REVIEW ARTICLE

Drug Safety 1999 Jun; 20 (6): 489-503
0114-5916/99/0006-0489/$07.50/0

A Risk-Benefit Assessment of Metformin in Type 2 Diabetes Mellitus

Harry C.S. Howlett[1] and *Clifford J. Bailey*[2]

1 Clinical Research, Merck Lipha, West Drayton, England
2 Department of Pharmaceutical and Biological Sciences, Aston University, Birmingham, England

Contents

Abstract

Metformin has been used for over 40 years as an effective glucose-lowering agent in type 2 (noninsulin-dependent) diabetes mellitus. Typically it reduces basal and postprandial hyperglycaemia by about 25% in more than 90% of patients when either given alone or coadministered with other therapies including insulin during a programme of managed care.

Metformin counters insulin resistance and offers benefits against many features of the insulin resistance syndrome (Syndrome X) by preventing bodyweight gain, reducing hyperinsulinaemia and improving the lipid profile. In contrast to sulphonylureas, metformin does not increase insulin secretion or cause serious hypoglycaemia. Treatment of type 2 diabetes mellitus with metformin from diagnosis also offers greater protection against the chronic vascular complications of type 2 diabetes mellitus.

The most serious complication associated with metformin is lactic acidosis which has an incidence of about 0.03 cases per 1000 patients years of treatment and a mortality risk of about 0.015 per 1000 patient-years. Most cases occur in patients who are wrongly prescribed the drug, particularly patients with impaired renal function (e.g. serum creatinine level >130 μmol/L or >1.5 g/L). Other major contraindications include congestive heart failure, hypoxic states and advanced liver disease. Serious adverse events with metformin are predictable rather than spontaneous and are potentially preventable if the prescribing guidelines are respected.

Gastrointestinal adverse effects, notably diarrhoea, occur in less than 20% of patients and remit when the dosage is reduced.

The life-threatening risks associated with metformin are rare and could mostly be avoided by strict adherence to the prescribing guidelines. Given the 4 decades of clinical experience with metformin, its antihyperglycaemic efficacy and benefits against Syndrome X, metformin offers a very favourable risk-benefit assessment when compared with the chronic morbidity and premature mortality among patients with type 2 diabetes mellitus.

The global prevalence of type 2 (noninsulin-dependent) diabetes mellitus is predicted to escalate to 146 and 215 million for the years 2000 and 2010, respectively.[1] Rapid cultural and social changes leading to unhealthy lifestyles and behavioural patterns are key factors in the high prevalence of diabetes mellitus in younger age groups (20 to 30 years). This trend is particularly concerning since the duration of diabetes mellitus together with the level of metabolic control are determinants in the clinical course of the disease and its effects on long term complications.

1. Burden of Diabetes Mellitus

Patients with type 2 diabetes mellitus have a reduced life expectancy with loss of 5 to 10 years on average if diagnosed in middle age (40 to 60 years).[2] In developed countries, age-specific mortality rates are approximately twice those for persons without diabetes mellitus (table I).[3-5]

Microvascular complications affecting the retina and kidney, and neuropathic diseases are classically associated with the chronic morbidity in type 2 diabetes mellitus. Both the degree and duration of hyperglycaemia are recognised as key factors in the onset and progression of the underlying disease processes. Results from the United Kingdom Prospective Diabetes Study (UKPDS) and other prospective studies in patients with type 2 diabetes mellitus have confirmed that intervention therapy to lower the state of hyperglycaemia delays the onset and progression of microvascular complications.[13-15]

Complications affecting the large blood vessels are not specific to diabetes but patients with type 2 diabetes mellitus are prone to premature atherosclerotic disease with an increased predisposition to thrombosis, leading to coronary heart disease, stroke and premature death.[6-9] Furthermore, the frequency of complications imposes a heavy burden on the quality of life of patients with type 2 diabetes mellitus and the provision of adequate healthcare with related costs (table I).[10-12]

2. Insulin Resistance

A common feature of type 2 diabetes mellitus is the presence of insulin resistance. Recent evidence

Table I. The burdens of type 2 diabetes mellitus

Type of burden	Burden of type 2 diabetes mellitus
Medical[2-9]	
Mortality	
life expectancy (diagnosis at 40 to 60 years of age)	↓ 5 to 10y
death rate	↑ >2 times
fatal coronary heart disease	↑ 2 to 4 times
fatal stroke	↑ 2 to 3 times
Morbidity	
coronary heart disease	↑ 2 to 3 times
cerebrovascular disease	↑ >2 times
peripheral vascular disease	↑ 2 to 3 times
nephropathy (proteinuria >300mg/24h)	↑ 5 to 32%
retinopathy at diagnosis	18%[a]
retinopathy over lifetime	80%[a]
retinopathy leading to blindness	2%[a]
peripheral neuropathy	60%[a]
hypertension at diagnosis	35%[a]
foot ulceration	7%[a]
Direct costs[10-12]	
community and hospital service for diabetes management	~10 to 15% total healthcare budget

a Percentage of patients.

↑ signifies an increase in incidence compared with nondiabetic individuals (% prevalence data).

has emerged linking the state of insulin resistance and compensatory hyperinsulinaemia with several cardiovascular risk factors namely obesity, dyslipidaemia, glucose intolerance and type 2 diabetes mellitus, hypertension and possibly other risk factors such as hypofibrinolysis.[16-18] The term 'insulin resistance syndrome' or Syndrome X is used to describe the clustering together of these risk factors.

Growing awareness that the pathogenesis of type 2 diabetes mellitus and related complications may have a shared antecedent, namely insulin resistance, raises the question of what might be the most appropriate therapeutic approach? Present therapeutic algorithms prefer to compartmentalise the different manifestations of the syndrome leading to the treatment of individual symptoms as demanded.

An alternative approach would be to treat the underlying state of insulin resistance with the expectation of redressing a fundamental cause of glucose intolerance and associated cardiovascular risk factors.

Currently, therapeutic options to counter insulin resistance are limited to established agents for the treatment of type 2 diabetes mellitus. The biguanide drug metformin has been available as a glucose-lowering agent for over 40 years in Europe and since 1995 in the US.[19] Being an antihyperglycaemic agent that counters insulin resistance, metformin contrasts with the sulphonylureas which stimulate insulin secretion, and with α glucosidase inhibitors such as acarbose which delay intestinal carbohydrate digestion.

This review evaluates the benefits and risks associated with metformin in order to define its clinical utility within the context of the total burden of diabetes mellitus.

3. Efficacy and Benefits of Therapy

The pharmacological and clinical effects of metformin have been described in many well controlled investigative trials.[20-23] Whilst primarily used to lower blood glucose in patients with type 2 diabetes mellitus, there is growing evidence that the ability of metformin to counter insulin resistance may accrue benefits against other cardiovascular risk factors including obesity, dyslipidaemia, hypofibrinolysis and hypertension, although overall results for the latter suggest a neutral effect for metformin (table II). It may also benefit other states of insulin resistance such as polycystic ovarian syndrome,[43-46] acanthosis nigricans[47] and android adiposity[48] and can reduce the insulin requirement in patients with type 2 or type 1 (insulin-dependent) diabetes mellitus.[49-57]

The mechanism of action of metformin is likely to be multifactorial, reflecting the drug's low molecular weight, high solubility, ionic status at phys-

Table II. Potential benefits of metformin

Reported effects	Change from baseline	
	range	%
Effects on glucose metabolism[20,21,24-27]		
Fasting blood glucose level	↓ 2 to 4 mmol/L	↓ 20 to 30
Postprandial blood glucose level	↓ 3 to 6 mmol/L	↓ 30 to 40
Glycated haemoglobin HbA_{1C} level	↓ 1 to 2%	↓ 10 to 25
Effects on insulin levels[20,28]		
Fasting plasma insulin level	↓ 0 to 3.5 μU/ml	↓ 0 to 20%
Effects on lipid metabolism [20,21,24-27]		
Serum triglyceride level	↓ 0 to 1.10 mmol/L	↓ 0 to 30%
Serum cholesterol level	↓ 0 to 0.35 mmol/L	↓ 0 to 10%
Serum LDL cholesterol level	↓ 0 to 1.00 mmol/L	↓ 0 to 25%
Serum VLDL cholesterol level	↓ 0 to 0.60 mmol/L	↓ 0 to 39%
Serum HDL cholesterol level	↑ 0 to 0.16 mmol/L	↑ 0 to 17%
Serum free fatty acid level	↓ 0 to 0.15 mmol/L	↓ 0 to 14%
Effects on vascular and haematology indices		
Blood pressure[29-36]	Neutral effect	
PAI-1 antigen level[37,38]	↓ 10 to 15 ng/ml	↓ 10 to 45
Peripheral blood flow[39-41]	↑ 0 to 1.0 ml/100ml tissue/min	↑ 0 to 25
Effects on bodyweight[20,21,24,25,27]		
Bodyweight	↓ 0 to 4kg	↓ 0 to 6
Serious hypoglycaemic episodes[19-21,28,42]		
Monotherapy	Negligible	

