REVIEW

Metformin: A Review of Its Use in the Treatment of Type 2 Diabetes

N. Papanas and E. Maltezos

Outpatient Clinic of Obesity, Diabetes and Metabolism, Second Department of Internal Medicine, Democritus University of Thrace, Greece. Email: papanasnikos@yahoo.gr

Abstract: Metformin is now the most widely prescribed oral hypoglycemic agent. This review outlines its use in the treatment of type 2 diabetes. The main mechanisms of action include reduction of appetite and of intestinal carbohydrate absorption, inhibition of hepatic gluconeogenesis, and increased glucose uptake by peripheral tissues. Metformin has been established as the drug of choice for the first-line treatment of type 2 diabetes. According to broadly accepted guidelines, it should be administered early at diagnosis of this metabolic disorder, alongside diet and exercise. This agent may also be safely and efficaciously combined with all other oral hypoglycemic agents, enabling a useful additive effect. Additionally, it may be prescribed in conjunction with insulin. This combination aims to offset insulin resistance, reduce insulin requirements and minimize weight gain. Of greater importance, metformin has been consistently shown to have a favorable effect on cardiovascular risk factors and to improve cardiovascular outcomes. Interestingly, the efficacy of metformin is accompanied by excellent safety: caution is only needed to avoid the drug in patients with obvious contraindications (mainly chronic renal failure, congestive heart failure, chronic obstructive pulmonary disease, liver disease). Moreover, the cost-effectiveness of metformin has been established. Generally, metformin is an excellent choice both in the specialized setting and in primary health care.

Keywords: diabetes mellitus, metformin, oral hypoglycemic agents, treatment

This article is available from http://www.la-press.com.

Introduction

During the last 20 years type 2 diabetes mellitus has become a major health issue reaching epidemic proportions.[1,2] It has recently been estimated that nearly 6% of the world's adults are affected by this condition.[3] As a result, patients have a considerably increased risk of vascular disease, which may affect both large arteries (macrovascular, i.e. cerebrovascular, coronary and peripheral arterial disease), and small arteries (microvascular disease, i.e. retinopathy, neuropathy and nephropathy).[4,5] Overall, these chronic vascular complications lead to increased morbidity and mortality.[4,6] In an effort to optimize glycemic control and also to reduce the burden of diabetic complications, several classes of oral hypoglycemic agents have been developed.[7,8] Biguanides represent one of the oldest classes of oral hypoglycemic agents used in the management of type 2 diabetes mellitus.[9] Phenformin was the first biguanide to be marketed in the 1950's, while buformin and metformin soon followed.[9–11] This review outlines the use of metformin. Not only is this drug the most widely prescribed antidiabetic agent[12] in the management of type 2 diabetes, but it has also been recommended as the first line treatment of choice in patients without contraindications.[7,8]

Search Strategy

Article search was based on the PubMed database up to December 2008 using combinations of the following keywords: combination, diabetes mellitus, efficacy, metformin, oral hypoglycemic agents, treatment. All types of articles (randomized controlled trials, original studies, review articles, case reports) were included. Publications were studied in full, but only the abstracts were considered for studies not written in English.

Metformin: Place in Therapy

Metformin has now been on the market for more than 50 years and has been established as the first-line agent of choice for the management of type 2 diabetes. In this context, the joint guidelines issued by the American Diabetes Association and the European Association for the Study of Diabetes strongly and repeatedly suggest that this agent should be used alongside lifestyle modification at diagnosis of type 2 diabetes.[7,8] In this way, metformin is anticipated to

reduce insulin resistance, contribute to weight loss, and play a significant role in the improvement of cardiovascular outcomes.[7,8,13,14] A further advantage is that metformin can safely and efficaciously be combined with all other oral anti-diabetic agents.[7,8,13,14] Such combinations enable an additive effect of metformin and the other agents, whether these act in an insulin-secretory or insulin-sensitizing mode.[7,8] Similarly, metformin may be administered in conjunction with insulin. All in all, metformin is an excellent choice both in the specialized setting and in primary health care.[7,8,13,14]

Pharmacokinetic Profile, Metabolism and Mechanism of Action

Like phenformin, metformin is a derivative of guanidine, the active ingredient in goat's rue, that had empirically been used as a treatment for diabetes in the middle ages.[9,10] In the digestive tract, it is absorbed by the small intestine.[15] Its oral bioavailability ranges between 40% and 60%, and gastrointestinal absorption is virtually complete after 6 hours of oral administration.[16–18] A negative correlation has been described between oral dose and drug absorption.[16,17] Following absorption, metformin is rapidly distributed, without binding to plasma proteins. In contrast to phenformin, metformin does not undergo liver metabolism and is excreted unchanged by the kidneys.[16,17] Mean plasma half-life following oral administration ranges between 4 and 8.7 hours.[16,19] Plasma half-life is significantly prolonged in patients with renal impairment and shows a close relationship to creatinine clearance.[16,19] Metformin has no clinically relevant interactions with other drugs, because it is not metabolized and does not inhibit the metabolism of other drugs.[16,20] There are only anecdotal reports on drug interactions in healthy volunteers, indicating that metformin levels may be reduced by guar gum and α-glucosidase inhibitors, and may be increased by cimetidine.[16] However, these observations have not been confirmed in the diabetic population.[16,20]

Metformin appears to have several, incompletely understood but complementing each other, modes of action (Table 1).[21,22] The main mechanisms include anorexiogenesis, reduction of intestinal carbohydrate absorption, inhibition of hepatic gluconeogenesis, as well as increased glucose uptake by peripheral tissues.[21–23] Reduced appetite is a useful action of

Table 1. Metformin: mechanisms of action.

Mechanisms
Reduction of appetite
Diminished intestinal carbohydrate absorption leading to reduced post-prandial hyperglycemia
Inhibition of hepatic gluconeogenesis: inhibition of Krebs cycle and/or oxidative phosphorylation by activation of AMP kinase
Enhancement of insulin-stimulated glucose transport in skeletal muscle: increased recruitment and activity of GLUT4 glucose transporters and enhanced non-oxidative glucose disposal into skeletal muscle
Increased free fatty acid esterification and inhibition of lipolysis in adipose tissue
Protection of β-cells from glucose toxicity and lipotoxicity: protection of β-cell secretory capacity
Increased secretion of glucagon-like peptide-1 (GLP-1)

metformin, contributing to weight loss, which is beneficial, given that the vast majority of patients are obese.[21] Diminished intestinal carbohydrate absorption plays a role in reducing post-prandial hyperglycemia,[21,24] which is now regarded as a cardinal factor in the induction of oxidative stress leading to cardiovascular complications.[25] Evidence for this effect of metformin on the intestine comes mainly from animal and, to a lesser extent, from human studies.[26,27] It appears that metformin delays intestinal glucose absorption and shifts this absorption more distally along the intestine.[26,27] Additionally, it increases anaerobic glucose metabolism in the intestine, leading to reduced passage of glucose from the luminal to the serosal side of the intestine.[26,27] Inhibition of hepatic gluconeogenesis and increased peripheral glucose uptake by metformin are major effects that offset insulin resistance, and their molecular basis is being increasingly studied.[28–30] At the hepatocellular level, metformin acts on the mitochondria by inhibiting Krebs cycle and/or oxidative phosphorylation by activation of AMP kinase.[28] More recent experimental evidence points to a potent inhibitory effect of metformin on the phosphorylation of the transcriptional coactivator of CREB (cAMP response element-binding protein) at serine 436.[29,30] This effect is mediated by an atypical protein kinase C (PKC iota/lambda), triggers the dissociation of important transcription complexes and reduces the expression of genes that promote gluconeogenesis.[30] Insulin-stimulated glucose transport in insulin-resistant human skeletal muscle is also augmented by metformin administration.[31–33] Increased recruitment and activity of GLUT4 glucose

transporters and enhanced non-oxidative glucose disposal into skeletal muscle have been documented.[31–33] In adipose tissue, metformin promotes free fatty acid esterification and inhibits lipolysis.[31–33] The increase in peripheral (muscle and adipose tissue) glucose disposal may lead to a 20%–30% reduction in glucose levels.[31–33] Of note, reduction of glucose levels and of lipolysis protects β-cells from glucose toxicity and lipotoxicity, respectively.[31–33] In this manner, metformin may protect β-cell secretory function.[33,34] Finally, latest investigations indicate that increased secretion of glucagon-like peptide-1 (GLP-1) may be a further, hitherto unknown mechanism contributing to the efficacy of metformin.[35] Overall, the diversity and the collective efficacy of the aforementioned cellular actions of metformin justify its characterization as a "mulititasking medication".[13]

