Is There Evidence That Oral Hypoglycemic Agents Reduce Cardiovascular Morbidity or Mortality? No

SAMEER A. KASSEM, MD, PHD
ITAMAR RAZ, MD

Diabetes induces a high degree of morbidity and significant reduction of life expectancy in affected subjects. Microvascular complications include retinopathy, nephropathy, and neuropathy, which frequently are underlying factors of major morbidity and disability associated with diabetes. However, macrovascular complications, and mainly cardiovascular disease, are still the leading causes of death in diabetic subjects. Thus, improved cardiovascular outcome will have a clearly favorable effect on mortality in this group of patients.

Since the introduction of the U.K. Prospective Diabetes Study (UKPDS) trials in 1998, it has become widely accepted that controlling hyperglycemia improves microvascular outcome in diabetic patients (1,2). However, to date, there is no compelling evidence that improving glycemic control has, in itself, beneficial effects on macrovascular complications and cardiovascular clinical end points.

Although hyperglycemia is the hallmark of diabetes, it is still unclear whether there is a causative relationship between increased blood glucose levels and the evolution of arterial atherosclerosis. Moreover, other metabolic disorders that have been clearly linked to plaque formation seem to coexist with, rather than being caused by, hyperglycemia. These metabolic abnormalities include dyslipidemia, abdominal obesity, hypertension, low-grade inflammation, and coagulopathies. This hypothesis is supported by the findings of Haffner et al. (3) from a population-based study of diabetes and cardiovascular disease. In this study, it was demonstrated that normoglycemic subjects who subsequently developed diabetes had an atherogenic pattern of risk factors, including dyslipidemia, overweight, insulin resistance, and hypertension, years before frank diabetes was diagnosed (3). In another study, Haffner et al. (4) clearly demonstrated that diabetic patients without previous myocardial infarction (MI) have as high a risk of MI as nondiabetic patients with previous MI. Overall, these findings support the hypothesis that diabetes and other atherogenic risk factors are manifestations of one entity leading to arterial atherosclerosis. The constellation of insulin resistance and abnormal glucose metabolism with other atherogenic risk factors is commonly referred to as the metabolic syndrome.

DIABETES, ENDOTHELIAL DYSFUNCTION, AND SYSTEMIC INFLAMMATION IN CARDIOVASCULAR DISEASE

— Endothelial dysfunction is a characteristic feature of atherosclerosis, and studies indicate that it may predict long-term disease progression, as well as the rates of cardiovascular events. The endothelial system is the largest endocrine organ in primates, where it serves as an internal nonclotting lining of blood vessels by producing a number of anticoagulant factors including nitric oxide, prostacyclin, tissue plasminogen activator, protein C, and protein S. It also functions as a semi-permeable membrane for macromolecules in the bloodstream. The endothelium regulates vascular smooth muscle tone through the release of substances such as nitric oxide (NO), prostacyclin, and endothelin. It also plays a key role in platelet adhesion and aggregation by secreting a number of prothrombotic agents including von Willebrand factor, plasminogen activator inhibitor, and tissue factor (5).

Dysfunction of the endothelial system involves disruption of barrier integrity, allowing LDL molecules leakage into the vessel wall. Diseased endothelial cells express molecules that allow leukocyte binding and penetration into the subendothelial space. Leukocytes, mainly T-cells, together with endothelial cells produce and release various cytokines that attract monocytes driven to differentiate into phagocytes. Within the vessel wall, LDL molecules are rapidly oxidized and engulfed by phagocytes to form foam cells. Enhanced LDL oxidation in diabetic subjects is attributed to increased production of reactive oxygen species and an impaired scavenging system. Accumulation of foam cells attracts other inflammatory cells and fibroblasts that produce collagen fibers and create the fibrous cap surrounding the lipid core. Local cytokines and macrophage-derived matrix metalloproteinases partially degrade the fibrous cap, rendering it prone to rupture. Contact between the blood and the procoagulant lipid core initiates thrombus formation and vessel occlusion. The local inflammatory response is accompanied by generalized inflammation that is reflected by increased plasma levels of interleukin (IL)-1, IL-6, C-reactive protein, tumor necrosis factor-α (TNF-α), and complement components. These inflammatory molecules are also increased in insulin resistance, confirming the association between this entity and atherosclerosis development and progression. Insulin resistance is also associated with increased platelet activation and impaired fibrinolytic activity (5).