HDL = high density lipoprotein; **LDL** = low density lipoprotein; **PAI-1** = plasminogen activator inhibitor-1; **VLDL** = very low density lipoprotein; ↑ signifies an increase; ↓ signifies a decrease.

iological pH 7.4 and widespread distribution within many tissues (fig.1; table III).[58-64] Metformin appears to improve insulin action through a variety of cellular targets.[65] Most notably metformin can increase insulin-receptor tyrosine kinase activity,[66-69] increase glycogen synthase activity,[70,71] and translocation of glucose transporters (GLUT1 and GLUT4) into the plasma membrane.[72-75]

Metformin can probably also act independently of insulin (provided there is already a presence of insulin) to enhance glucose metabolism in the intestinal wall[76-78] and possibly erythrocytes,[79] although the extent to which these are direct effects of the drug or indirect consequences of an improved metabolic environment remains to be established. Actions of metformin responsible for the glucose-lowering effect include a suppression of hepatic glucose output, enhancement of insulin-stimulated glucose uptake with increased glucose oxidation and storage into glycogen and fat, inhibition of fatty acid oxidation and increased glucose turnover in the splanchnic bed.[80-87]

When used alone, or in combination with other antidiabetic agents, metformin decreases fasting or random blood glucose levels by approximately 2 to 4 mmol/L (20 to 30%) [table II].[20,21,24-26,88] Several studies have shown an accompanying fall in glycated haemoglobin levels of 1 to 2% (absolute values). Whilst some 90% of patients are reported to respond to metformin, including the elderly,[89-91] the magnitude of the effect appears to be related to the level of basal hyperglycaemia, the dosage of metformin (0.5 to 2.5 g/day) and the continuing presence of some insulin secreting capability.[21,26,92,93]

In patients with type 2 diabetes mellitus whose disease cannot be controlled by diet alone, metformin monotherapy offers equivalent long

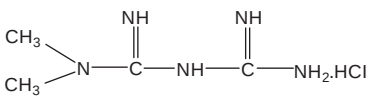

Fig. 1. Chemical structure of metformin.

Table III. Characteristics of metformin[58-64]

Physico-chemical properties	Hydrophilic, ionised at pH 7.4, pKa 11.5
Bioavailability	50-60%; upper GI absorption $t_{½}$ 0.9-2.6h
Plasma concentration	Max 2 μg/ml (10^{-5}mol/L) peak 1-2h
Plasma $t_{½}$	1.5-4.9h
Metabolism	Not metabolised
Distribution	Vd 3.1 L/kg. Minimal plasma protein binding. High concentration in GI tract, salivary glands and liver
Elimination	Urine; ~90% in 12h. Secreted by renal tubules. Plasma clearance ~450 ml/min
Dosage range	1-2.55 g/day (3 g/day max. some countries). Divided dose with meals

GI = gastrointestinal; **max.** = maximum; **$t_{½}$** = elimination half life; **Vd** = volume distribution.

term glycaemic control to that achieved with first and second generation sulphonylureas.[27,28,42,94-99] The secondary treatment failure rate to metformin is estimated to be about 10% per annum in agreement with findings for other oral agents. Treatment failure is thought to reflect the underlying pathology and natural history of diabetes mellitus rather than the drug itself.[19]

Metformin can also be used in combination with a sulphonylurea when either agent alone does not achieve adequate glycaemic control. Combination therapy offers additive or synergistic glucose-lowering efficacy,[93,100-106] and is preferably instituted before there is evidence of 'secondary sulphonylurea failure'.

Additionally metformin has been shown to exert beneficial effects against hyperinsulinaemia, obesity and dyslipidaemia in patients with type 2 diabetes mellitus.[20,21] Numerous clinical studies have reported a bodyweight stabilising or bodyweight reducing effect of metformin in the short term[27] and after 9 years of follow-up.[99] For this reason metformin is often recommended for patients with type 2 diabetes mellitus who are overweight, although it is equally effective in patients who are not obese.[107,108]

The outcome of appetite and energy balance studies to explain the effects of metformin on bodyweight are inconclusive,[81,82,109] but the enhancement of insulin action rather than increased insulin

supply offers one possible explanation.[21] Increased glucose turnover, especially in the splanchnic bed, is another possibility.[78]

Impaired glucose tolerance is a condition of insulin resistance situated within the continuum from normal glucose homeostasis to frank type 2 diabetes mellitus.[110] In Western societies, more than 5% of younger adults and more than 20% of older individuals (>65 years old) exhibit impaired glucose tolerance,[110,111] and in 1 to 10% of these individuals their condition is variously estimated to deteriorate into type 2 diabetes mellitus each year.[112-114]

The possibility that metformin might have a prophylactic effect to reduce the conversion rate from impaired glucose tolerance to type 2 diabetes mellitus is presently under investigation in the Diabetes Prevention Programme (DPP) which involves patients from ethnic minorities in the US and the Early Diabetes Intervention Trial (EDIT) in the UK.[115]

In type 2 diabetes mellitus, the improved lipid profile observed with metformin is variable and affected by the extent of pre-existing hypertriglyceridaemia and hypercholesterolaemia.[116-123] The finding of significant lipid changes in patients without diabetes mellitus after metformin therapy is confirmation that the lipid-lowering action is in part independent of the drug's antihyperglycaemic action.[124-126]

Given either as a monotherapy or in combination with a sulphonylurea, metformin is usually associated with modest reductions (<10%) in plasma triglyceride, total cholesterol and low density lipoprotein cholesterol levels, and small elevations in plasma high density lipoprotein cholesterol levels have been reported.[20,21,24,25]

Additionally, recent evidence has shown marked benefits of treatment in reducing postprandial lipaemia.[127,128] Animal studies have indicated a protective action of metformin against atheroma, plus improved arteriolar vasomotion and capillary perfusion.[129,130] In the UKPDS, intensive treatment with metformin from the diagnosis of type 2 diabetes mellitus in overweight patients decreased the risk of diabetes-related death by 42% compared with conventional (diet) therapy during a mean follow-up of 10.7 years.[99] This was associated with a decreased risk of any diabetes-related end-point (including micro- and macrovascular complications) by 32%.[99] However, this was not seen after 6 years follow-up when metformin was added to the treatment regimens of patients who were not adequately controlled on sulphonylurea therapy.

Metformin has several potentially beneficial haematological and rheological effects.[131] Evidence collected over the years has consistently shown metformin to accelerate clot lysis, and more recently several studies have shown that the drug augments the fibrinolytic pathway by reducing plasminogen activator inhibitor-1 in both individuals with diabetes[37,38] and individuals without diabetes.[132,133]

An antithrombotic action of metformin has been observed in animals with laser-induced carotid thrombi.[134,135] Metformin has also been shown to improve erythrocyte deformability,[136] and enhance limb blood flow in patients with type 2 diabetes mellitus[39] and during leg plethysmography studies in patients with peripheral vascular disease,[40,41] although claims of lowered blood pressure in some studies[29,30] have not been confirmed by others.[31-36]

4. Risks and Adverse Events of Therapy

Since its introduction in 1957, worldwide experience with metformin has exceeded an estimated 40 million patient-years of use,[137] giving an extensive insight into the risks and adverse effects.