Efficacy: Major Clinical Studies

The efficacy of metformin, both in *monotherapy* and in *combination* therapy, has been documented by a large number of studies, the most important of which will be briefly described in this section. Overall, metformin monotherapy has been estimated to lower HbA_{1c} by approximately 1.5%.[8] In combination, metformin can also significantly lower HbA_{1c}, and the magnitude of the effect depends on the therapeutic combination, the follow-up of the study and the type of subjects recruited.[8,19]

The glucose-lowering effect of metformin is clearly dose-dependent.[36–38] In a 14-week, multicenter, double-blind study, Garber et al randomized 451 patients to placebo or metformin with doses of 500, 1000, 1500, 2000, or 2500 mg daily over 11 weeks.[36] HbA_{1c}

dropped by −0.6% to −2.0% with increasing daily metformin dose (500 to 2000 mg), and differences between dosage groups were significant (p < 0.05).[36] This favorable dose-response relationship has been confirmed.[37,38] Fujioka et al randomized 742 patients to metformin extended-release 500 mg once daily, 1000 mg once daily, 1500 mg once daily, 2000 mg once daily, 1000 mg twice daily or placebo for 16 weeks, demonstrating a clear dose-response relationship at daily metformin doses between 500 mg and 1500 mg.[38] In comparison with placebo, treatment differences amounted to −0.6% (500 mg once daily), −0.7% (1000 mg once daily), −1.0% (1500 mg once daily) and −1.0% (2000 mg once daily).[38] It appears that 1500 mg and 2000 mg per day represent the optimal metformin dosages for most patients.[36,38]

Metformin *monotherapy* has been assessed in a number of studies. A German trial randomized 96 patients to metformin 2×850 mg/day, acarbose 3×100 mg/day or placebo.[39] It was shown that both drugs were equally active compared with placebo (p < 0.05 for the comparisons with placebo): HbA_{1c} dropped to 9.8% with placebo, 8.5% with acarbose, and 8.7% with metformin.[39] Similarly, a study of 205 patients with recently diagnosed type 2 diabetes, who were randomized to either 30 mg pioglitazone or 850 mg metformin daily with titrations upward to 45 mg and 2550 mg, respectively, showed that both drugs were equally active.[40] Specifically, HbA_{1c} and fasting plasma glucose were comparable at the end of the study (pioglitazone: −1.3% reduction of HbA_{1c}, p < 0.0001 vs. baseline; metformin: −1.5% reduction of HbA_{1c}, p < 0.0001 vs. baseline; pioglitazone vs. metformin: p = 0.280).[40] However, pioglitazone was significantly more effective than metformin in improving sensitivity (reduction of fasting serum insulin, p = 0.003; homeostasis model assessment, p = 0.002).[40]

The ADOPT (A Diabetes Outcomes Progression Trial) Study group evaluated rosiglitazone (4–8 mg), metformin (850–1700 mg), and glyburide (5–10 mg) as initial treatment for patients with newly diagnosed type 2 diabetes in a double-blind, randomized, trial of 4360 patients with a median treatment duration of 4 years.[41] The primary outcome was the time to monotherapy failure, defined as fasting plasma glucose exceeding 180 mg/dl.[41] Incidence of monotherapy failure at 5 years was 15% with rosiglitazone, 21% with metformin and 34% with glyburide.[41] Thus, rosiglitazone was associated with 32% lower failure risk as compared with metformin (p < 0.001) and 63% lower failure risk as compared with glyburide (p < 0.001).[41] However, there was no difference in the proportion of patients reaching a glycemic target of HbA_{1c} lower than 7%.[41] Moreover, metformin-treated patients had more gastrointestinal untoward effects, but lower body weight (mean difference: 6.9 kg) than those receiving rosiglitazone.[41]

A 24-week, randomized, double-blind, placebo-controlled trial allocated 1091 patients with type 2 diabetes to sitagliptin 100 mg/metformin 1000 mg, sitagliptin 100 mg/metformin 2000 mg, metformin 1000 mg, metformin 2000 mg, sitagliptin 100 mg, or placebo.[42] In monotherapy, both agents accomplished significant reductions in HbA_{1c}, which were slightly more pronounced with metformin (−1.30% with metformin 2000 mg, −0.99% with metformin 1000 mg and −0.83% with sitagliptin 100 mg).[42] The comparison with the other dipeptidyl peptidase-4 (DPP-4) inhibitor, vildagliptin, was the aim of a double-blind, randomized, study of one-year treatment with vildagliptin (100 mg daily, n = 526) or metformin (up to 2000 mg daily, n = 254) in drug-naïve patients.[43] Once more, both agents accomplished significant reductions in HbA_{1c}, which were slightly more pronounced with metformin (−1.4% with metformin and −1.0% with vildagliptin).[43] Thus, the statistical non-inferiority of 50 mg vildagliptin twice daily to 1000 mg metformin twice daily could not be established.[43] Of note, body weight was unchanged with vildagliptin (p = 0.17), but was lowered with metformin (p < 0.001).[43] Diarrhea, nausea and abdominal pain were twice more frequent with metformin, while hypoglycemia was similarly rare in both groups (<1%).[43]

The efficacy of metformin *monotherapy* has been evaluated in a very comprehensive Cochrane review.[44] In this review, 29 trials with 5259 participants were included.[44] Metformin was compared with sulphonylureas (13 trials), glitazones (3 trials), meglitindes (2 trials), α-glucosidase inhibitors (2 trials), placebo (12 trials), diet (3 trials) and insulin (2 trials).[44] Metformin monotherapy was linked with a significant benefit in glycemic control, weight reduction, lipidemic profile and diastolic

blood pressure.[44] In terms of glycemic control, metformin was significantly superior to placebo or diet and modestly better than sulphonylureas.[44] Serum lipids and body weight were also improved with metformin than with sulphonylureas.[44] The authors concluded that placebo, sulphonylureas, α-glucosidase inhibitors, glitazones, meglitinides, insulin and diet could not produce a more favorable effect on glycemic control, body weight, or serum lipids than metformin.[44]

Metformin *combination* therapy has been the object of several studies. Evidence from these works documents that metformin can safely and efficaciously be combined with all types of oral hypoglycemic agents and/or insulin. The first type of combination therapy involves the addition of a sulphonylurea. In a study of 165 patients, Hermann et al found that the combination of metformin (500–1500 mg) and glibenclamide (5–10 mg) is safe and clinically useful.[45] When the two agents were combined, a significantly ($p = 0.026$) greater reduction of fasting plasma glucose was observed ($p = 0.013$).[45] In another randomized, double-blind, controlled study, 213 patients allocated to metformin (850–1500 mg) and glyburide (5–10 mg) had lower mean fasting plasma glucose concentrations (187 ± 4 vs. 261 ± 4 mg/dl, $p < 0.001$) and HbA_{1c} ($7.1\% \pm 0.1\%$ vs. $8.7\% \pm 0.1\%$, $p < 0.001$) than 210 patients allocated to glyburide alone.[46]

Moreover, in a French randomized, multicenter study, 372 patients were treated for 5 months with metformin (850 mg three times per day), glimepiride (starting dose 1 mg and titration up to 6 mg) or metformin and glimepiride.[47] Combination treatment produced significantly greater reductions of HbA_{1c} (changes: $+0.07\% \pm 1.20\%$ for metformin, $+0.27\% \pm 1.10\%$ for glimepiride, $-0.74\% \pm 0.96\%$ for combination treatment, $p < 0.001$), fasting blood glucose (changes: $+14.4 \pm 7.2$ mg/dl for metformin, $+12.6 \pm 55.8$ mg/dl for glimepiride and -32.4 ± 39.6 mg/dl for combination treatment, $p < 0.001$) and post-prandial blood glucose (changes: $+19.8 \pm 106.2$ mg/dl for metformin, $+1.8 \pm 91.8$ mg/dl for glimepiride and -46.8 ± 70.2 mg/dl for combination treatment, $p < 0.001$) than either agent alone.[47] Improved efficacy was accompanied by significantly ($p = 0.039$) more frequent symptomatic hypoglycemia in the combination group.[47]