Thus, a comprehensive approach and management of all identified risk factors is needed to improve cardiovascular outcome in diabetes. Recently published studies demonstrated that intensified treatment of multiple risk factors in diabetic patients results in marked reduction

From the Diabetes Unit, Department of Internal Medicine, Hadassah Medical Center, Jerusalem, Israel.
Corresponding author: Sameer A. Kassem, sameerkassem@gmail.com.
The publication of this supplement was made possible in part by unrestricted educational grants from Eli Lilly, Ethicon Endo-Surgery, Generex Biotechnology, Hoffmann-La Roche, Johnson & Johnson, LifeScan, Medtronic, MSD, Novo Nordisk, Pfizer, sanofi-aventis, and WorldWIDE.
DOI: 10.2337/dc09-S335

of cardiovascular risk and cardiovascular mortality (6). Overall, an antidiabetic agent will ideally address multiple risk factors to prove beneficial for the prevention of atherosclerosis in diabetic subjects. Until we have solid evidence of improved cardiovascular clinical outcomes related to tight glucose control, we should be cautious when interpreting findings that mainly demonstrate reduction of risk factors or surrogate markers. That being said, correcting hyperglycemia should be attempted to prevent microvascular complications and possibly delay atherosclerosis progression and macrovascular complications.

ORAL HYPOGLYCEMIC AGENTS AND CARDIOVASCULAR CLINICAL OUTCOME: IS THERE EVIDENCE?

— The uncertainty that oral hypoglycemic agents (OHAs) contribute to the prevention of macrovascular complications affects decision-making by physicians and patients worldwide. This uncertainty is a direct outcome of multiple factors: diversity of drugs from different classes, a huge amount of information that is largely derived from industry-sponsored clinical trials, and aggressive marketing. In a systematic review by Bolen et al. (7), 216 studies of OHAs were analyzed. They concluded that the evidence of OHAs reducing cardiovascular mortality is still inconclusive. Our current review describes the status of evidence on the cardiovascular risk factors and on clinical outcome for different OHAs.

Sulfonylureas

Sulfonylureas exert their activity through induction of insulin release by pancreatic β-cells. Upon binding to sulfonylurea receptor 1 (SUR1) on the β-cell membrane, these agents induce closure of the adjacent potassium ATP-dependent (K_{ATP}) channel leading to membrane depolarization. Subsequent opening of voltage-gated calcium channels in the plasma membrane leads to increased intracellular calcium concentrations and insulin release (8).

In addition to being potent hypoglycemic agents, the use of sulfonylureas is accompanied by considerable weight gain and worsening obesity, together with the adverse consequences of this undesirable side effect (8). Although some studies demonstrated modest improvement in the lipid profile, the change with sulfonylurea therapy did not reach statistical significance (9). In the study by Charbonnel et al. (10), gliclazide monotherapy was associated with a 5% reduction in LDL levels and 14% in triglycerides over 52 weeks' follow-up. When added to metformin therapy, gliclazide had a minor effect on LDL (3%) and triglyceride (7%) levels (11). The improved lipid profile observed with gliclazide was modest compared with pioglitazone therapy in the latter two studies. This finding induced the inevitable assumption that improved lipid profile was solely a reflection of better glycemic control with gliclazide. It is noteworthy that the effect of metiglinide therapy on lipid profile has been inconsistent among different studies.

There is no evidence that sulfonylureas have positive effects on blood pressure. Nevertheless, a 52-week treatment with glyburide was associated with a small increase in systolic blood pressure (12). Minor blood pressure reduction (0.7 mmHg systolic and 0.6 mmHg diastolic) was associated with gliclazide therapy (13). However, patients on gliclazide had an increased incidence of newly diagnosed hypertension and exacerbation of existing hypertension, compared with metformin and pioglitazone therapy in the same study.

Studies examining the effect of sulfonylurea therapy on microalbuminuria revealed conflicting results. Gliclazide monotherapy was demonstrated to exert a positive effect on microalbuminuria in diabetic subjects (14). However, when added to existing metformin therapy, gliclazide had no additional renoprotective benefit in one study (14) and even deleterious effects in another (11).