4.1 Lactic Acidosis

Lactic acidosis is the most serious risk with metformin. Adverse event reports have recorded an incidence of <0.01 to 0.09 (average about 0.03) cases per 1000 patient years of treatment, with a mortality of about 50% (table IV).[137-145]

These reports are often incomplete, and some lack evidence of raised blood lactate levels to confirm the diagnosis of lactic acidosis. In many cases

Table IV. Reported incidence and mortality risk of lactic acidosis amongst patients taking metformin[137-145]

Country	Years	Patient-years of treatment	Total no. of cases (nonfatal/fatal)	Total incidence (cases per 1000 patient-years of treatment)	Mortality rate (fatal cases per 1000 patient-years of treatment)
UK	1976-1986	400 000	11 (4/7)	0.027	0.017
Switzerland	1972-1977	29 800	2 (2/0)	0.067	
Sweden	1972-1981	83 500	7 (5/2)	0.084	0.024
	1987-1991	100 100	3 (1/2)	0.029	0.019
	1987-1997	227 644	12 (3/9)	0.053	0.039
France	1984-1992	2 476 061	73 (40/33)	0.029	0.013
	1993-1997	1 928 486	68 (35/33)	0.035	0.017
USA	1995-1996	1 000 000	47 (27/20)	0.047	0.020
	1995-1997	2 893 900	93 (62/31)	0.032	0.011

there is no measurement of the blood metformin concentration, and in others the concentration was undetectable. Indeed, the background (natural) incidence of lactic acidosis amongst patients with type 2 diabetes mellitus is uncertain, although a recent study in the US has estimated 0.097 to 0.169 events per 1000 patient years.[146] As these rates are indistinguishable from incidence rates reported for metformin this leads to the possibility that metformin may sometimes be an incidental factor that is not responsible for the lactic acidosis.[19,20,147,148] Since the presenting features of lactic acidosis are often vague,[149,150] the diagnosis may not be correct even if lactate levels are raised. Elevated blood lactate levels occur in cardiogenic shock and other conditions with hypoxaemia and hypoperfusion. Some reports may be wrongly attributed cases of ketoacidosis in patients with late-onset type 1 diabetes mellitus or other types of acidosis.[151,152]

From published accounts it is evident that most cases of metformin-associated lactic acidosis have occurred in patients who should not have been prescribed this drug. The most commonly overlooked contraindication has been renal insufficiency.[147,153,154] Since metformin is eliminated in the urine it is likely that renal insufficiency will cause an accumulation of the drug in body tissues. Abnormally high concentrations of metformin in the liver and possibly other tissues (e.g. intestinal wall) appear to increase anaerobic glucose metabolism and raise lactate levels.[64,78,155] Metformin can also reduce non-oxidative and oxidative lactate utilisation.[81] These effects may be exacerbated by coexistent liver disease or cardiopulmonary disease, precipitating lactic acidosis.[147,156,157] Metformin is associated primarily with a type B lactic acidosis in which severe tissue hypoxia is not implicated.

An analysis of 110 published cases (pre-1993) of lactic acidosis in patients prescribed metformin (53% female, 51% >65 years old) found 52 cases (47%) had a fatal outcome, 72 (65%) patients had renal disease, 41 (37%) patients had a cardiovascular condition, and 13 (12%) patients had liver disease.[147] Metformin concentration was measured in 42 (38%) of these patients, and the blood metformin concentration was abnormally high (>5 mg/L) in 26 (23%) patients, undetectable in 4 (3%) patients and normal (<5 mg/L) in 12 (11%) patients. In many of the patients who did not have pre-existing renal disease, an acute renal problem (e.g. after intravenous urography with iodinated contrast media or dehydration) was noted, emphasising the importance of normal renal function as a mandatory precaution against metformin-associated lactic acidosis.

There was no apparent association with gender, duration of therapy or dosage of drug, although most patients had more than one risk factor for lactic acidosis (renal disease, congestive heart disease, liver disease, septicaemia, alcohol abuse, ob-

structive pulmonary disease and multiple medication). Likelihood of fatality was not predicted by any particular presenting factor, and may be more dependent on the treatment given. However, patients in whom the lactic acidosis had a fatal outcome on average showed greater lactataemia, lower pH, a larger anion gap and multiple risk factors.[147]

Of 47 cases of metformin-associated lactic acidosis that occurred in the US between May 1995 and June 1996, 20 (42%) had a fatal outcome and 43 (91%) patients had 1 or more pre-existing risk factors for lactic acidosis.[145] The most common risk factor was cardiac disease, with 18 (38%) patients having congestive heart failure. 13 (27%) patients had renal insufficiency and 2 of these patients were already receiving dialysis. These and other examples[158-160] serve to re-emphasise that a majority of cases of metformin-associated lactic acidosis are potentially avoidable if the exclusion criteria are explicitly observed.[161]

Although a discussion of treatment strategies for lactic acidosis is beyond the bounds of this article, it must be noted that metformin is dialysable.[162] Dialysis has been used in about half of the cases reported in the literature with a 64% survival rate (25 out of 39 patients survived).[147]

When comparing the mortality risks of metformin with the other main antidiabetic drugs, it is pertinent to note that sulphonylureas and insulin carry a risk of fatal hypoglycaemia.[163-166] Studies comparing metformin-associated lactic acidosis with sulphonylurea-induced hypoglycaemia have found a similar incidence of mortality. In Switzerland, mortality from sulphonylurea-induced hypoglycaemia from 1960 to 1969 was 0.014/1000 patient-years.[138] In Sweden fatal hypoglycaemia during therapy with glibenclamide (glyburide) from 1972 to 1981 was 0.033/1000 patient-years.[139] These mortality figures are comparable with fatalities from metformin-associated lactic acidosis (0 to 0.024/1000 patient-years) in the same population (table IV). The incidence of insulin-induced hypoglycaemic coma has been estimated to be as high as 100/1000 patient-years,[167] although mortality is <5% for patients admitted to hospital.[166] Hypoglycaemia is the suspected cause of 2 to 4% of deaths amongst patients with type 1 diabetes mellitus,[168] but the mortality rate amongst patients with type 2 diabetes mellitus is likely to be lower due to protection by insulin resistance.

4.2 Gastrointestinal Events

Gastrointestinal disturbances occur in up to 20% of patients starting metformin therapy.[22,169] They include nonspecific abdominal discomfort, metallic taste, nausea, anorexia and diarrhoea. The latter may reflect an alteration in the absorption of bile salts.[170] The disturbances are usually transient, and if they do not remit spontaneously they resolve quickly when the dosage is lowered. Continued diarrhoea may require the drug to be discontinued, but overall less than 5% of patients do not tolerate metformin.[22,97,107,171]

4.3 Haematological and Other Events

Metformin reduces absorption of cyanocobalamin (vitamin B_{12}) in the distal ileum, and 30% of patients receiving long term metformin therapy (4 to 5 years) have shown an abnormal Schilling test.[172] Subnormal serum cyanocobalamin levels occur in <10% of patients and appear to be due to insufficient dietary calcium. This is reversible by calcium supplementation and seems to have little clinical impact, although it is recommended that haemoglobin levels are checked annually, and cyanocobalamin supplementation given if required. There have been 5 cases of megaloblastic anaemia associated with metformin. Folate absorption can be reduced by metformin, but without apparent clinical effects. Very occasionally cutaneous hypersensitivity reactions and a single case of vasculitis with pneumonitis have been reported.[173,174]

5. Recommendations for Clinical Use of Metformin

Metformin is used in over 90 countries for patients with type 2 diabetes mellitus whose disease

cannot be controlled by diet alone,[19] and its unique role is recognised in nationally approved treatment guidelines in Europe and the North America.[175,176]

In numerous clinical trials, metformin has proved as effective as other treatments in treating the hyperglycaemia in asymptomatic patients with type 2 diabetes mellitus.[20,24,25,27] The bodyweight-stabilising, lipid-lowering and anti-hyperinsulinaemic effects of metformin make this drug a particularly suitable choice for patients with diabetes mellitus who are carrying excess fat, and exhibiting dyslipidaemia and hyperinsulinaemia.

Diabetes mellitus is a progressive chronic illness, and a near-normal level of glycaemic control (HbA_{1C} level <7%, fasting glucose level <7 mmol/L) is difficult to achieve and maintain irrespective of the treatment modality.[99] In patients who are not adequately controlled with oral monotherapy, either with metformin or a sulphonylurea, the likelihood of unremitting deterioration in β-cell function supports the proposal by Hermann et al.[98] in 1994 to consider combination therapy as an early option, focused on a minimal dosing plan. The joint targeting of insulin resistance with metformin and relative insulin deficiency with a sulphonylurea would provisionally appear to be a helpful tactic to improve and prolong the control of hyperglycaemia in patients with type 2 diabetes mellitus.[101]

Combination of metformin with the α glucosidase inhibitor, acarbose, has proved additionally effective in treating hyperglycaemia.[177,178] Although acarbose can decrease metformin absorption, there is no evidence that the dosage of metformin should be increased, and surprisingly there is no reported increase in gastrointestinal intolerance.