A 4-month double-blind, multicenter trial allocated 411 patients to metformin 500 mg, glibenclamide 5 mg, metformin-glibenclamide 500 mg/2.5 mg or metformin-glibenclamide 500 mg/5 mg.[48] The reductions in HbA_{1c} and fasting plasma glucose proved significantly ($p < 0.05$) more pronounced for metformin-glibenclamide 500 mg/2.5 mg (-1.20% and -47.16 mg/dl) and 500 mg/5 mg (-0.91% and -42.12 mg/dl), compared with metformin (-0.19% and -10.26 mg/dl) or glibenclamide (-0.33% and -13.14 mg/dl).[48] The glycemic endpoint of $HbA_{1c} < 7\%$ was accomplished significantly ($p = 0.001$) more frequently by patients receiving metformin-glibenclamide 500 mg/2.5 mg and 500 mg/5 mg (75% and 64%, respectively) than those receiving glibenclamide (42%) and metformin (38%) alone.[48] These favorable effects were obtained with lower metformin and glibenclamide doses in the combined treatment group than in patients receiving either drug alone.[48] In a 16-week, randomized, double-blind trial, 639 patients inadequately controlled on at least half-maximal dose of sulphonylurea were assigned to glyburide 10 mg, metformin 500 mg, glyburide/metformin 2.5 mg/500 mg, or glyburide/metformin 5 mg/500 mg.[49] Glyburide/metformin combination succeeded in reducing HbA_{1c} by -1.7% more than glyburide alone ($p < 0.001$) and by -1.9% more than metformin alone ($p < 0.001$), ultimately leading to lower fasting plasma glucose levels than glyburide ($p < 0.001$) or metformin groups ($p < 0.001$).[49]

The additive effect of glipizide/metformin combination was assessed in a randomized a multicenter, parallel-group, active-controlled trial recruiting 247 patients.[50] Patients were randomized to glipizide 30 mg, metformin 500 mg, or glipizide/metformin 5/500 mg tablets for 18 weeks.[50] Maximum total daily doses were glipizide 30 mg, metformin 2000 mg, and glipizide/metformin 20/2000 mg.[50] Glipizide/metformin combination exerted a superior effect in terms of HbA_{1c} reduction ($p < 0.001$), as well as improvement ($p < 0.05$) of fasting glucose levels and 3-hour postprandial glucose levels than did either drug in single therapy.[50] Four times more patients attained $HbA_{1c} < 7.0\%$ with glipizide/metformin (36.3%) than either glipizide (8.9%) or metformin (9.9%) alone.[50] In another multicenter, double-blind, placebo-controlled study, 122 patients with type 2 diabetes inadequately controlled on a stable metformin

dose of at least 1000 mg were randomized to add-on 2.5 mg glipizide GITS or add-on placebo. Overall, glipizide significantly improved glucose control.[51] In patients receiving metformin plus glipizide, HbA_{1c} was reduced from 7.45% ± 0.1% to 6.8% ± 0.1%, compared with a change from 7.64% ± 0.1% to 7.46% ± 0.1%, in the placebo group (p < 0.0002).[51] In the metformin plus glipizide group, fasting glucose was reduced from 154 ± 4 mg/dl to 132 ± 4 mg/dl, compared with a change from 156 ± 4 mg/dl to 153 ± 5 mg/dl in the placebo group (p < 0.0002).[51]

Other types of combination therapy include the addition of meglitindes, α-glucosidase inhibitors, glitazones, newer agents, or insulin. In 467 patients on high-dose metformin, add-on nateglinide led to significant reductions of HbA_{1c} (−0.36%, p = 0.003, with nateglinide 60 mg; −0.59%, p < 0.001, with nateglinide 120 mg), linked with a modest decrease of fasting glucose levels.[52] In a more recent double-blind randomized trial of 262 patients suboptimally controlled on maximal metformin doses, nateglinide plus metformin and gliclazide plus metformin combinations proved equally efficacious in terms of final HbA_{1c} (−0.14% for nateglinide vs. −0.27% for gliclazide; p = 0.396) and proportion of patients (40% vs. 47.4%) achieving an endpoint HbA_{1c} < 7%.[53] Fasting plasma glucose changed from baseline to 52 weeks by −3.6 mg/dl with nateglinide and −12.6 mg/dl with gliclazide (p = 0.096).[53]

There is also considerable experience with repaglinide plus metformin combination.[54] This combined therapy may reduce fasting plasma glucose by −39.6 mg/dl and HbA_{1c} by −1.4%.[54] The efficacy and safety of this combination render it a valuable option in the management of patients with type 2 diabetes, according to some experts.[55,56] Therefore, a new repaglinide/metformin fixed-dose combination tablet for either twice or three times per day administration has now been developed.[56]

In a 12-month, multicenter, randomized, double-blind, placebo-controlled study, 354 patients were assigned to placebo or acarbose (initial dose 50 mg, titration to 100 mg, and finally to a maximum of 200 mg) in addition to their usual diet/metformin/sulfonylurea/insulin regimen.[57] Compared with placebo, acarbose significantly lowered postprandial glucose from 318.6 mg/dl to 237.6 mg/dl for the diet alone group, from 347.4 mg/dl to

284.4 mg/dl for the metformin group, from 372.6 mg/dl to 298.8 mg/dl for the sulfonylurea group, and from 331.2 mg/dl to 282.6 mg/dl for the insulin group (p < 0.01 vs. placebo).[57] Initially, mean HbA_{1c} amounted to 6.7% ± 0.2% for the diet alone group, 7.8% ± 0.2% for the metformin group, 8.0% ± 0.2% for the sulfonylurea group, and 7.7% ± 0.2% for the insulin group.[57] At the end of the trial period, HbA_{1c} was lower in patients receiving acarbose than in patients receiving placebo; the difference was −0.9% for the diet alone group (P = 0.005), −0.8% for the metformin group (p = 0.011), −0.9% for the sulfonylurea group (P < 0.002), and −0.4% for the insulin group (p = 0.077).[57]

The efficacy of metformin plus acarbose combination has been confirmed in a more recent multicenter, randomized, double-blind, placebo-controlled trial enrolling 89 overweight patients inadequately controlled by metformin.[58] These were randomized to acarbose (titrated up to 100 mg three times daily) or placebo.[58] Metformin plus acarbose yielded a significant reduction of both mean HbA_{1c} by −1.02% (p = 0.0001) and mean fasting glucose by −20.38 mg/dl (p = 0.0395).[58] Metformin has also been successfully combined with miglitol, a very rarely used α-glucosidase inhibitor.[59] In a multicenter, double-blind, placebo-controlled study, 324 patients were allocated to either placebo, miglitol alone (titrated to 100 mg three times a day), metformin alone (500 mg three times a day), or miglitol plus metformin for 36 weeks.[59] Metformin plus miglitol demonstrated a reduction in HbA_{1c} of −1.78% (p = 0.002).[59] Fasting plasma glucose (−44.8 vs. −20.4 mg/dl; p = 0.0025) and postprandial glucose (−59.0 vs. −18.0 mg/dl; p = 0.0001) were also significantly improved.[59] In another work published in the same year, miglitol (titrated to 100 mg three times a day) added to metformin (1500–2250 mg/day) was compared to placebo added to metformin in 152 patients.[59] Miglitol plus metformin led to a significant reduction of HbA_{1c} (−0.21% with miglitol vs. +0.22% with placebo, p = 0.011) and a significant reduction of post-meal glucose (final values: 248.4 mg/dl for miglitol vs. 284.4 mg/dl for placebo, p = 0.0007).[60]

The combination of metformin and glitazones (rosiglitazone and pioglitazone) has been adequately investigated. A randomized, double-blind, placebo-controlled 26-week trial recruited 348 patients with a

mean HbA_{1c} of 8.8%, allocated to 2.5 g metformin plus placebo, 2.5 g metformin plus 4 mg rosiglitazone, or 2.5 g metformin plus 8 mg rosiglitazone.[61] Compared with the metformin-placebo group, HbA_{1c} decreased by −1.0% in the 4 mg metformin-rosiglitazone group and by −1.2% in the 8 mg metformin-rosiglitazone group (p < 0.001).[61] Likewise, fasting plasma glucose decreased by −39.8 mg/dl and −52.9 mg/dl compared placebo group (p < 0.001).