The effects of sulfonylureas on inflammatory markers are conflicting, and the studies examining these end points are relatively small, raising questions about their validity.

Concerns about increased cardiovascular risk upon sulfonylurea therapy originate from physiologic and clinical data. While SUR1 is expressed in β-cells, SUR2A and SUR2B are expressed in cardiomyocytes and smooth muscle cells, respectively. The K_{ATP} channel in cardiomyocytes has an important function in its adaptation to cardiac ischemia. In ischemic conditions, the K_{ATP} is kept open, allowing muscle relaxation, vascular dilatation, and reduced oxygen demand. On pharmacologic closure of the channel, the cardiac adaptation mechanism is impaired, leading to increased muscle cell necrosis and more extensive cardiac damage in response to acute ischemia. Namely, glibenclamide was shown to exert detrimental effects on cardiomyocyte adaptation to ischemia in animal models. A possible interaction between its benzamido moiety and the SUR2A in cardiomyocytes constitutes the physiologic explanation for possible adverse cardiac events related to glibenclamide. However, it was also demonstrated that glibenclamide was associated with reduced rates of cardiac arrhythmias on ischemia in animal models.

In 1970, the University Group Diabetes Program demonstrated a significant increase in cardiovascular mortality in the tolbutamide-treated group compared with placebo and insulin therapy (15). The University Group Diabetes Program results were extensively criticized due to randomization errors, the inclusion of nondiabetic patients, and poor compliance. However, shortly thereafter, other clinical trials were published showing the same type of results: less survivors after MI in diabetic patients treated with oral antidiabetic therapy in comparison with diet only, or insulin therapy (16). Although recent studies made a distinction between the older-generation sulfonylureas and the newer agents, the fear of glibenclamide containing the benzamido group still exists. Noteworthy, unlike glibenclamide, tolbutamide lacks the benzamido group, and thus the increased mortality described in the University Group Diabetes Program could not be attributed to interaction between this moiety and SUR2A solely.

In the UKPDS, combination therapy of metformin and sulfonylureas was associated with an increased risk of diabetes-related death (hazard ratio [HR] 1.96) and fatal MI (HR 1.79) (2). In a more recent retrospective population-based cohort study, sulfonylurea therapy was associated with increased cardiovascular mortality with a 2.1 HR for older sulfonylurea agents (chlorpropamide or tolbutamide) and 1.3 for newer drugs such as glyburide (17). Furthermore, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, intensive glucose control was associated with a significant increase in hypoglycemic events and cardiovascular mortality (18). Although subanalysis of the contribution of different glucose-lowering agents to the increased mortality in this study is not available, the association of higher rates of hypoglycemia and increased cardiovascular mortality is in-

evitable. These findings increase the concern regarding adverse cardiovascular effects that sulfonylureas may exert, considering the frequent hypoglycemic events associated with this class of drugs.

Metformin

Metformin lowers plasma glucose levels by suppressing hepatic gluconeogenesis and glycogenolysis, while increasing peripheral sensitivity to insulin. Its beneficial effects on glucose metabolism are not accompanied by weight gain, a clear advantage over other commonly used OHAs. Multiple randomized controlled trials examined the effect of metformin therapy on blood pressure in diabetic patients. The results of these studies were inconsistent, ranging from no effect to a small positive effect on diastolic blood pressure (13,19).

The effect of metformin on lipid profile is favorable. It significantly reduces plasma triglyceride levels, a result related to improved glucose levels (9). Modest reduction in LDL levels was demonstrated with metformin therapy. However, analysis of 29 trials failed to demonstrate significant elevation in HDL levels with metformin (19). Studies also failed to demonstrate a clear benefit of metformin on microalbuminuria in diabetic patients (14).

The effect of metformin on systemic inflammation that accompanies atherosclerosis has been examined. Although it is associated with reduced oxidative stress and lower C-reactive protein levels in treated subjects, metformin therapy led to increased plasma levels of TNF-α in lean subjects. Noteworthy, the TNF-α levels did not change in obese subjects treated with metformin (20). Metformin also exerts a positive influence on endothelial dysfunction and coagulation abnormalities related to diabetes.