Switching patients with type 2 diabetes mellitus from oral agents to insulin, in the expectation of better glycaemic control, is not without problems of bodyweight gain,[42,104] peripheral hyperinsulinaemia and possible cardiovascular risk.[179,180] A combined treatment programme of bedtime insulin and metformin twice daily with the main meals offers the opportunity for more effective glycaemic control with a diminished insulin requirement, reduced hyperinsulinaemia and reduced bodyweight gain.[49] Indeed, it was recently found in the US that re-initiation of combined oral metformin and sulphonylurea therapy to C-peptide positive patients with insulin-treated type 2 diabetes mellitus enabled a sufficient reduction in insulin dosage so that more than 70% of patients could stop insulin while showing improved glycaemic control and a reduction in bodyweight.[52]

It is always recommended that metformin is taken with meals to minimise any gastrointestinal effects, and it is important to titrate up the dose gradually to determine the lowest most effective dose.[21] A maximum approved daily dosage is 2.55g (or exceptionally 3g in some countries) although maximum efficacy is usually achieved below the maximum dose.[92]

Used as a monotherapy metformin is unlikely to cause serious hypoglycaemia, even if a meal is delayed or missed.[20,21,28] This offers advantages for the elderly, those who live alone or have changing meal patterns, and those pursuing activities in which unrecognised neuroglycopenia would be especially dangerous (e.g. driving).

When co-prescribed with treatment modalities that carry an attendant risk of hypoglycaemia, careful titration of the metformin dosage is required to maintain an adequate safety margin.

6. General Precautions

When choosing metformin, it is essential to ensure normal renal function. Special care should be exercised with the elderly (e.g. by the eighth decade) and patients with advanced cardiovascular complications.

Renal function gradually declines with advancing age, leaving the elderly more vulnerable to incomplete elimination of metformin.[181] It is emphasised that renal function should be checked in every patient, irrespective of age, before starting metformin, and at least annually during therapy.[21] However, in octogenarians a normal serum creatinine level (e.g. <130 μmol/L, <1.5 g/L) should be

substantiated with a creatinine clearance test. Although the renal clearance of metformin is about 3.5 times greater than creatinine clearance due to extensive tubular secretion of the drug, there is a significant correlation between the most rapid phase of metformin elimination and the rate of creatinine clearance.[59-61] Since renal function must be sufficient to maintain clearance of a steady-state maximum dosage regimen of metformin, it is undesirable for the glomerular filtration rate to fall below 50% of normal. To ensure an adequate margin of safety it is suggested that the creatinine clearance value should be >90 ml/min, although discretion must be exercised to take account of lean body mass, gender and the coexistence of medical conditions and concurrent medications.

While metformin monotherapy may have vasoprotective actions its usage is contraindicated in patients with advanced cardiovascular disease.[19,20] Any patient at risk of hypoxia from circulatory decompensation is therefore excluded from metformin therapy, notably congestive heart failure and acute myocardial infarction. Severe infection, septicaemia, history of lactic acidosis and respiratory insufficiency are further contraindications. Unstable diabetic states and severe occlusive vascular disease should remain as contraindications for metformin until the antiatherogenic and antithrombotic potentials of the drug have been more thoroughly investigated in these conditions.

Additional precautions against the risk of lactic acidosis include the exclusion of patients who abuse alcohol and any patient with significant clinical or laboratory evidence of liver disease. It should be remembered that patients with type 2 diabetes mellitus are predisposed to hyperlactataemia[160] and that liver diseases are more common amongst patients with diabetes.[182]

Use of an intravascular radiological contrast medium in patients taking metformin requires caution, but does not prohibit emergency procedures, including angiography and urography. Metformin can be discontinued at the time of the procedure (prior discontinuation is not necessary). Thereafter metformin should be withheld for a minimum of 48 hours and reinstated only after renal function is confirmed as normal. Disruption of diabetes management can be kept to a minimum if care is exercised in maintaining the patient in an adequate state of hydration during the radiological procedure.

Awareness of initial gastrointestinal reactions and long term checks on cyanocobalamin levels have been noted previously. Although metformin is not known to have any adverse events during pregnancy or lactation, there is insufficient evidence to support its use at these times and current advice is to recommend insulin in preference to oral agents.[20]

Finally, metformin shows relatively few drug interactions beyond the risk of hypoglycaemia when used in combination with a sulphonylurea. Cimetidine competes with metformin for a common transport system in the renal tubules reducing metformin's rate of urinary excretion.[183] In certain circumstances a dosage reduction for metformin may need to be considered. Potential interactions with other cationic drugs eliminated by tubular secretion have not been observed in clinical practice. Small pharmacokinetic changes of no clinical significance have been observed for coadministration of metformin with furosemide (frusemide) or nifedipine.[137]

7. Conclusions

Type 2 diabetes mellitus exerts a significant toll on life expectancy and the many routine and enriching aspects of daily living. Diabetes management should be aimed at reducing the burden of complications in the long term, and providing symptomatic relief in the short term to improve the quality of life. Fundamental to both the metabolic and vascular complications is the unifying concept of insulin resistance. Metformin reduces insulin resistance in type 2 diabetes mellitus and exerts significant effects on the accompanying cardiovascular risk factors of Syndrome X.

The long term glycaemic control achieved with metformin is comparable with sulphonylureas and is independent of age and degree of obesity. Combination of metformin with a sulphonylurea or with

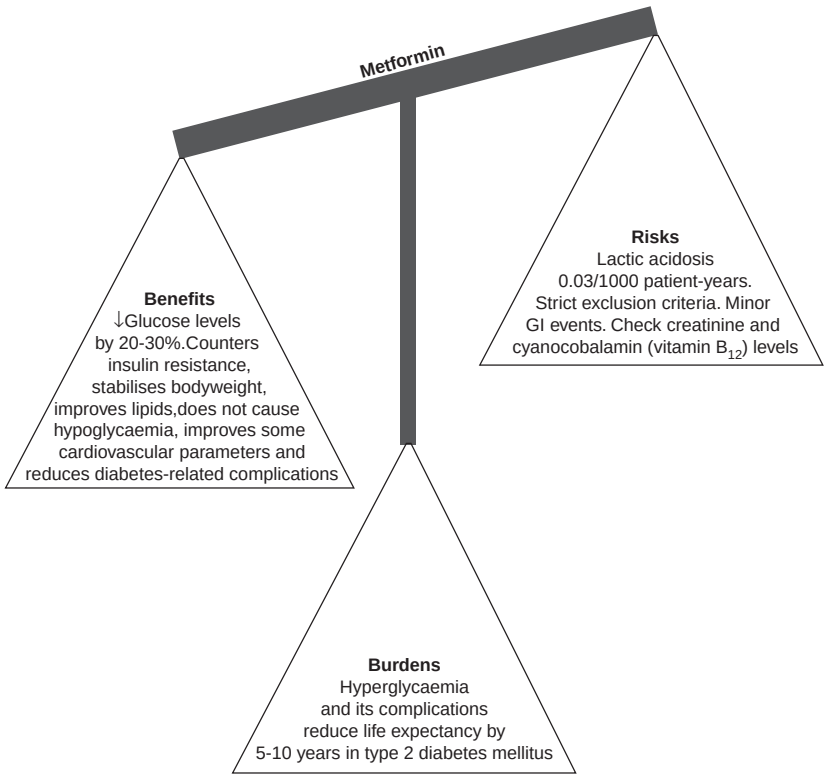

Fig. 2. Key elements in the risk-benefit assessment of metformin against the burdens of type 2 (noninsulin-dependent) diabetes mellitus.

insulin has been effective in treating the progressive hyperglycaemia in patients who are severely diabetic and who are inadequately controlled by monotherapy alone.