In 116 Mexican patients inadequately controlled with 2.5 g/day metformin, who were randomized to add-on rosiglitazone 2 mg or 4 mg twice daily vs. placebo, HbA_{1c} decreased significantly in the rosiglitazone 2 mg twice daily (−0.7%; p = 0.0052) and 4 mg twice daily (−1.2%; p = 0.0008) groups, but increased in the placebo group (+0.3%; p = 0.2651).[62] Fasting glucose also diminished in a dose-ordered manner compared with placebo (p ≤ 0.0019 and p = 0.0006, respectively).[62] Another work showed fixed rosiglitazone/metformin 4 mg/2 g per day combination superior to 2.5 g per day metformin in 551 patients.[63] Specifically, HbA_{1c} was reduced from 7.4% to 7.1% as compared with 7.5% to 7.4% (p = 0.001).[63] Fasting plasma glucose was reduced from 166.2 mg/dl to 144.1 mg/dl as compared with 169.3 mg/dl to 164.0 mg/dl (p < 0.001).[63] The glycemic target of $HbA_{1c} < 7.0\%$ was attained in 54% of patients treated with rosiglitazone/metformin and 36% in the metformin-only group (Odds Ratio: 2.42; p < 0.001).[63]

In a multicenter, double-blind, randomized 24-week study, 766 subjects on a stable dose of 1000 mg/day metformin were randomized to rosiglitazone 4 mg/day or metformin 1500 mg/day for 8 weeks.[64] Rosiglitazone plus metformin treatment led to a mean reduction of HbA_{1c} by −0.93%, and high-dose metformin (2 g per day) led to a comparable mean reduction of −0.71%.[64] Significantly (p < 0.05) more subjects arrived at an $HbA_{1c} < 7\%$ in the rosiglitazone plus metformin group than the metformin only group (58.1% versus 48.4%).[64] Moreover, Garber et al randomized 318 patients to metformin-glibenclamide (1000/5 mg per day) or metformin 500 mg plus rosiglitazone 4 mg (1000–2000 mg/4 mg per day) for 24 weeks.[65] Metformin-glibenclamide-treated patients had significantly greater reductions of HbA_{1c} (−1.5%) and fasting glucose (−46 mg/dl) than metformin-rosiglitazone-treated patients (−1.1%, p < 0.001; −36 mg/dl, p = 0.03).[65]

At the end of the study, HbA_{1c} was lower than 7% in more patients receiving metformin-glibenclamide than in those on metformin plus rosiglitazone (60 vs. 47%, p < 0.05).[65]

An Italian study in 99 type 2 diabetic patients with metabolic syndrome compared add-on glimepiride (2 mg/day) to add-on rosiglitazone (4 mg/day) in patients on a stable metformin dose of 1500 mg/day.[66] Both treatments significantly (p < 0.05 vs. baseline) reduced BMI, HbA_{1c}, fasting and post-prandial glucose.[66] In patients receiving metformin plus glimepiride, BMI was reduced from 26.5 ± 1.3 kg/m^2 to 25.2 ± 1.4 kg/m^2, HbA_{1c} was reduced from 7.7% ± 0.5% to 7.0% ± 0.7%, fasting glucose was reduced from 164 ± 20 mg/dl to 152 ± 20 mg/dl and postprandial glucose was reduced from 185 ± 18 mg/dl to 171 ± 21 mg/dl.[66] In patients receiving metformin plus rosiglitazone, BMI was reduced from 25.9 ± 1.3 kg/m^2 to 24.5 ± 1.1 kg/m^2, HbA_{1c} was reduced from 7.4% ± 0.6% to 6.8% ± 0.6%, fasting glucose was reduced from 156 ± 25 mg/dl to 139 ± 19 mg/dl and postprandial glucose was reduced from 190 ± 22 mg/dl to 170 ± 18 mg/dl.[66] In the rosiglitazone group, significant (p < 0.05 vs. baseline) improvements were also observed in fasting plasma insulin, as well as homeostasis model assessment index, but significant reductions in total cholesterol, LDL-Cholesterol and Apo B (p < 0.05) were obtained in the glimepiride group.[66]

As regards pioglitazone, a 16-week, double-blind trial randomizing 328 patients to once-daily pioglitazone 30 mg + 1000 mg metformin or placebo + 1000 mg metformin showed that pioglitazone plus metformin therapy led to significant decreases in HbA_{1c} (−0.83%) and fasting plasma glucose (−37.7 mg/dl) compared with placebo + metformin (p ≤ 0.05), which were accompanied by significant (p ≤ 0.05) improvements in triglycerides (−18.2%) and HDL-cholesterol (+8.7%).[67] A further work randomized 639 patients inadequately controlled on gliclazide to additional treatment with either pioglitazone (15–45 mg/day) or metformin (850–2550 mg/day).[68] At the end of the trial, mean reduction in HbA_{1c} was −0.89% for pioglitazone plus gliclazide and −0.77% for metformin plus gliclazide (p = 0.200).[68] Pioglitazone improved serum lipids, but was associated with considerable increase in weight (+3.7 kg), whereas metformin led to a mean weight loss of −1.7 kg.[68]

Umpierrez et al randomized 203 type 2 diabetic patients poorly controlled on metformin (>1 g/day) to 2–4 mg glimepiride or 30 mg pioglitazone.[69] Both treatments achieved comparable improvements in HbA_{1c} (p = 0.0001) and fasting glucose (p < 0.05), but glimepiride was linked with faster glycemic control, lower total and LDL cholesterol levels and increased risk of hypoglycemia.[69]

The combination of metformin with DPP-4 inhibitors (sitagliptin, vildagliptin and the newer saxagliptin) is another therapeutic option. The efficacy and safety of sitagliptin, added to metformin therapy was assessed in a French randomized placebo-controlled trial recruiting 701 patients poorly controlled on metformin ≥1500 mg per day.[70] This confirmed the superiority of add-on sitagliptin (100 mg per day) over placebo in HbA_{1c} and fasting glucose.[70] HbA_{1c} was reduced from 7.96% ± 0.81% to 7.26% ± 0.97% with sitagliptin and from 8.03% ± 0.82% to 7.95% ± 1.10% with placebo (p < 0.001).[70] Fasting glucose was reduced from 169.2 ± 41.4 mg/dl to 151.2 ± 39.6 mg/dl with sitagliptin and increased from 172.8 ± 41.4 mg/dl to 178.2 ± 50.4 with placebo (p < 0.001).[70] Significantly (p < 0.05) more patients arrived at an HbA_{1c} < 7% with sitagliptin (47%) than with placebo (18.3%), and this was accomplished without any increase in hypoglycemias and other side-effects.[70] Another group conducted a randomized trial of 1172 patients inadequately controlled on metformin monotherapy (>1000 mg per day).[71] These were assigned to sitagliptin 100 mg per day or glipizide 5 mg/day (uptitrated to a potential maximum 20 mg/day).[71] It was shown that the combination of metformin plus sitagliptin was equally effective in reducing HbA_{1c} as metformin plus glipizide.[71] An HbA_{1c} < 7% was accomplished in 63% of patients receiving sitagliptin and 59% of those receiving glipizide.[71] Fasting plasma glucose changes from baseline were −10.0 mg/dl for sitagliptin and −7.5 mg/dl and for glipizide.[71] Brazg et al randomized 28 patients on a stable metformin dose (≥1500 mg per day) to addition of sitagliptin 100 mg twice daily vs. placebo.[72] Compared with placebo, sitagliptin plus metformin succeeded in reducing mean glucose (by −17.6 mg/dl vs. −2.7 mg/dl, p = 0.004), fasting glucose (by −23.1 mg/dl vs. −7.7 mg/dl, p < 0.001) and fructosamine (by −24.8 mmol/l vs. −6.5 mmol/l, p < 0.001).[72]

There is also data to support the combination of metformin with vildagliptin or saxagliptin. A study in 780 drug-naïve patents showed that significantly (p < 0.001) more patients attain the target of HbA_{1c} < 7% with metformin plus vildagliptin combination than with either metformin (titrated to 2000 mg daily) or vildagliptin (100 mg daily) alone.[43] In a further investigation of 107 patients, vildagliptin (50 mg daily) or placebo was added to metformin treatment (1.5–3.0 mg/day).[73] HbA_{1c} decreased significantly with vildagliptin vs. placebo (mean between-group difference: −1.0% ± 0.2%; p < 0.001).[73] This also held true for fasting glucose (mean difference: −16.2 ± 5.4 mg/dl; p = 0.016).[73] Bosi et al conducted a double-blind, randomized, multicenter, study in 544 patients on a stable metformin dose ≥1500 mg per day.[74] These were allocated to the addition of 50 mg vildagliptin, 100 mg vildagliptin, or placebo.[74] HbA_{1c} was reduced by −0.7% ± 0.1% (p < 0.001) with 50 mg and by −1.1 ± 0.1% (p < 0.001) with 100 mg vildagliptin.[74]

The newer saxagliptin may be combined with metformin as well. A randomized, double-blind, placebo-controlled study of saxagliptin (2.5, 5, or 10 mg once daily) or placebo, added to stable dose of metformin (1500 to 2500 mg) in 743 patients showed the efficacy of this combination.[75] In a dose-dependent fashion, HbA_{1c} was reduced (−0.59%, −0.69%, and −0.58% vs. +0.13% with placebo; p < 0.0001).[75] Fasting glucose showed the same decrease (−14.31 mg/dl, −22.03 mg/dl, and −20.50 mg/dl vs. +1.24 mg/dl with placebo; p < 0.0001).[75] Therefore, DPP-4 inhibition plus metformin is now emerging as a new promising therapeutic choice in type 2 diabetes.[76]