The effect of metformin on clinical surrogate markers of cardiovascular disease was addressed by Matsumoto et al. (21). In this study, metformin therapy was associated with attenuated progression of carotid intima-media thickness (IMT). However, the results of this study are questionable because of its open-label design, and the limited number of subjects included. Moreover, the validity of the association between IMT progression and future cardiovascular events was not completely confirmed. In the study by Salonen and Salonen (22), the increase in cardiovascular events was not significantly related to carotid IMT. In another study by Bots et al., the association between IMT and cardiovascular events did not reach statistical significance after other risk factor adjustment (23). This was in contrast to the incidence of stroke that was clearly related to IMT.

The UKPDS trial was the first to demonstrate improved clinical outcome with metformin in diabetic subjects. Metformin monotherapy in conjunction with diet improved cardiovascular outcome with a 39% reduction in MI rates, compared with conventional therapy alone in overweight patients (2). Moreover, the UKPDS post-trial monitoring study demonstrated 33% risk reduction in the metformin-treated patients (7). Increased insulin sensitivity and enhanced fibrinolytic activity due to reduction in plasminogen activator inhibitor 1 levels are possible explanations for the favorable result (24).

Nevertheless, in a combined analysis of the data from the same trial and a supplementary trial where metformin was given in combination with sulfonylureas, the effect of metformin on cardiovascular outcomes was not substantiated, due to increased cardiovascular mortality in the combination group (HR 1.96) (2).

In a retrospective population-based cohort study, metformin was associated with a slight decrease in cardiovascular mortality. However, this change did not reach statistical significance (17). Given together, accumulating data indicate a possible favorable effect of metformin therapy on cardiovascular outcome (25); however, additional data are still needed to prove that metformin significantly reduces cardiovascular events and cardiovascular mortality in diabetic patients.

Thiazolidinediones

Thiazolidinediones (TZDs) activate the transcription factor peroxisome proliferator–activated receptor (PPAR)-γ. Upon activation, PPAR-γ modulates the expression of genes that are involved in glucose and lipid metabolism leading to decreased insulin resistance and improved β-cell function. The TZDs are associated with weight gain, increase in subcutaneous fat, and a possible decrease in visceral adipose tissue (26). The two most frequently used TZDs, rosiglitazone and pioglitazone, have differential effects on lipid profile. Pioglitazone lowers triglycerides and increases HDL levels with a neutral effect on LDL. Rosiglitazone increases HDL and LDL, leaving the triglyceride levels unchanged (26,27). It is noteworthy that these results were described in patients who were not on lipid-lowering agents. In a study of patients who had already been treated with statins, switching from rosiglitazone to pioglitazone resulted in reduced triglycerides and LDL levels, rendering HDL unchanged (28).

Thiazolidinediones exert favorable effects on hypertension by lowering both systolic and diastolic blood pressure when compared with placebo and with other OHAs (29). The blood pressure–lowering properties of TZDs are at least in part related to improved endothelial function and restoration of vascular reactivity.

As a monotherapy and in combination, TZDs reduce microalbuminuria, suggesting renoprotective properties and improved endothelial function (14).

In general, TZDs demonstrate anti-inflammatory features, with reduction in C-reactive protein and TNF-α levels (27), and increased adiponectin plasma concentrations in treated patients (30). The TZDs also seem to have beneficial effects on plaque stability and fibrinolytic activity.

Several studies examined the effect of TZDs on clinical surrogate markers of cardiovascular complications. Pioglitazone therapy was associated with reduced carotid IMT compared with glimepiride, independently from glycemic control (31). However, cardiovascular outcome results cannot be extrapolated from these data because of the lack of a solid association between IMT and cardiovascular outcome. Likewise, the reduction in the rate of stent restenosis with rosiglitazone (32) and pioglitazone (33) assessed by coronary angiography cannot be conclusively interpreted as a reduction in cardiovascular events. The interaction between these drugs and the tissue repair reaction at the site of stent placement and its relevance to cardiac events needs further investigation.