Metformin offers advantages over sulphonylureas and insulin in controlling bodyweight gain, inducing a fall rather than a rise in peripheral insulin levels and avoiding episodes of hypoglycaemia. Improvements in dyslipidaemia and hypofibrinolysis suggest that metformin may help to reduce cardiovascular complications during long term use.

Most patients have an acceptable tolerance to metformin provided it is taken with the main meals and the dosage is titrated appropriately. Gastrointestinal symptoms are usually transient and respond rapidly to dosage adjustment.

Great care should be taken in patient selection and monitoring to minimise the risk of lactic acidosis. Patients with renal impairment, congestive heart failure, recent myocardial infarction, severe hepatic disease, and any medical condition leading to hypoxaemia are strictly contraindicated. Since most patients with metformin-associated lactic acidosis should not have been taking the drug due to pre-existing contraindications, ongoing prescriber education is paramount to avoid drug misuse.

Metformin is an effective and well established therapy for type 2 diabetes mellitus (fig. 2). Its versatility as a first- or second-line therapy in combination with other treatment modalities enables the drug to be employed in a managed care programme to optimise glycaemic control. The drug's safety profile and restrictions on use are well documented. It is concluded that metformin presents a

very favourable risk-benefit analysis against the multiple burdens of type 2 diabetes mellitus.

References

1. Amos AF, McCarthy DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabetic Med 1997; 14 Suppl. 5: S7-85
2. Panzram G. Mortality and survival in type 2 (non-insulin dependent) diabetes mellitus. Diabetologia 1987; 30: 123-31
3. Fuller J. Mortality trends and causes of death in diabetic patients. Diabete Metab 1993; 19: 96-9
4. Eschwege E, Balkau B, Fontbonne A. The epidemiology of coronary heart disease in glucose-intolerant and diabetic subjects. J Intern Med 1994; 236: 5-11
5. Geiss LS, Hermann WH, Smith PJ. Mortality in non-insulin dependent diabetes: diabetes in America. National Institute of Diabetes and Digestive and Kidney Disease. 2nd ed. Bethesda (MD): US Department of Health and Human Services. 1995 NIH publication. Report no.: 95-1468: 233-58
6. National Institute of Diabetes and Digestive and Kidney Diseases. Diabetes statistics. Bethesda (MD): US Department of Health and Human Services. 1994 NIH publication. Report no.: 94-3822
7. United Kingdom Prospective Diabetes Study Group. UK Prospective diabetes study 6: complications in newly diagnosed type 2 diabetic patients and their association with different clinical and biochemical risk factors. Diabetes Res 1990; 13: 1-11
8. Walters DP, Gatling W, Mullee R, et al. The distribution and severity of diabetic foot disease: a community study with a comparison to a non-diabetic group. Diabetic Med 1992; 9: 354-8
9. Hasslacher CH. Similar risks of nephropathy in patients with type 1 or type 2 diabetes mellitus. Nephrol Dial Transpl 1989; 4: 859-63
10. Rubin RJ, Altman WM, Mendelson DN. Health care expenditure for people with diabetes 1992. J Clin Endocrinol Metab 1994; 78: 809A-F
11. British Diabetic Association. Counting the cost: the real impact of non-insulin dependent diabetes. King's Fund Policy Institute; London: British Diabetic Association Publications, 1996
12. Costa B, Arroyo J, Sabate A. The economics of pharmacotherapy for diabetes mellitus. Pharmacoeconomics 1997; 11: 139-58
13. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53
14. Ohkubo Y, Kishikawa H, Araki, E et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomised prospective 6 year study. Diabetes Res Clin Pract 1995; 28: 103-17
15. Klein R. Hyperglycaemia and microvascular and macrovascular disease in diabetes. Diabetes Care 1995; 18: 258-68
16. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-607
17. De Fronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidaemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991; 14: 173-94
18. Haffner SM, Miettinen H. Insulin resistance implications for type II diabetes mellitus and coronary heart disease. Am J Med 1997; 103: 152-62
19. Bailey CJ, Turner RC. Metformin. N Engl J Med 1996; 334: 574-9
20. Hermann LS, Melander A. Biguanides: basic aspects and clinical uses. In: Alberti KGMM, DeFronzo RA, Keen H, et al., editors. International textbook of diabetes mellitus. 2nd ed. Chichester: John Wiley & Sons Ltd 1997: 841-64
21. Bailey CJ. Biguanides and NIDDM. Diabetes Care 1992; 15: 755-72
22. Hermann LS. Metformin. A review of its pharmacological properties and therapeutic use. Diabete Metab 1979; 5: 233-45
23. Balfour JA, Clissold SP. Management of non-insulin-dependent diabetes mellitus: defining the role of metformin. Dis Manage Health Outcomes 1997; 1: 49-59
24. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. Am J Med 1997; 102: 99-110
25. 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
26. De Fronzo RA, Goodman AM, Multicentre study group. Efficacy of metformin in patients with non-insulin dependent diabetes mellitus. N Engl J Med 1995; 333: 541-9
27. Campbell IW, Howlett HCS. Worldwide experience of metformin as an effective glucose-lowering agent: a meta-analysis. Diabetes Metab Rev 1995; 11 Suppl. 1: S57-62
28. United Kingdom Prospective Diabetes Study Group. UK Prospective diabetes study 24: a 6 year, randomised, controlled trial comparing sulphonylurea, insulin and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. Ann Intern Med 1998; 128: 165-75
29. Chan JC, Tomlinson B, Critchley JA, et al. Metabolic and hemodynamic effects of metformin and glibenclamide in normotensive NIDDM patients. Diabetes Care 1993; 16: 1035-8
30. Giugliano D, De Rosa N, Di Mario G, et al. Metformin improves glucose lipid metabolism, and reduces blood pressure in hypertensive, obese women. Diabetes Care 1993; 16: 1387-90
31. Campbell IW, Duncan CD, Patton NW, et al. The effect of metformin on glycaemic control, intermediary metabolism and blood pressure in non-insulin dependent diabetes mellitus. Diabetic Med 1987; 4: 337-41
32. Marfella R, Acampora R, Verrazzo G, et al. Metformin improves hemodynamic and rheological responses to L-arginine in NIDDM patients. Diabetes Care 1996; 19: 934-9
33. Sundaresan P, Lykos D, Daher A, et al. Comparative effects of glibenclamide and metformin on ambulatory blood pressure and cardiovascular reactivity in NIDDM. Diabetes Care 1997; 20: 692-7
34. Dorella M, Giusto M, Da Tos V, et al. Improvement of insulin sensitivity by metformin treatment does not lower blood pressure of non-obese insulin-resistant hypertensive patients with normal glucose tolerance. J Clin Endocrinol Metab 1996; 81: 1568-74
35. Gudbjornsdottir HS, Friberg P, Elam M, et al. The effect of metformin and insulin on sympathetic nerve activity, norepinephrine spillover and blood pressure in obese, insulin resistant, normoglycemic, hypertensive men. Blood Press 1994; 3: 394-403