Metformin can also be safely and efficaciously combined with GLP-1 analogues (exenatide, liraglutide). Initially, a trial in 109 metformin-treated patients showed that exenatide can reduce HbA_{1c} (p ≤ 0.006) over placebo.[77] At the end of the study, HbA_{1c} < 7% was attained by 15% of exenatide-treated patients vs. 4% of those receiving placebo.[77] In another trial, 156 patients were randomized to placebo or exenatide at 2.5, 5.0, 7.5, or 10.0 μg twice daily.[78] HbA_{1c} was dose-dependently reduced (−0.1% ± 0.1%, −0.3% ± 0.1%, −0.4% ± 0.1%, −0.5% ± 0.0%, and −0.5% ± 0.1% for placebo and 2.5, 5.0, 7.5, and 10.0 μg exenatide, respectively; p < 0.0001).[78] Fasting plasma glucose was also reduced (+6.8 ± 4.1 mg/dl, −20.1 ± 5.2 mg/dl,

−21.2 ± 3.9 mg/dl, −17.7 ± 4.8 mg/dl, and −17.3 ± 4.4 mg/dl for placebo and 2.5, 5.0, 7.5, and 10.0 µg exenatide, respectively; p = 0.0006).[78] Similarly, in 150 patients poorly controlled with maximal doses of metformin, add-on exenatide resulted in a mean HbA_{1c} reduction of 1%, which was sustained after 82 weeks.[79] At 30 weeks, 46% had within-target HbA_{1c} below 7%, aproportion increasing to 59% at 82 weeks.[79] A triple-blind, placebo-controlled, 30-week study of 336 patients uncontrolled by maximal dose of metformin found that adding 5 or 10 µg exenatide reduced HbA_{1c} by 0.78% ± 0.10% (10 µg) or 0.40% ± 0.11% (5 µg) (p < 0.002 vs. placebo).[80] Overall, 46% (10 µg), 32% (5 µg), and 13% (placebo) achieved $HbA_{1c} \leq$ 7% (p < 0.01 vs. placebo).[80]

Likewise, liraglutide plus metformin appears promising. Nauck randomized 144 type 2 diabetic subjects on metformin treatment (1000 mg twice daily) to metformin plus liraglutide (increasing dose of 0.5 to 2 mg daily), liraglutide, metformin, or metformin plus glimepiride (2–4 mg).[81] Liraglutide plus metformin combination was the most efficacious regimen, leading to a significant reduction in HbA_{1c} by −0.8% and fasting glucose by −70.2 mg/dl.[81]

Interestingly, metformin can be effectively combined with two hypoglycemic agents as part of a triple antidiabetic therapy. Four hundred and forty-one patients on high-dose metformin ($\geq$1500 mg) and glimepiride ($\geq$4 mg) were randomized to 100 mg once daily or placebo.[82] The triple regimen lowered HbA_{1c} by −0.89% relative to placebo.[82] Kendall et al studied 733 patents on metformin $\geq$1,500 mg/day plus maximal doses of sulphonylurea to 5 µg or 10 µg exenatide twice daily or placebo.[83] Changes in HbA_{1c} were −0.77% ± 0.08% (10-µg arm; p < 0.0001 vs. placebo), −0.55% ± 0.07% (5-µg arm; p < 0.0001 vs. placebo), and +0.23% ± 0.07% (placebo).[83] The favorable effect of this combination has been confirmed by other studies as well.[84,85] In 222 patients on maximal doses of metformin plus sulfonylurea, the addition of 5 µg or 10 µg exenatide conferred a significant (p < 0.05) benefit over placebo.[84] Reduction in HbA_{1c} amounted to −0.8% ± 0.1% with 5 µg and −1.0% ± 0.1% with 10 µg.[84] Heine et al randomized 551 patients on maximal doses of metformin and sulfonylurea to either insulin glargine (titrated to maintain fasting blood glucose <100 mg/dl) or 10 µg exenatide twice daily.[85] Both exenatide and insulin glargine reduced HbA_{1c} by −1.11%.[85] Interestingly, exenatide appeared to target mainly postprandial glucose and glargine exerted its main effect on fasting glucose.[85]

Finally, metformin can effectively be combined with insulin. The aim of using metformin in insulin-treated patients is to offset insulin resistance, reduce insulin requirements and minimize weight gain. A Finnish trial randomized 96 patients to bedtime intermediate-acting insulin plus glyburide and placebo, metformin and placebo, glyburide and metformin, or a second injection of intermediate-acting insulin in the morning.[86] The greatest reduction of HbA_{1c} was accomplished in the bedtime insulin and metformin group (from 9.7% ± 0.4% to 7.2% ± 0.2%; p < 0.001, compared with baseline and p < 0.05 compared with other groups).[86] This therapeutic combination also succeeded in the lowest hypoglycemia rates (p < 0.05 compared with other groups) and in absence of weight gain (p < 0.001 compared with all other groups).[86] Another trial randomized 110 patients to bedtime insulin glargine with metformin or bedtime insulin NPH with metformin for 36 weeks.[87] Metformin was efficacious in both insulin combinations: final HbA_{1c} was 7.14% ± 0.12% with glargine and 7.16% ± 0.14% with NPH.[87] Glargine plus metformin reduced symptomatic hypoglycemia and dinner-time hyperglycemia.[87]

Not to be underestimated, metformin can be used in conjunction with various types of insulin. An international trial randomized 315 patients who were on metformin and/or a sulfonylurea with a stable dose of 0 to 2 daily insulin injections to receive insulin lispromix 50 (50% insulin lispro-protamine suspension and 50% lispro) three times daily plus metformin or bedtime insulin glargine plus metformin for 24 weeks.[88] Both combinations managed to improve metabolic control. Metformin fared better with lispromix50 than glargine in terms of HbA_{1c}, post-prandial hyperglycemia and glycemic variability, whereas metformin plus glargine was superior in lowering fasting plasma glucose.[88]

Safety

Metformin is considered one of the safest oral hypoglycemic agents.[12,90] It reduces insulin resistance, but does not promote insulin secretion from β-cells, and thus it is not associated with increased risk of hypoglycemia.[12,90] Minor untoward effects include nausea and diarrhea. They are usually mild

and wane over the first days of treatment.[12,14,89] Nonetheless, they may be dose-limiting and reduce patient compliance.[12,14,89] Such side effects may be minimized by using the sustained-release metformin formulation, which has been shown to be much better tolerated.[90,91]

The major untoward effect is lactic acidosis.[12,92–94] This condition still has a mortality up to 50%.[12,92–94] However, it is now extremely rare, its incidence ranging between 0.01 and 0.15 per 1000 patient-years.[13,21,93–99] More importantly, it virtually only occurs in patients with obvious contra-indications to metformin use.[12,99] Contraindications are related to conditions predisposing to tissue hypoxia (congestive heart failure, chronic obstructive pulmonary disease, severe infection or gangrene), to liver disease, as well as to intrinsic or functional reduction of renal function (chronic renal failure, congestive heart failure, advanced age).[12,21,100,101] This is explicable on the basis that metformin is cleared by the kidneys and that elevated serum lactic acid concentration may result either from severe tissue hypoxia or from reduced hepatic clearance owing to liver disease.[12,21,100,101] Age itself is a much questioned contraindication, but most cases of lactic acidosis have been described in elderly patients, and several authors suggest avoidance of metformin in patients aged at least 80.[12,102–105]

Recently, the utility of the abovementioned contraindications has been debated.[11,95,100,101,103,106–108] Even in patients with contra-indications, metformin-associated lactic acidosis is very rare and occurs due to a superimposed medical condition.[11,103] Mortality is then closely related with the degree of hypoxia, rather than serum metformin levels, casting doubt on the causal role of metformin.[11,103] More impressively, several studies have shown that a considerable proportion of patients receiving metformin have formal contraindications to its use and yet never develop lactic acidosis.[11,95,100,101,103,106–108] Nevertheless, these studies have been criticized for their retrospective observational design and for the variable interpretation of contraindications.[12,102] In practice, lactic acidosis remains a potentially lethal condition, and, therefore, the clinician should assess patients carefully before prescribing metformin, in order to avoid those with serious contraindications.[12] As long as contraindications and warnings are respected, metformin may be safely administered with almost no lactic acidosis.[109,110]