In the Comparison of Pioglitazone vs. Glimepiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes (PERISCOPE) study, coronary atheroma volume was assessed by intravascular coronary ultrasound. In this study, pioglitazone was associated with 0.16% decrease in percent atheroma volume, compared with glimepiride, where percent atheroma volume was increased by 0.73% (34). Although promising, these findings could not be considered clear favorable clinical outcomes.

Data from recent years induced concern regarding the cardiovascular safety

of TZDs. The meta-analysis by Nissen and Wolski (35) demonstrated an increased incidence of MI in patients treated with rosiglitazone. Although not statistically significant, a trend of increased cardiovascular death ($P = 0.06$) is a cause for concern. In a subsequent meta-analysis by Singh et al. (36), the data on increased MI was confirmed. However, the data on cardiovascular mortality was not reproduced.

The effect of pioglitazone on clinical outcome was examined in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study (37). In this study, pioglitazone was examined for secondary prevention in patients with established macrovascular disease. Although post hoc analysis of the subgroup with previous MI demonstrated significant risk reduction of recurrent MI, or acute coronary syndrome (38), no significant reduction in cardiovascular events was demonstrated in the original study. In a recent meta-analysis of randomized trials, pioglitazone was associated with reduction in all-cause mortality but had no effect on nonfatal coronary events (39).

α-Glucosidase inhibitors

By inhibiting intestinal glucosidases, α-glucosidase inhibitors result in delayed carbohydrate absorption and flattening of the postprandial glucose curve. Despite consistent results on improved glycemia with these agents, the majority of studies demonstrated no effect on lipid profile, blood pressure, or microalbuminuria (9). In the STOP-NIDDM study, acarbose therapy was alleged to be associated with decreased rates of MI (40). However, these findings were profoundly questioned because of study design and mainly the very small number of subjects included. Thus, large and well-designed trials examining clinical end points with α-glucosidase inhibitors are lacking.

Finally, there is no clear evidence that good glycemic control improves macrovascular complication risk. Despite the large amount of data on the effects of OHAs on different metabolic and clinical surrogate markers, the evidence for favorable cardiovascular clinical outcome is relatively sparse. Nevertheless, there are serious safety concerns for some OHAs, such as sulfonylureas and TZDs. Additional studies are needed to further characterize the benefits and impairments of the commonly used OHAs.

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

References

1. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33): UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837–853
2. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34): UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854–865
3. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 1990;263:2893–2898
4. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234
5. Ajjan R, Grant PJ. Coagulation and atherothrombotic disease. Atherosclerosis 2006;186:240–259
6. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–591
7. Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, Wiley C, Selvin E, Wilson R, Bass EB, Brancati FL. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007;147:386–399
8. Davies MJ. Insulin secretagogues. Curr Med Res Opin 2002;18 (Suppl. 1):s22–s30
9. Buse JB, Tan MH, Prince MJ, Erickson PP. The effects of oral anti-hyperglycaemic medications on serum lipid profiles in patients with type 2 diabetes. Diabetes Obes Metab 2004;6:133–156
10. Charbonnel BH, Matthews DR, Schernthaner G, Hanefeld M, Brunetti P. A long-term comparison of pioglitazone and gliclazide in patients with type 2 diabetes mellitus: a randomized, double-blind, parallel-group comparison trial. Diabet Med 2005;22:399–405
11. Matthews DR, Charbonnel BH, Hanefeld M, Brunetti P, Schernthaner G. Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study. Diabete Metab Res Rev 2005;21:167–174
12. St John Sutton M, Rendell M, Dandona P, Dole JF, Murphy K, Patwardhan R, Patel J, Freed M. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. Diabetes Care 2002;25:2058–2064
13. Belcher G, Lambert C, Goh KL, Edwards G, Valbuena M. Cardiovascular effects of treatment of type 2 diabetes with pioglitazone, metformin and gliclazide. Int J Clin Pract 2004;58:833–837
14. Erdmann E. Microalbuminuria as a marker of cardiovascular risk in patients with type 2 diabetes. Int J Cardiol 2006;107:147–153
15. Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 1970;19 (Suppl.):789–830
16. Soler NG, Bennett MA, Pentecost BL, Fitzgerald MG, Malins JM. Myocardial infarction in diabetics. Q J Med 1975;44:125–132
17. Simpson SH, Majumdar SR, Tsuyuki RT, Eurich DT, Johnson JA. Dose-response relation between sulfonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. CMAJ 2006;174:169–174
18. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
19. Wulffele MG, Kooy A, de Zeeuw D, Stehouwer CD, Gansevoort RT. The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. J Intern Med 2004;256:1–14
20. Carlsen SM, Waage A, Grill V, Folling I. Metformin increases circulating tumour necrosis factor-alpha levels in non-obese non-diabetic patients with coronary heart disease. Cytokine 1998;10:66–69
21. Matsumoto K, Sera Y, Abe Y, Tominaga T, Yeki Y, Miyake S. Metformin attenuates progression of carotid arterial wall thickness in patients with type 2 diabetes. Diabetes Res Clin Pract 2004;64:225–228
22. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245–1249
23. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997;96:1432–1437
24. Cusi K, Consoli A, DeFronzo RA. Metabolic effects of metformin on glucose and

