MI or ischemic stroke. Although there are more hospitalization for heart failure in the saxagliptin arm.23
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Patients with type 2 diabetes frequently have existing risk factors for CHF, such as coronary artery disease or hypertension, which can act synergistically to increase the risk of CHF.\textsuperscript{[22]} In monotherapy with thiazolidinediones, pedal edema was seen in 3–5% of patients, although the percentage increased when thiazolidinediones were administered in combination with other oral agents.\textsuperscript{[22]} Moreover, when thiazolidinediones are used in combination with insulin, the rate of edema increases, ranging from 13.1% to 16.2%.\textsuperscript{[22]}

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In contrast to these proposed benefits, the clinical significance of these effects remains to be determined. Figure 2 outlines the cardiovascular effects of DPP inhibitors.

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**Figure 2. Glitazones and its vascular effects**

**Figure 3. Cardiovascular effects of DPP-4 inhibitors**
Examining patients with type 2 diabetes and other cardiovascular risk factors or those with established cardiovascular disease, adding sitagliptin to usual care did not increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events.1-3


20. Read PA, Khan FZ, Heck PM, Hoole SP, Dutta DP. DPP-4 inhibition by sitagliptin improves the myocardial response to dobutamine stress and mitigates stunning in a pilot study of patients with...
Patients with type 2 diabetes have an inherent, elevated risk for cardiovascular disease that likely begins well in advance of a diagnosis of chronic hyperglycemia. As with treatment of dyslipidemia, hypertension, and hypercoagulability, when indicated, glycemic control is a critical element in a multifactorial approach to management of cardiovascular risk in patients with diabetes. Owing to the varied mechanisms of many commonly prescribed antidiabetic therapies, these agents have the potential either to mitigate or increase the risk for cardiovascular events in patients with diabetes. In some cases, the risk imposed by the nonglycemic adverse cardiovascular events, hospitalization for heart failure, or other adverse events.  

**Conclusion**

Patients with type 2 diabetes have an inherent, elevated risk for cardiovascular disease that likely begins well in advance of a diagnosis of chronic hyperglycemia. As with treatment of dyslipidemia, hypertension, and hypercoagulability, when indicated, glycemic control is a critical element in a multifactorial approach to management of cardiovascular risk in patients with diabetes. Owing to the varied mechanisms of many commonly prescribed antidiabetic therapies, these agents have the potential either to mitigate or increase the risk for cardiovascular events in patients with diabetes. In some cases, the risk imposed by the nonglycemic adverse cardiovascular events, hospitalization for heart failure, or other adverse events.

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Address for correspondence
Dr. A. K. Pancholia: Email: dpancholia@gmail.com

Diabetes Association in memory of Frederick Banting, wherein he put forward the hypothesis that insulin resistance and impaired glucose tolerance are a common cause of central obesity (male-type or apple-shaped obesity), diabetes and hypertension (high blood pressure). In his lecture, he also introduced to the medical community “Syndrome X,” an important factor leading to cardiovascular disease, now known as the metabolic syndrome.

Gerald M. “Jerry” Reaven (born July 28, 1928) is an American endocrinologist and Professor Emeritus in Medicine at the Stanford University School of Medicine in Stanford, California, United States. Dr. Reaven is called the “Father of Insulin Resistance,” and is accredited with developing the insulin suppression test, which was the first method to quantitatively measure insulin-mediated glucose uptake in humans.

Dr. Reaven graduated from the University of Chicago in 1949 and obtained his medical degree in 1953. He then continued on at the University of Chicago as an intern in medicine. After his internship, he joined Stanford University School of Medicine as a research fellow and later spent two years in the U.S. Army medical corps. Following military service, he completed his residency at the University of Michigan. He then returned to Stanford and undertook a U.S. Public Health Service research post, where he received a full professorship in 1970.

Dr. Reaven, along with John W. Farquhar, has carried out a series of research on insulin resistance and diabetes, which dates back to 1968. However, he received significant prominence with his now-famous Banting Lecture in 1988 (organized by the American Diabetes Association in memory of Frederick Banting), wherein he put forward the hypothesis that insulin resistance and impaired glucose tolerance are a common cause of central obesity (male-type or apple-shaped obesity), diabetes and hypertension (high blood pressure). In his lecture, he also introduced to the medical community “Syndrome X,” an important factor leading to cardiovascular disease, now known as the metabolic syndrome.

Apart from his work at Stanford, in 1996, Reaven was appointed as Senior Vice President of Research at Shuan Pharmaceuticals, Inc. in South San Francisco, California. As of 2013, Reaven has published 760 peer-reviewed articles and has co-authored over 500 publications. He is a member of several research organizations and has received numerous awards for his research achievements, including the William S. Middleton Award for outstanding achievement in medical research from the Veterans Administration, the Banting Medal for Scientific Achievement Award from the American Diabetes Association, the Banting Memorial Lecture from the British Diabetes Association and the Fred Conrad Koch Award from The Endocrine Society. He is a co-author of a popular book regarding Syndrome X and its effects on cardiovascular diseases.