36. Snorgaard O, Kober L, Carlsen J. The effect of metformin on blood pressure and metabolism in non-diabetic hypertensives. J Intern Med 1997; 242: 407-12
37. Grant PJ. The effects of high and medium dose metformin therapy on cardiovascular risk factors in patients with type II diabetes. Diabetes Care 1996; 19: 64-6
38. Nagi DK, Yudkin JS. Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects. Diabetes Care 1993; 16: 621-9
39. Jansson PE, Anderson OK, Gudbjornsdottir HS, et al. The effect of metformin on adipose tissue metabolism and peripheral blood flow in subjects with NIDDM. Diabetes Care 1996; 19: 160-4
40. Sirtori CR, Franceschini G, Gianfranceschi G, et al. Metformin improves peripheral vascular flow in non hyperlipidemic patients with arterial disease. J Cardiovasc Pharmacol 1984; 6: 914-23
41. Montanari G, Bondioli A, Rizzato G, et al. Treatment with low dose metformin in patients with peripheral vascular disease. Pharmacol Res 1992; 25: 63-73
42. United Kingdom Prospective Diabetes Study Group. UK prospective diabetes study 16: overview of 6 years therapy of type II diabetes: a progressive disease. Diabetes 1995; 44: 1249-58
43. Sattar N, Hopkinson ZEC, Greer IA. Insulin sensitising agents in polycystic ovary syndrome. Lancet 1998; 351: 305-7
44. Velazquez EM, Mendoza S, Hamer T, et al. Metformin therapy in women with polycystic ovary syndrome reduces hyperinsulinaemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating menstrual regularity and pregnancy. Metabolism 1994; 43: 647-55
45. Velazquez EM, Mendoza SG, Wang P, et al. Metformin therapy is associated with a decrease in plasma plasminogen activator inhibitor -1, lipoprotein(a), and immunoreactive insulin levels in patients with the polycystic ovary syndrome. Metabolism 1997; 46: 454-7
46. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome p450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. N Engl J Med 1996; 335: 617-23
47. Lee PJ, Cranston I, Amiel SA. Effect of metformin on glucose disposal and hyperinsulinaemia in a 14 year old boy with acanthosis nigricans. Horm Res 1997; 48: 88-92
48. Fontbonne A, Aline-Charles M, Juhan-Vague I. The effect of metformin on the metabolic abnormalities associated with upper body fat distribution. Diabetes Care 1996; 19: 920-6
49. Hermann LS. Combination therapy with insulin and metformin. Endocr Practice 1998; 4: 404-12
50. Giugliano D, Quatraro A, Consoli G, et al. Metformin for obese insulin treated diabetic patients: improvement in glycaemic control and reduction of metabolic risk factors. Eur J Clin Pharmacol 1993; 44: 107-12
51. Yki-Jarvinen H, Nikkila K, Ryysy L, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes. Ann Intern Med 1999; 130: 389-96
52. Bell DSH, Mayo MS. Outcome of metformin-facilitated reinitiation of oral diabetic therapy in insulin-treated patients with non-insulin-dependent diabetes mellitus. Endocr Practice 1997; 3: 73-6
53. Robinson AC, Burke J, Robinson S, et al. The effects of metformin on glycaemic control and serum lipids in insulin-treated NIDDM patients with suboptimal metabolic control. Diabetes Care 1998; 21: 701-5
54. Daniel JR, Hagmeyer KO. Metformin and insulin: is there a role for combination therapy? Ann Pharmacother 1997; 31: 474-80
55. Golay A, Guillet-Dauphiné N, Fendel A, et al. The insulin sparing effect of metformin in insulin-treated diabetic patients. Diabetes Metab Rev 1995; 11 Suppl. 1: S63-7
56. Pagano G, Taguaferro V, Carta Q, et al. Metformin reduces insulin requirement in type 1 (insulin dependent) diabetes. Diabetologia 1983; 24: 351-4
57. Gin H, Messerchmitt C, Brottier E, et al. Metformin improved insulin resistance in type 1, insulin-dependent diabetic patients. Metabolism 1985; 34: 923-5
58. Schafer G. Biguanides: molecular mode of action. Res Clin Forums 1979; 1: 21-32
59. Scheen AJ. Clinical pharmacokinetics of metformin. Clin Pharmacokin 1996; 30: 359-71
60. Sambol NC, Chiang J, O'Connor M, et al. Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with non-insulin-dependent diabetes mellitus. J Clin Pharmacol 1996; 36: 1012-21
61. Sirtori CR, Franceschini G, Galli-Kienie M, et al. Disposition of metformin (N, N-dimethyl biguanide) in man. Clin Pharmacol Ther 1978; 24: 683-93
62. Pentakainen PJ, Neuvonen PJ, Penttila A. Pharmacokinetics of metformin after intravenous and oral administration to man. Eur J Clin Pharmacol 1979; 16: 195-202
63. Tucker GT, Casey C, Philiips PJ, et al. Metformin kinetics in healthy subjects and in patients with diabetes mellitus. Br J Clin Pharmacol 1981; 12: 235-46
64. Wilcock C, Bailey CJ. Accumulation of metformin by tissues of the normal and diabetic mouse. Xenobiotica 1994; 24: 49-57
65. Wiernsperger NF. Preclinical pharmacology of biguanides. Oral antidiabetics. In: Puls W, editor. Handbook of experimental pharmacology. Berlin: Springer Verlag, 1996: 305-58
66. Rossetti L, DeFronzo RA, Gherzi R, et al. Effect of metformin treatment on insulin action in diabetic rats: in vivo and in vitro correlations. Metabolism 1990; 39: 425-35
67. Santos RF, Nomizo R, Wajhenberg BL, et al. Changes in insulin receptor tyrosine kinase activity associated with metformin treatment of type 2 diabetes. Diabete Metab 1995; 21: 274-80
68. Dominguez LJ, Davidoff AJ, Srinivas PR, et al. Effects of metformin on tyrosine kinase activity, glucose transport and intracellular calcium in rat vascular smooth muscle. Endocrinology 1996; 137: 113-21
69. Stith BJ, Goalstone ML, Espinoza R, et al. The antidiabetic drug metformin elevates receptor tyrosine kinase activity and inositol 1,4,5-triphosphate mass in Xenopus oocytes. Endocrinology 1996; 137: 2990-9
70. Johnson AB, Webster JM, Sum CF, et al. The impact of metformin therapy on hepatic glucose production and skeletal muscle glycogen synthase activity in overweight type II diabetic patients. Metabolism 1993; 42: 1217-22
71. Detaille D, Wiernsperger N, Devos P. Potentiating effect of metformin on insulin-induced glucose uptake and glycogen metabolism within xenopus oocytes. Diabetologia 1998; 41: 2-8
72. Matthei S, Hamann A, Klein HH, et al. Association of metformin's effect to increase insulin-stimulated glucose transport with potentiation of insulin-induced translocation of glucose transporters from intracellular pool to plasma membrane in rat adipocytes. Diabetes 1991; 40: 850-7
73. Hundal HS, Ramlal T, Reyes R, et al. Cellular mechanism of metformin action involves glucose transporter translocation