Cost-Effectiveness

Metformin has also proved cost-effective. The overall beneficial cost-effectiveness ratio has been estimated in various countries. In the UKPDS, cross-sectional surveys of non-inpatient healthcare use and quality of life revealed that the drug was cost-saving and that it increased life expectancy.[111] A further analysis estimated the costs and effectiveness of intensive blood glucose control in overweight type 2 diabetes patients in China.[112] Provided that one is willing to pay for quality-adjusted life year gained, intensive blood glucose control with metformin appears to be cost-effective.[112] The average incremental costs of 11 years of intensive treatment with metformin amounted to 16400 US$ per quality-adjusted life year gained. The incremental cost-effectiveness ratio favored metformin at 20 years (with 11700 US$) and 30 years (with 9600 US$).[112] Using the UKPDS results, modelling techniques were applied to the Swiss health system, in order to estimate the cost-effectiveness of the management type 2 diabetic patients by conventional vs. intensive control with metformin.[113] Total cost (including both diabetes therapy and management of new-onset complications) and survival were determined over an 11-year period.[113] Mean total cost per patient was 10877 Swiss Francs for conventional vs. 9950 Swiss Francs for intensive control with metformin.[113] In addition, intensive control with metformin prolonged survival by a mean of 0.43 life-years per patient.[113] A further analysis evaluated the cost-effectiveness of metformin vs. lifestyle changes for patients with impaired glucose tolerance in Australia, France, Germany, Switzerland, and the United Kingdom.[114] Both interventions were cost-effective in all countries, except for United Kingdom, where cost was slightly increased with either intervention.[114] In a similar patient sample in the USA, intensive lifestyle, metformin, and placebo were compared.[115] Compared with placebo, the cost per quality-adjusted life year gained amounted to $1100 for lifestyle intervention $31300 for metformin.[115] In terms of societal burden, the cost per quality-adjusted life year gained was $8800 dollars for lifestyle intervention and $29900 for metformin.[115] Overall, lifestyle intervention exhibited

a superior cost-effectiveness over metformin.[115] Importantly, lifestyle intervention was cost-effective in all ages, whereas metformin was not sufficiently cost-effective for subjects aged older than 65.[115] Finally, in the Indian Diabetes Prevention Programme, lifestyle modification and metformin were compared.[116] Direct per subject costs over three years were $61 in the control group, $225 with lifestyle modification, $220 with metformin, and $270 with both modalities.[116] Thus, both lifestyle modification and metformin were cost-effective, the former more so than the latter.[116]

Evidence for Additional Beneficial Effects Beyond Glycemic Control

It is now widely accepted that metformin has a favorable effect on serum lipids, inflammation and cardiovascular disease.[110,117–119] This effect is strong enough to translate into clinical benefit. The UKPDS demonstrated that metformin was the only oral agent to reduce any diabetes-related endpoint by 32% (p = 0.002), diabetes-related death by 42% (p = 0.017) and all-cause mortality by 36% (p = 0.011).[120] This reduction was sustained in the 20 year follow-up analysis, which again showed that metformin reduced any diabetes-related endpoint by 21% (p = 0.01), myocardial infarction by 33% (p = 0.005) and all-cause mortality by 27% (p = 0.002).[121] More recently, a randomized trial from Holland examined the effect of add-on metformin vs. placebo on cardiovascular morbidity in insulin-treated type 2 diabetic patients.[122] Metformin succeeded in almost 40% improvement of macrovascular disease after a median follow-up period of 4.3 years.[122]

The overall vasculoprotective effect of metformin has been corroborated in a Cochrane analysis, which estimated a metformin-induced significant risk reduction for myocardial infarction (p = 0.02), diabetes-related death (p = 0.03) and all-cause mortality (p = 0.01).[44] A systematic review of cardiovascular outcomes associated with oral hypoglycemic agents also came to the conclusion that metformin could lead to a 26% risk reduction in cardiovascular mortality as compared to any other treatment or placebo.[123]

Furthermore, metformin has beneficial effects on blood pressure, lipid profile and coagulation.[110,119] The effect on blood pressure is rather moderate. According to a systematic review, this agent could only lower systolic blood pressure by −1.09 mm Hg (p = 0.30) and diastolic blood pressure by −0.97 mm Hg (p = 0.11).[124]

As regards serum lipids, Nagi and Yudkin reported a significant beneficial effect of metformin on serum triglycerides (p = 0.034), total cholesterol (p = 0.002) and LDL-cholesterol (p = 0.002), but not on HDL-cholesterol.[125] The hypolipidemic action of metformin has also been shown in conjunction with insulin: a randomized trial found that addition of this drug resulted in significant reductions of total cholesterol (p = 0.032) and LDL-cholesterol (p = 0.028) without any effect on triglycerides and HDL-cholesterol.[126] Overall, metformin has consistently demonstrated a favorable, even though modest, effect on LDL-cholesterol, independently of glycemic control.[44,124,127] In comparison with other agents, metformin succeeds in a reliable reduction of LDL-cholesterol by a mean of −10 mg/dl.[44,124,127] The action on other lipidemic parameters is less documented. According to the systematic review by Wulffelé et al however, this biguanide reduced not only LDL-cholesterol (p < 0.00001), but serum triglycerides (p = 0.003) and total cholesterol (p < 0.0001) as well.[124] Metformin has been also shown to improve fibrinolysis by reducing plasminogen activator inhibitor-1 (p = 0.001).[125]

The mechanisms by which metformin protects the heart and the large vessels appear to be manifold and possibly mutually interacting, but remain incompletely understood.[110,119] Generally, most beneficial actions are attributable to the amelioration of insulin resistance.[110,119] In addition, metformin has been proposed to harbor anti-oxidant activity, offset advanced glycation end-products, improve microcirculation and reduce inflammation.[110,119]

Conclusions

Metformin has a long history in the management of type 2 diabetes and is now the most widely prescribed oral hypoglycemic agent.[12–14] Its main modes of action encompass anorexiogenesis, reduction of intestinal carbohydrate absorption, inhibition of hepatic gluconeogenesis, as well as increased glucose uptake by peripheral tissues.[21–23] Metformin has been established as the drug of choice for the first-line treatment of type 2 diabetes, and its administration has been strongly suggested at diagnosis of this metabolic disorder, alongside diet and exercise.[7,8] It may also be successfully combined with all other oral hypoglycemic agents and insulin.[45,50,55,61,70,74,86] Of greater importance, this agent has been consistently

shown to improve cardiovascular outcomes.[119–122] This beneficial effect may be sustained several years after discontinuation of the drug.[121] The efficacy of metformin is accompanied by excellent safety: caution is only needed to avoid the drug in patients with contraindications.[12] Finally, the cost-effectiveness of metformin has been adequately established.[111–113]

