Metformin and heart failure: Safe after all?

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Lactic acidosis is a very rare, serious and sometimes fatal condition that can occur in people with diabetes who are taking metformin. People who have heart failure are thought to be at increased risk of developing lactic acidosis when on metformin therapy (Jones et al, 2003). In the US, package inserts for metformin assert that it is absolutely contraindicated in heart failure.

Eurich et al (abstracted on right) describe their large database survey of 12 272 people with diabetes who were new users of oral antidiabetic agents in Canada between 1991 and 1996. Individuals with incident heart failure (n=1833) were grouped according to whether they had metformin monotherapy (n=208), sulphonylurea monotherapy (n=773) or combination therapy (n=852). The average age was 72 years.

Compared with sulphonylurea monotherapy, fewer deaths occurred in the group receiving metformin monotherapy and combination therapy; there were also fewer hospitalisations, even after adjusting for multiple confounding variables.

An editorial in the same issue of *Diabetes Care* concludes that there is now a case for mounting a reanalysis of the current prescribing indications for metformin in patients with heart failure in the US (Inzucchi, 2005). This is in line with views expressed in the UK (Jones et al, 2003) where, for many doctors, metformin is not felt to be contraindicated in people with stable controlled heart failure, but only in those with unstable heart failure.

Jones GC, Macklin JP, Alexander WD (2003) Contraindications to the use of metformin. *British Medical Journal* **326**(7379): 4–5

Inzucchi SE (2005) Metformin and heart failure: innocent until proven guilty. *Diabetes Care* **28**(10): 2585–7

DIABETES CARE

Clinical inertia improved by feedback from a diabetes specialist

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 An example of clinical inertia in the primary care setting is the failure of clinicians to intensify therapy for people with type 2 diabetes and high glucose levels.

2 This was a 3-year controlled trial in a primary care clinic in the US involving 4138 people with type 2 diabetes; all were seen by a total of 345 internal medicine residents over the 3 years.

3 Instead of consultative advice, interventions included: hard copy computerised reminders with patient-specific recommendations for management at time of each visit and/or face-to-face feedback, with an endocrinologist, on the medicine resident's performance for 5 minutes every 2 weeks. Patients were randomised to one of these interventions or the control, no intervention.

4 Glycaemic control significantly improved over 2 years for patients in the intervention groups compared with the control group.

5 The authors conclude that partnering general medical staff with those specialising in diabetes is an important option which works to the advantage of the patient, and providing feedback to the care providers can improve outcomes.

Phillips LS, Ziemer DC, Doyle JP et al (2005) An endocrinologist-supported intervention aimed at providers improves diabetes management in a primary care site. *Diabetes Care* **28**(10): 2352–60

DIABETES CARE

Metformin shown to be effective in people with heart failure

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 Despite an increasing evidence base supporting the use of metformin in people with type 2 diabetes and heart failure, currently, in the US and Canada, it is contraindicated in such people owing to fears of lactic acidosis.

2 This study aimed to evaluate the association between metformin and clinical outcomes in people with type 2 diabetes and heart failure.

3 A total of 1833 people new to oral antidiabetic agents and with type 2 diabetes and heart failure were identified from the Saskatchewan health databases. Two hundred and eight people were on metformin monotherapy, 773 were on sulphonylurea monotherapy and 852 were on a combination of both.

4 Fewer deaths occurred in the groups using metformin compared with a sulphonylurea alone: 404 (52%) for sulphonylurea monotherapy versus 69 (33%) for metformin monotherapy (hazard ratio 0.70 [95% confidence interval 0.54–0.91]) and 263 (31%) for those on combination therapy (0.61 [0.52–0.72]).

5 Significant reductions in hospitalisation rates were also observed in the groups using metformin. Hospitalisation rates were 85% (n=658) for sulphonylurea monotherapy versus 77% (n=160; 0.83 [0.70–0.99]) for metformin monotherapy and 80% (n=681; 0.86 [0.77–0.96]) for combination therapy.

6 No significant difference between groups in the time to first hospitalisation was observed.

7 The authors conclude that this study adds more to the growing body of evidence indicating that metformin should be used for people with type 2 diabetes and heart failure.