from an intracellular pool to the plasma membrane in L6 muscle cells. Endocrinol 1992; 131: 1165-73
74. Kozka U, Holman GD. Metformin blocks down regulation of cell surface GLUT4 caused by chronic insulin treatment of rat adipocytes. Diabetes 1993; 42: 1159-65
75. Hamann A, Benecke H, Greten H, et al. Metformin increases glucose transporter protein and gene expression in human fibroblasts. Biochem Biophys Res Commun 1993; 196: 382-7
76. Cuber JC, Bosshard A, Vidal H, et al. Metabolic and drug distribution studies do not support direct inhibitory effects of metformin on intestinal glucose absorption. Diabete Metab 1994; 20: 532-9
77. Bailey CJ. Metformin and intestinal glucose handling. Diabete Metab Rev 1995; 11: S23-S32
78. Bailey CJ, Wilcock C, Day C. Effect of metformin on glucose metabolism in the splanchnic bed. Br J Pharmacol 1992; 105: 1009-13
79. Yoa RG, Rapin JR, Wiernsperger NF, et al. Demonstration of defective glucose uptake and storage in erthrocytes from non-insulin dependent diabetic patients and effects of metformin. Clin Exp Pharmacol Physiol 1993; 20: 563-7
80. Cusi K, Consoli A, DeFronzo RA. Metabolic effects of metformin on glucose and lactate metabolism in non-insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1996; 81: 4059-67
81. Stumvoll M, Nurjhan N, Perriello G, et al. Metabolic effects of metformin in non-insulin dependent diabetes mellitus. N Engl J Med 1995; 333: 550-4
82. Perriello G, Misericordia P, Volpi E, et al. Acute antihyperglycaemic mechanisms of metformin in NIDDM. Diabetes 1994; 43: 920-8
83. Riccio A, Del Prato S, Vigili de Kreutzenberg S, et al. Glucose and lipid metabolism in non-insulin dependent diabetes. Effect of metformin. Diabete Metab 1991; 17: 180-4
84. McIntyre HD, Paterson CA, Ma A, et al. Metformin increases insulin sensitivity and basal glucose clearance in type 2 (non-insulin dependent) diabetes mellitus. Aust NZ J Med 1991; 21: 714-9
85. Nosadini R, Avogaro A, Trevison R, et al. Effect of metformin on insulin stimulated plasma turnover and insulin binding to receptors in type II diabetes. Diabetes Care 1987; 10: 62-7
86. Jackson RA, Hawa MI, Jaspan JB, et al. Mechanism of metformin action in non-insulin-dependent diabetes. Diabetes 1987; 36: 532-40
87. De Fronzo RA, Barzilai N, Simonson DC. Mechanism of metformin action in obese and lean non-insulin dependent diabetic subjects. J Clin Endocrinol Metab 1991; 73: 1294-301
88. Dornan TL, Heller SR, Peck GM. Double-blind evaluation of efficacy and tolerability of metformin in NIDDM. Diabetes Care 1991; 14: 342-4
89. Josephkutty S, Potter JM. Comparison of tolbutamide and metformin in elderly diabetic patients. Diabetic Med 1990; 7: 510-4
90. Gregorio F, Ambrosi F, Filipponi P, et al. Is metformin safe enough for ageing type 2 diabetic patients. Diabete Metab 1996; 22: 43-50
91. Jennings PE. Oral antihyperglycaemics: considerations in older patients with non-insulin-dependent diabetes mellitus. Drugs Aging 1997; 10: 323-31
92. Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind placebo controlled, dose response trial. Am J Med 1997; 102: 491-7
93. Hermann LS, Schersten B, Melander A. Antihyperglycaemic efficacy response prediction and dose-response relations of treatment with metformin and sulphonylureas, alone and in primary combination. Diabetic Med 1994; 11: 953-60
94. Campbell IW, Menzies DG, Chalmers J, et al. One year comparative trial of metformin and glipizide in type 2 diabetes mellitus. Diabetes Metab 1994; 20: 394-400
95. McAlpine LG, McAlpine CH, Waclawski ER, et al. A comparison of treatment with metformin and gliclazide in patients with non-insulin dependent diabetes. Eur J Clin Pharmacol 1988; 34: 129-32
96. Collier A, Watson HHK, Patrick AW, et al. Effect of glycaemic control, metformin and gliclazide on platelet density and aggregability in recently diagnosed type 2 (non-insulin dependent) diabetic patients. Diabete Metab 1989; 15: 420-5
97. Clarke BF, Duncan LJP. Comparison of chlorpropamide and metformin treatment on weight and blood glucose response of uncontrolled obese diabetics. Lancet 1968; I: 123-6
98. Hermann LS, Scheresten B, Bitzen P-O. Therapeutic comparison of metformin and sulphonylureas, alone and in various combinations. Diabetes Care 1994; 17: 1100-9
99. United Kingdom 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
100. Holman RR, Steemson J, Turner RC, et al. Sulphonylurea failure in type 2 diabetes: treatment with a basal insulin supplement. Diabetic Med 1987; 4: 457-62
101. United Kingdom Prospective Diabetes Study Group. UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulphonylurea-treated type 2 diabetes. Diabetes Care 1998; 21: 87-92
102. Trishitta V, Italia S, Mazzarino S, et al. Comparison of combined therapies in treatment of secondary failure to glyburide. Diabete Care 1992; 15: 539-42
103. Klein W. Sulphonylurea-metformin combination versus sulphonylurea-insulin combination in secondary failure of sulphonylurea monotherapy. Diabete Metab 1991; 17: 235-40
104. Groop L, Widen E, Franssila-Kallunki A, et al. Different effects of insulin and oral antidiabetic agents on glucose and energy metabolism in type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1989; 32: 599-605
105. Marena S, Tagliaferro V, Montegrosso G, et al. Metabolic effects of metformin addition to chronic glibenclamide treatment in type 2 diabetes. Diabete Metab 1994; 20: 15-9
106. Hermann LS. Biguanides and sulphonylureas as combination therapy in NIDDM. Diabetes Care 1990; 13 Suppl. 3: 37-41
107. Clarke BF, Campbell IW. Comparison of metformin and chlorpropamide in non-obese, maturity onset diabetics uncontrolled by diet. BMJ 1977; 2: 1576-8
108. Noury J, Nandeuil A. Comparative three month study of the efficacies of metformin and gliclazide in the treatment of NIDD. Diabete Metab 1991; 17: 209-212
109. Chong PK, Jung RT, Rennie MJ, et al. Energy expenditure in type 2 diabetic patients on metformin and sulphonylurea therapy. Diabetic Med 1995; 12: 401-8
110. De Fronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM. A balanced overview. Diabetes Care 1992; 15: 318-68
111. Garancini MP, Calori G, Ruotolo G, et al. Prevalence of NIDDM and impaired glucose tolerance in Italy: an OGTT-based population study. Diabetologia 1995; 38: 306-13

112. Tuomilehto J, Knowler WC, Zimmet P. Primary prevention of non-insulin-dependent diabetes mellitus. Diabetes Metab Rev 1992; 8: 339-53
113. Harris MI. Impaired glucose tolerance: prevalence and progression to NIDDM. IDF Bulletin 1996; 41: 12-5
114. Alberti KGMM. The clinical implications of impaired glucose tolerance. Diabetic Med 1996; 13: 927-37
115. Chiasson JL. Possible therapeutic approaches to impaired glucose tolerance. IDF Bull 1996; 41: 16-20
116. Abbasi F, Kamath V, Rizvi AA, et al. Results of a placebo controlled study of the metabolic effects of the addition of metformin to sulphonylurea-treated patients. Diabetes Care 1997; 20: 1863-9
117. Gregorio F, Ambrosi F, Manfrini S. Metformin, plasma glucose and free fatty acids in type II diabetic out-patients: results of a clinical study. Diabetes Res Clin Pract 1997; 37: 21-33
118. Reaven G, Johnston P, Hollenbeck C, et al. Combined metformin-sulphonylurea treatment of patients with non-insulin-dependent diabetes mellitus in fair to poor glycaemic control. J Clin Endocrinol Metab 1992; 74: 1024-6
119. Del Prato S, Marchetto S, Pipitone A, et al. Metformin and free fatty acid metabolism. Diabetes Metab Rev 1995; 11 Suppl. 1: S33-41
120. Wu M-S, Johnston P, Sheu WH-H, et al. Effect of metformin on carbohydrate and lipoprotein metabolism in NIDDM patients. Diabetes Care 1990; 13: 1-8
121. Rains SGH, Wilson GA, Richmond W, et al. The effect of glibenclamide and metformin on serum lipoproteins in type 2 diabetes. Diabetic Med 1988; 5: 653-8
122. Rains SGH, Wilson GA, Richmond W, et al. The reduction of low density lipoprotein cholesterol by metformin is maintained with long-term therapy. J R Soc Med 1989; 82: 93-4
123. Taylor KG, John WG, Matthews KA, et al. A prospective study of the effect of 12 months treatment on serum lipids and apolipoproteins A-1 and B in type 2 (non-insulin-dependent) diabetes. Diabetologia 1982; 23: 507-10
124. Carlsen SM, Rossvoll O, Bjerve KS, et al. Metformin improves blood lipid pattern in non-diabetic patients with coronary heart disease. J Intern Med 1996; 239: 227-33
125. Montaguti U, Celin D, Ceredi C. Efficacy of the long-term administration of metformin in hyperlipidaemic patients. Res Clin Forum 1979; 1: 95-103
126. Gustafson A, Bjorntorp P, Fahlen M. Metformin administration in hyperlipidaemic states. Acta Med Scand 1971; 190: 491-4
127. Jeppeson J, Zhou M-Y, Chen Y-DI, et al. Effect of metformin on post-prandial lipemia in patients with fair to poorly controlled NIDDM. Diabetes Care 1994; 17: 1093-9
128. Grosskopf I, Ringel Y, Charach G, et al. Metformin enhances clearance of chylomicrons and chylomicron remnants in non-diabetic mildly overweight glucose-tolerant subjects. Diabetes Care 1997; 20: 1598-602
129. Marquie G. Effect of metformin on lipid metabolism in the rabbit aortic wall. Atherosclerosis 1978; 30: 165-75
130. Marquie G. Metformin action on lipid metabolism in lesions of experimental aortic atherosclerosis of rabbits. Atherosclerosis 1983; 47: 7-17
131. Intaglietta M, Sirtori CR, Standl E, et al., editors. Vascular disease and diabetes mellitus – a new approach. Proceedings of an international workshop; 1988 Feb 4-5: Switzerland. Diabete Metab 1988; 14: 473-617
132. Vague P, Juhan Vague I, Alessi MC, et al. Metformin decreases the high plasminogen activator inhibitor capacity, plasma insulin and triglyceride levels in non-diabetic obese subjects. Thromb Haemost 1987; 57: 326-8
133. Landin K, Tengborn T, Smith U. Metformin and metoprolol CR treatment in non-obese men. J Intern Med 1994; 235: 335-41
134. Weichert W, Breddin HK. Antithrombotic effects of metformin in laser injured arteries. Diabete Metab 1988; 14: 540-3
135. Massad L, Plotkine M, Allux M, et al. Antithrombotic drugs in a carotid occlusion model: beneficial effect of the antidiabetic agent, metformin. Diabete Metab 1988: 14: 544-8
136. Barnes AJ, Willars EJ, Clark PA, et al. Effects of metformin on haemorheological indices in diabetes. Diabete Metab 1988; 14: 608-9
137. Data on file. Merck-Lipha, Lyon, France, 1999
138. Berger W. Incidence of severe side effects during therapy with sulphonylureas and biguanides. Horm Metab Res 1985; 15 Suppl.: 111-5
139. Campbell IW. Metformin and the sulphonylureas: the comparative risk. Horm Metab Res 1985; 15 Suppl.: 105-11
140. Cohen RD. The relative risks of different biguanides in the causation of lactic acidosis. Res Clin Forums 1979; 1: 126-34
141. Lucis OJ. The status of metformin in Canada. Can Med Assoc J 1983; 128: 24-6
142. Bailey CJ, Nattrass M. Treatment - metformin. Baillieres Clin Endocrinol Metab 1988; 2: 455-76
143. Wiholm BE, Myrhed M. Metformin - associated lactic acidosis in Sweden 1977-1991. Eur J Clin Pharmacol 1993; 44: 589-91
144. Data on file. French National Drug Adverse Effect Surveillance Commission, Paris, 1998
145. Misbin RI, Green L, Stadel BV, et al. Lactic acidosis in patients with diabetes treated with metformin. N Engl J Med 1998; 338: 265
146. Brown JB, Pedula K, Barzilay J, et al. Lactic acidosis rates in type 2 diabetes. Diabetes Care 1998; 21: 1659-1663
147. Sirtori CR, Pasik C. Re-evaluation of a biguanide metformin: mechanism of action and tolerability. Pharmacol Res 1994; 30: 187-228
148. Lalau JD, Lacroix C, Compagnon P, et al. Role of metformin accumulation in metformin-associated lactic acidosis. Diabetes Care 1995; 18: 779-84
149. Arieff AI. Pathogenesis of lactic acidosis – current concepts. Diabetes Rev 1994; 2: 168-76
150. Cohen RD. Lactic acidosis. Diabetes Rev 1994; 2: 86-97
151. Turner RC, Bailey CJ. Lactic acidosis associated with Glucophage use in a man with normal renal and hepatic function. Diabetes Care 1997; 20: 233
152. Cusi K, Consoli A. Alcoholic ketoacidosis and lactic acidosis. Diabetes Rev 1994; 2: 195-208
153. Luft D, Schmulling RM, Eggstein M. Lactic acidosis in biguanide-treated diabetes: a review of 330 cases. Diabetologia 1978; 14: 75-87
154. Assan R, Heuclin C, Ganeval D, et al. Metformin-induced lactic acidosis in the presence of acute renal failure. Diabetologia 1977; 13: 211-7
155. Jalling O, Olsen C. The effects of metformin compared to the effects of phenformin on the lactate production and the metabolism of isolated parenchymal rat liver cell. Acta Pharmacol Toxicol 1984; 54: 327-32
156. Gill GV, Alberti KGMM. Lactic acidosis. Pract Diabetes 1985; 2: 15-9
157. Cohen RD, Woods HF. Clinical and biochemical aspects of lactic acidosis. Oxford; Blackwell Scientific, 1976
158. Ryder REJ. Lactic acidotic coma with multiple medication including metformin in a patient with normal renal function. Br J Clin Pract 1984; 38: 229-30
159. Hutchinson SMW, Catterall JR. Metformin and lactic acidosis - a reminder. Br J Clin Pract 1987; 41: 673-4