Disclosures

The authors report no conflicts of interest.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care.* 2004;27:1047–53.
2. Coliaguri S, Borch-Johnsen K, Glümer C, Vistisen D. There really is an epidemic of type 2 diabetes. *Diabetologia.* 2005;48:1459–63.
3. Mayor S. Diabetes affects nearly 6% of the world's adults. *BMJ.* 2006;333:1191.
4. Bloomgarden ZT. Diabetes complications. *Diabetes Care.* 2004;27:1506–14.
5. Bloomgarden ZT. Cardiovascular disease in diabetes. *Diabetes Care.* 2008;31:1260–6.
6. Winer N, Sowers JR. Epidemiology of diabetes. *J Clin Pharmacol.* 2004;44:397–405.
7. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia.* 2006;49:1711–21.
8. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia.* 2009;52:17–30.
9. Krall LP, Camerini-Davalos R. Early clinical evaluation of a new oral non-sulphonylurea hypoglycemic agent. *Proc Soc Exp Biol Med* 1957;95:345–7.
10. Ungar G, Freedman L, Shapiro SL. Pharmacological studies of a new oral hypoglycemic drug. *Proc Soc Exp Biol Med.* 1957;95:190–2.
11. Holstein A, Stumvoll M. Contraindications can damage your health—is metformin a case in point? *Diabetologia.* 2005;48:2454–9.
12. Papanas N, Monastiriotis C, Christakidis D, Maltezos E. Metformin and lactic acidosis in patients with type 2 diabetes—from pride and prejudice to sense and sensibility. *Acta Clin Belg.* 2009;64:42–8.
13. Bailey CJ. Metformin: a multitasking medication. *Diabetes Vasc Dis Res.* 2008;5:156.
14. Papanas N, Maltezos E, Mikhailidis D. Metformin: diamonds are forever. *Expert Opin Pharmacother.* 2009 Aug 13. [Epub ahead of print].
15. Vidon N, Chaussade S, Noel M, et al. Metformin in the digestive tract. *Diabetes Res Clin Pract.* 1988;4:223–9.
16. Scheen AJ. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet.* 1996;30:359–71.
17. Dunn CJ, Peters DH. Metformin. A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus. *Drugs.* 1995;49:721–49.
18. Pentikäinen PJ, Neuvonen PJ, Penttilä A. Pharmacokinetics of metformin after intravenous and oral administration to man. *Eur J Clin Pharmacol.* 1979;16:195–202.
19. Tucker GT, Casey C, Phillips PJ, et al. Metformin kinetics in healthy subjects and patients with diabetes mellitus. *Br J Clin Pharmacol.* 1981;12:235–46.
20. Scheen AJ. Drug interactions of clinical importance with antihyperglycaemic agents: an update. *Drug Saf.* 2005;28:601–31.
21. Bailey CJ, Turner RC. Metformin. *New Engl J Med.* 1996;334:574–9.
22. Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. *Biochem J.* 2000;348:607–14.
23. Edgerton DS, Johnson KM, Cherrington AD. Current strategies for the inhibition of hepatic glucose production in type 2 diabetes. *Front Biosci.* 2009;14:1169–81.
24. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin dependent diabetes. *New Engl J Med.* 1995;333:550–4.
25. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA.* 2006;295:1681–7.
26. Bailey CJ, Mynett KJ, Page T. Importance of the intestine as a site of metformin-stimulated glucose utilization. *Br J Pharmacol.* 1994;112:671–5.
27. Bailey CJ, Wilcock C, Scarpello JHB. Metformin and the intestine. *Diabetologia.* 2008;51:1552–3.
28. Musi N, Hirshman MF, Nygren J, et al. Metformin increases AMP-activated protein kinase activity in skeletal muscle of subjects with type 2 diabetes. *Diabetes.* 2002;51:2074–81.
29. White MF. Metformin and insulin meet in a most atypical way. *Cell Metab.* 2009;9:485–7.
30. He L, Sabet A, Djedjos S, et al. Metformin and insulin suppress hepatic gluconeogenesis through phosphorylation of CREB binding protein. *Cell.* 2009;137:635–46.
31. Galuska D, Zierath J, Thörne A, Sonnenfeld T, Wallberg-Henriksson H. Metformin increases insulin-stimulated glucose transport in insulin-resistant human skeletal muscle. *Diabete Metab.* 1991;17:159–63.
32. Galuska D, Nolte LA, Zierath JR, Wallberg-Henriksson H. Effect of metformin on insulin-stimulated glucose transport in isolated skeletal muscle obtained from patients with NIDDM. *Diabetologia.* 1994;37:826–32.
33. Giannarelli R, Aragona M, Coppelli A, Del Prato S. Reducing insulin resistance with metformin: the evidence today. *Diabetes Metab.* 2003;29:6S28–35.
34. Ferner RE, Rawlins MD, Alberti KGMM. Impaired B-cell responses improve when fasting blood glucose concentration is reduced in non-insulin dependent diabetes. *Quat J Med.* 1988;250:137–46.
35. Lindsay JR, Duffy NA, McKillop AM, et al. Inhibition of dipeptidyl peptidase IV activity by oral metformin in Type 2 diabetes. *Diabet Med.* 2005;22:654–7.
36. Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med.* 1997;103:491–7.
37. Scarpello JHB. Optimal dosing strategies for odelling the clinical response to metformin in type 2 diabetes. *Br J Diabetes Vasc Dis.* 2001;1:28–36.
38. Fujioka K, Brazg RL, Raz I, et al. Efficacy, dose-response relationship and safety of once-daily extended-release metformin (Glucophage XR) in type 2 diabetic patients with inadequate glycaemic control despite prior treatment with diet and exercise: results from two double-blind, placebo-controlled studies. *Diabetes Obes Metab.* 2005;7:28–39.
39. Hoffmann J, Spengler M. Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II Study. *Am J Med.* 1997;103:483–90.
40. Pavo I, Jermendy G, Varkonyi TT, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2003;88:1637–45.
41. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med.* 2006;355:2427–43.
42. Goldstein BJ, Feinglos MN, Lunceford JK, et al. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care.* 2007;30:1979–87.
43. Schweizer A, Couturier A, Foley JE, Dejager S. Comparison between vildagliptin and metformin to sustain reductions in HbA$_{1c}$ over 1 year in drug-naïve patients with Type 2 diabetes. *Diabet Med.* 2007;24:955–61.

44. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2005;3:CD002966.

45. Hermann LS, Scherstén B, Melander A. Antihyperglycaemic efficacy, response prediction and dose-response relations of treatment with metformin and sulphonylurea, alone and in primary combination. *Diabet Med*. 1994;11:953–60.

46. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med*. 1995;333:541–9.

47. Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S. Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. *Diabet Med*. 2001;18:828–34.

48. Marre M, Howlett H, Lehert P, Allavoine T. Improved glycaemic control with metformin-glibenclamide combined tablet therapy (Glucovance) in Type 2 diabetic patients inadequately controlled on metformin. *Diabet Med*. 2002;19:673–80.

49. Blonde L, Rosenstock J, Mooradian AD, Piper BA, Henry D. Glyburide/metformin combination product is safe and efficacious in patients with type 2 diabetes failing sulphonylurea therapy. *Diabetes Obes Metab*. 2002;4:368–75.

50. Goldstein BJ, Pans M, Rubin CJ. Multicenter, randomized, double-masked, parallel-group assessment of simultaneous glipizide/metformin as second-line pharmacologic treatment for patients with type 2 diabetes mellitus that is inadequately controlled by a sulfonylurea. *Clin Ther*. 2003;25:890–903.

51. Feinglos M, Dailey G, Cefalu W, et al. Effect on glycemic control of the addition of 2.5 mg glipizide GITS to metformin in patients with T2DM. *Diabetes Res Clin Pract*. 2005;68:167–75.

52. Marre M, Van Gaal L, Usadel KH, Ball M, Whatmough I, Guitard C. Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. *Diabetes Obes Metab*. 2002;4:177–86.

53. Ristic S, Collober-Maugeais C, Cressier F, Tang P, Pecher E. Nateglinide or gliclazide in combination with metformin for treatment of patients with type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone: 1-year trial results. *Diabetes Obes Metab*. 2007;9:506–11.

54. Moses R. Repaglinide in combination therapy. *Diabetes Nutr Metab*. 2002;15:33–8.

55. Raskin P. Oral combination therapy: repaglinide plus metformin for treatment of type 2 diabetes. *Diabetes Obes Metab*. 2008;10:1167–77.

56. Raskin P, Lewin A, Reinhardt R, Lyness W; Repaglinide/Metformin Fixed-Dose Combination Study Group. Twice-daily and three-times-daily dosing of a repaglinide/metformin fixed-dose combination tablet provide similar glycaemic control. *Diabetes Obes Metab*. 2009 Jun 16. [Epub ahead of print].

57. Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. *Ann Intern Med* 1994;121:928–35.

58. Phillips P, Karrasch J, Scott R, Wilson D, Moses R. Acarbose improves glycemic control in overweight type 2 diabetic patients insufficiently treated with metformin. *Diabetes Care*. 2003;26:269–73.

59. Chiasson JL, Naditch L; Miglitol Canadian University Investigator Group. The synergistic effect of miglitol plus metformin combination therapy in the treatment of type 2 diabetes. *Diabetes Care*. 2001;24:989–94.

60. Van Gaal L, Maislos M, Schernthaner G, Rybka J, Segal P. Miglitol combined with metformin improves glycaemic control in type 2 diabetes. *Diabetes Obes Metab*. 2001;3:326–31.

61. Fonseca V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA*. 2000;283:1695–702.

62. Gómez-Perez FJ, Fanghänel-Salmón G, Antonio Barbosa J, et al. Efficacy and safety of rosiglitazone plus metformin in Mexicans with type 2 diabetes. *Diabetes Metab Res Rev*. 2002;18:127–34.

63. Bailey CJ, Bagdonas A, Rubes J, et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. *Clin Ther*. 2005;27:1548–61.

64. Weissman P, Goldstein BJ, Rosenstock J, et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. *Curr Med Res Opin*. 2005;21:2029–35.

65. Garber A, Klein E, Bruce S, Sankoh S, Mohideen P. Metformin-glibenclamide versus metformin plus rosiglitazone in patients with type 2 diabetes inadequately controlled on metformin monotherapy. *Diabetes Obes Metab* 2006;8:156–63.

66. Derosa G, Gaddi AV, Piccinni MN, et al. Differential effect of glimepiride and rosiglitazone on metabolic control of type 2 diabetic patients treated with metformin: a randomized, double-blind, clinical trial. *Diabetes Obes Metab*. 2006;8:197–205.

67. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The Pioglitazone 027 Study Group. *Clin Ther*. 2000;22:1395–409.

68. Charbonnel B, Schernthaner G, Brunetti P, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. *Diabetologia*. 2005;48:1093–104.

69. Umpierrez G, Issa M, Vlajnic A. Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial. *Curr Med Res Opin*. 2006;22:751–9.