lactate metabolism in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1996;81:4059–4067
25. Selvin E, Bolen S, Yeh HC, Wiley C, Wilson LM, Marinopoulos SS, Feldman L, Vassy J, Wilson R, Bass EB, Brancati FL. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. Arch Intern Med 2008;168:2070–2080
26. Bailey CJ. Treating insulin resistance in type 2 diabetes with metformin and thiazolidinediones. Diabetes Obes Metab 2005;7:675–691
27. Goldberg RB, Kendall DM, Deeg MA, Buse JB, Zagar AJ, Pinaire JA, Tan MH, Khan MA, Perez AT, Jacober SJ. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care 2005;28:1547–1554
28. Berhanu P, Kipnes MS, Khan MA, Perez AT, Kupfer SF, Spanheimer RC, Demissie S, Fleck PR. Effects of pioglitazone on lipid and lipoprotein profiles in patients with type 2 diabetes and dyslipidaemia after treatment conversion from rosiglitazone while continuing stable statin therapy. Diab Vasc Dis Res 2006;3:39–44
29. Qayyum R, Schulman P. Cardiovascular effects of the thiazolidinediones. Diabetes Metab Res Rev 2006;22:88–97
30. Bajaj M, Suraamornkul S, Piper P, Hardies LJ, Glass L, Cersosimo E, Pratipanawatr T, Miyazaki Y, DeFronzo RA. Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. J Clin Endocrinol Metab 2004;89:200–206
31. Langenfeld MR, Forst T, Hohberg C, Kann P, Lubben G, Konrad T, Fullert SD, Sachara C, Pfutzner A. Pioglitazone decreases carotid intima-media thickness independently of glycemic control in patients with type 2 diabetes mellitus: results from a controlled randomized study. Circulation 2005;111:2525–2531
32. Choi D, Kim SK, Choi SH, Ko YG, Ahn CW, Jang Y, Lim SK, Lee HC, Cha BS. Preventative effects of rosiglitazone on restenosis after coronary stent implantation in patients with type 2 diabetes. Diabetes Care 2004;27:2654–2660
33. Nishio K, Sakurai M, Kusuyama T, Shigemitsu M, Fukui T, Kawamura K, Itoh S, Konno N, Katagiri T. A randomized comparison of pioglitazone to inhibit restenosis after coronary stenting in patients with type 2 diabetes. Diabetes Care 2006;29:101–106
34. Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, Jure H, De Larochelliere R, Staniloae CS, Mavromatis K, Saw J, Hu B, Lincoff AM, Tuzcu EM. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008;299:1561–1573
35. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–2471
36. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. JAMA 2007;298:1189–1195
37. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–1289
38. PROspective pioglitAzone Clinical Trial In macroVascular Events. www.proactive-results.com
39. Mannucci E, Monami M, Lamanna C, Gensini GF, Marchionni N. Pioglitazone and cardiovascular risk: a comprehensive meta-analysis of randomized clinical trials. Diabetes Obes Metab 2008;10:1221–1238
40. Zeymer U, Schwarzmaier-D'assie A, Petzinna D, Chiasson JL. Effect of acarbose treatment on the risk of silent myocardial infarctions in patients with impaired glucose tolerance: results of the randomised STOP-NIDDM trial electrocardiography substudy. Eur J Cardiovasc Prev Rehabil 2004;11:412–415