160. Gan SC, Bar J, Arieff AI, et al. Biguanide-associated lactic acidosis. Case report and review of the literature. Arch Intern Med 1992; 152: 2333-6
161. Chan NN, Brain HPS, Feher MD. Metformin associated lactic acidosis: a rare or very rare clinical entity? Diabet Med 1999; 16: 273-81
162. Lalau JD, Andrejak M, Moriniere P, et al. Hemodialysis is the treatment of lactic acidosis in diabetics treated by metformin: a study of metformin elimination. Int J Clin Pharmacol Ther Toxicol 1989; 27: 285-8
163. Krentz AJ, Ferner RE, Bailey CJ. Comparative tolerability profiles of oral antidiabetic agents. Drug Saf 1994; 11: 223-41
164. Ferner RE, Neil HAW. Sulphonylureas and hypoglycaemia. BMJ 1988; 296: 949-50
165. Seltzer HS. Drug-induced hypoglycaemia: a review of 1418 cases. Endocrinol Metab Clin North Am 1989; 18: 163-83
166. Frier BM. Hypoglycaemia and diabetes. Diabetic Med 1986; 3: 513-25
167. Gerich JE. Oral hypoglycaemic agents. N Engl J Med 1989; 321: 1231-45
168. Cryer PE, Frier BM. Hypoglycaemia. In: Alberti KGMM, DeFronzo RA, Keen H, et al., editors. International textbook of diabetes mellitus. 2nd ed. Chichester: John Wiley & Sons Ltd, 1997; 1193-214
169. Dandona P, Fonseca VA, Mier A, et al. Diarrhoea and metformin in a diabetic clinic. Diabetes Care 1983; 6: 472-4
170. Scarpello JHB, Hodgson E, Howlett HCS. Effect of metformin on bile salt circulation and intestinal motility in type 2 diabetes mellitus. Diabet Med 1998; 15: 651-6
171. Haupt E, Knick B, Koschinsky T, et al. Oral antidiabetic combination therapy with sulphonylureas and metformin. Diabete Metab 1991; 17 Suppl. 1: 224-31
172. Tomkin GH. Malabsorption of vitamin B12 in diabetic patients treated with phenformin: a comparison with metformin. BMJ 1973; 3: 673-5
173. Bergman U, Boman G, Wiholm BE. Epidemiology of adverse drug reactions to phenformin and metformin. BMJ 1978; 2: 464-6
174. Klapholz L, Leitersdorf E, Weinrauch L. Leucocytoclastic vasculitis and pneumonitis induced by metformin. BMJ 1986; 293: 483
175. Alberti KGMM, Gries FA. Management of non-insulin-dependent diabetes mellitus in Europe: a consensus view. Diabetic Med 1988; 5: 275-81
176. American Diabetes Association. Clinical Practice Recommendations 1996. The pharmacological treatment of hyperglycaemia in NIDDM. Diabetes Care 1996; 19 Suppl. 1: S54-S61
177. Vannasaeng S, Nitiyanant W, Vichayannat A, et al. Effects of alpha-glucosidase inhibitor (acarbose) combined with sulphonylureas or sulphonylurea and metformin in treatment of non-insulin-dependent diabetes mellitus. J Med Assoc Thai 1995; 78: 578-84
178. Josse RG. Acarbose for the treatment of type II diabetes: the results of a Canadian multi-centre trial. Diabetes Res Clin Pract 1995; 28 Suppl.: S167-72
179. Stout RW. Insulin and atheroma: 20 year perspective. Diabetes Care 1990; 13: 631-54
180. Despres JP, Lamarche B, Mauriege P, et al. Hyperinsulinaemia as an independent risk factor for ischaemic heart disease. N Engl J Med 1996; 334: 952-7
181. Sambol NC, Chiang J, Lin ET, et al. Kidney function and age are both predictors of pharmacokinetics of metformin. J Clin Pharmacol 1995; 35: 1094-102
182. Petrides AS. Liver disease and diabetes mellitus. Diabetes Rev 1994; 2: 2-17
183. Somogyi A, Stockley C, Keal J. Reduction of metformin renal tubular secretion by cimetidine in man. Br J Clin Pharmacol 1987; 23: 545-51

Correspondence and reprints: Dr *Harry Howlett,* Merck Lipha Pharmaceuticals, Harrier House, High Street, West Drayton, Middlesex, UB7 7QG, England.
E-mail: HHowlett@merck-lipha.co.uk