70. Charbonnel B, Karasik A, Liu J, Wu M, Meininger G; Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care*. 2006;29:2638–43.

71. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP; Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab*. 2007;9:194–205.

72. Brazg R, Xu L, Dalla Man C, Cobelli C, Thomas K, Stein PP. Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and beta-cell function in patients with type 2 diabetes. *Diabetes Obes Metab*. 2007;9:186–93.

73. Ahrén B, Pacini G, Foley JE, Schweizer A. Improved meal-related beta-cell function and insulin sensitivity by the dipeptidyl peptidase-IV inhibitor vildagliptin in metformin-treated patients with type 2 diabetes over 1 year. *Diabetes Care*. 2005;28:1936–40.

74. Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Care*. 2007;30:890–5.

75. Defronzo RA, Hissa MN, Garber AJ, et al. The Efficacy and Safety of Saxagliptin When Added to Metformin Therapy in Patients With Inadequately Controlled Type 2 Diabetes on Metformin Alone. *Diabetes Care*. 2009. [Epub ahead of print].

76. Ahrén B. Novel combination treatment of type 2 diabetes DPP-4 inhibition + metformin. *Diabetes Care*. 2007;30:890–5.

77. Fineman MS, Bicsak TA, Shen LZ, et al. Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care*. 2003;26:2370–7.

78. Poon T, Nelson P, Shen L, et al. Exenatide improves glycemic control and reduces body weight in subjects with type 2 diabetes: a dose-ranging study. *Diabetes Technol Ther*. 2005;7:467–77.

79. Ratner RE, Maggs D, Nielsen LL, et al. Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2006;8:419–28.

80. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005;28:1092–100.

81. Nauck MA, Hompesch M, Filipczak R, et al. Five weeks of treatment with the GLP-1 analogue liraglutide improves glycaemic control and lowers body weight in subjects with type 2 diabetes. *Exp Clin Endocrinol Diabetes*. 2006;114:417–23.

82. Hermansen K, Kipnes M, Luo E, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes Obes Metab*. 2007;9:733–45.

83. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care*. 2005;28:1083–91.

84. Riddle MC, Henry RR, Poon TH, et al. Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin. *Diabetes Metab Res Rev*. 2006;22:483–91.

85. Heine RJ, Van Gaal LF, Johns D, et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med*. 2005;143:559–69.

86. Yki-Järvinen H, Ryysy L, Nikkilä K, Tulokas T, Vanamo R, Heikkilä M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med*. 1999;130:389–96.

87. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia*. 2006;49:442–51.

88. Robbins DC, Beisswenger PJ, Ceriello A, et al. Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA$_{1c}$ and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. *Clin Ther*. 2007;29:2349–64.

89. Fox GN. Metformin in type 2 diabetes. *J Fam Pract*. 2004;53:900.

90. Blonde L, Dailey GE, Jabbour SA, Reasner CA, Mills DJ. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. *Curr Med Res Opin*. 2004;20:565–72.

91. Donnelly LA, Morris AD, Pearson ER. Adherence in patients transferred from immediate release metformin to a sustained release formulation: a population-based study. *Diabetes Obes Metab*. 2009;11:338–42.

92. Lalau J, Race J. Metformin and lactic acidosis in diabetic humans. *Diabetes Obes Metab*. 2000;2:131–7.

93. Misbin RI. The phantom of lactic acidosis due to metformin in patients with diabetes. *Diabetes Care*. 2004;27:1791–3.

94. Chang CT, Chen YC, Fang JT, Huang CC. Metformin-associated lactic acidosis: case reports and literature review. *J Nephrol*. 2002;15:398–402.

95. Emslie-Smith AM, Boyle DR, Evans JMM, Sullivan F, Morris AD. Contraindications to metformin therapy in patients with Type 2 diabetes— a population-base study of adherence to prescribing guidelines. *Diabet Med*. 2001;18:483–8.

96. Chan NN, Brain HP, Feher MD. Metformin-associated lactic acidosis: a rare or very rare clinical entity? *Diabet Med*. 1999;16:273–81.

97. Stang MR, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. *Diabetes Care*. 1999;22:925–7.

98. Berger W. Diabetic emergencies. *Schweiz Rundsch Med Prax*. 1997;86:308–13.

99. Salpeter SR, Greyber E, Pasternak G, Salpeter E. Risk of fatal and non-fatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2006;1:CD002967.

100. Calabrese AT, Coley KC, Da Pos SV, Swanson D, Rao RH. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med*. 2002;162:434–7.

101. Sulkin TV, Bosman D, Krentz A. Contraindications to metformin therapy in patients with NIDDM. *Diabetes Care*. 1997;20:925–9.

102. Fantus G. Metformin's contraindications: needed for now. *CMAJ*. 2005;173:505–7.

103. Holstein A, Egberts EH. Currently listed contraindications to the use of metformin—more harmful than beneficial? *Dtsch Med Wschr*. 2006;131:105–110.

104. Misbin RI, Green L, Stadel BV, Gueriguian JL, Gubbi A, Fleming GA. Lactic acidosis in patients with diabetes treated with metformin. *New Engl J Med*. 1998;338:265–6.

105. Calabrese AT, Coley KC, Da Pos SV, Swanson D, Rao RH. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. *Arch Intern Med*. 2002;162:434–7.

106. Kennedy L, Herman WH. Renal status among patients using metformin in a primary care setting. *Diabetes Care*. 2005;28:922–4.

107. Rakovac I, Jeitler K, Gfrerer RJ, et al. Patients with type 2 diabetes treated with metformin: prevalence of contraindications and their correlation with discontinuation. *Diabet Med*. 2005;22:662–3.

108. Rachmani R, Slavachevski I, Levi Z, Zadok BS, Kedar Y, Ravid M. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. *Eur J Intern Med*. 2002;13:428–33.

109. Cryer DR, Nicholas SP, Henry DH, Mills DJ, Stadel BV. Comparative outcomes study of metformin intervention versus conventional approach. *Diabetes Care*. 2005;28:539–43.

110. Scarpello JHB, Howlett HCS. Metformin monotherapy and clinical uses. *Diabetes Vasc Dis Res*. 2008;5:157–67.

111. Gray AM, Clarke P. The economic analyses of the UK prospective diabetes study. *Diabet Med*. 2008;25 Suppl 2:47–51.

112. Xie X, Vondeling H. Cost-utility analysis of intensive blood glucose control with metformin versus usual care in overweight type 2 diabetes mellitus patients in Beijing, P.R. China. *Value Health*. 2008;11 Suppl 1:S23–32.

113. Palmer AJ, Sendi PP, Spinas GA. Applying some UK Prospective Diabetes Study results to Switzerland: the cost-effectiveness of intensive glycaemic control with metformin versus conventional control in overweight patients with type-2 diabetes. *Schweiz Med Wochenschr*. 2000;130:1034–40.

114. Palmer AJ, Roze S, Valentine WJ, Spinas GA, Shaw JE, Zimmet PZ. Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the diabetes prevention program in Australia, France, Germany, Switzerland, and the United Kingdom. *Clin Ther*. 2004;26:304–21.

115. Herman WH, Hoerger TJ, Brandle M, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med*. 2005;142:323–32.

116. Ramachandran A, Snehalatha C, Yamuna A, Mary S, Ping Z. Cost-effectiveness of the interventions in the primary prevention of diabetes among Asian Indians: within-trial results of the Indian Diabetes Prevention Programme (IDPP). *Diabetes Care*. 2007;30:2548–52.

117. Molavi B, Rassouli N, Bagwe S, Rasouli N. A review of thiazolidinediones and metformin in the treatment of type 2 diabetes with focus on cardiovascular complications. *Vasc Health Risk Manag*. 2007;3:967–73.

118. Bailey CJ. Metformin: effects on micro- and macrovascular complications in type 2 diabetes. *Cardiovasc Drugs Ther*. 2008;22:215–24.

119. Papanas N, Maltezos E. Oral antidiabetic agents: anti-atherosclerotic properties beyond glucose lowering? *Curr Pharm Des*. 2009;15:3179–92.

120. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–65.

121. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577–89.

122. Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med*. 2009;169:616–25.

123. Selvin E, Bolen S, Yeh HC, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. *Arch Intern Med*. 2008;168:2070–80.

124. Wulffelé 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.

125. Nagi DK, Yudkin JS. Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects. A study of two ethnic groups. *Diabetes Care*. 1993;16:621–9.

126. Robinson AC, Burke J, Robinson S, Johnston DG, Elkeles RS. The effects of metformin on glycemic control and serum lipids in insulin-treated NIDDM patients with suboptimal metabolic control. *Diabetes Care.* 1998;21:701–5.

127. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med.* 2007;147:386–99.