Eurich DT et al (2005) Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. *Diabetes Care* **28**(10): 2345–51

DIABETES, OBESITY AND METABOLISM

HbA_{1c} levels lowered by vildagliptin

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 Vildagliptin enhances incretin hormone activity by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4). This study was designed to establish the dose required for vildagliptin to reduce HbA_{1c} levels in a safe and efficacious manner in people with type 2 diabetes.

2 Once-daily doses of vildagliptin at 50 mg and 100 mg achieved the most significant reduction in HbA_{1c} levels (P=0.003 and P=0.004, respectively) compared with placebo.

3 The authors conclude that, although safe and efficient at these doses, this trial was too short (at 12 weeks) and needs to be performed for longer.

Ristic S, Byiers S, Foley J, Holmes D (2005) Improved glycaemic control with dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes: vildagliptin (LAF237) dose response. *Diabetes, Obesity and Metabolism* **7**(6): 692–8

DIABETES CARE

Reduced mobility and physical disability have multiple causes in type 2 diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 As part of the Fremantle Diabetes Study, the authors aimed to determine longitudinal predictors of impaired mobility and physical disability in people with type 2 diabetes. The study population was divided into two groups (group 1, n=818; group 2, n=934) with similar baseline characteristics. In group 1, 28.5 % developed new mobility impairment; in group 2, 18.1 % developed new activities of daily living (ADL) disability.

2 The risk of mobility impairment was significantly increased by, for example, peripheral neuropathy and insulin treatment; taking exercise and being married lowered the risk.

3 The risk of developing new ADL disability was increased by, for example, baseline mobility problems, stroke and claudication.

4 In order to prevent the onset or progression of mobility impairment or new ADL disability different approaches may be needed, as both have multiple causes that are due to type 2 diabetes and related comorbidities.

Bruce DG, Davis WA, Davis TM (2005) Longitudinal predictors of reduced mobility and physical disability in patients with type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care* **28**(10): 2441–7

ENDOCRINE JOURNAL

Glimepiride plus insulin improves diabetes control

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Sixty-three people with poorly controlled insulin-treated type 2 diabetes participated in this trial to study the effects of glimepiride on HbA_{1c} levels, daily required insulin dose, body weight, blood pressure, plasma lipid concentrations and the number of hypoglycaemic events.

2 In the glimepiride plus insulin group, HbA_{1c} fell by 1.1 % (n=31; from 8.5 % to 7.4 %; P<0.0001) at week 12 of the study and continued to fall to study end (week 72); HbA_{1c} did not change in the insulin-alone group at week 12, and was slightly higher at study end.

3 The insulin plus glimepiride group showed a reduced need for insulin. The number of hypoglycaemic events did not differ between the two groups.

4 In conclusion, the authors state that, despite the small study size, the use of glimepiride as add-on therapy in people with poorly controlled insulin-treated type 2 diabetes is warranted.

Ose H, Fukui M, Kitagawa Y et al (2005) Efficacy of glimepiride in patients with poorly controlled insulin-treated type 2 diabetes mellitus. *Endocrine Journal* **52**(5): 563–9

'Inhaled insulin improves overall glycaemic control when added to or substituted for dual oral therapy.'

'Rosiglitazone/metformin combination is effective, is well tolerated and enables more people with type 2 diabetes to reach glycaemic targets.'

ANNALS OF INTERNAL MEDICINE

Glycaemic control improved by inhaled insulin

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 This open-label, randomised controlled trial aimed to analyse the effect on glycaemic control of inhaled insulin alone or in combination with dual oral therapy (insulin secretagogue [a sulphonylurea or repaglinide] and insulin sensitiser [a thiazolidinedione or metformin]) in people with type 2 diabetes after the failure of dual oral therapy.

2 The trial was composed of 309 people from 48 outpatient centres in the US and Canada; all had type 2 diabetes, had HbA_{1c} levels between 8% and 11% and were on dual oral therapy.

3 The primary end point measured was the change in HbA_{1c} from baseline to 12 weeks. Secondary outcomes included lowering HbA_{1c} to <8% or <7% and pulmonary function.

4 The intervention was inhaled insulin, titrated to blood glucose levels, administered alone or added to dual oral therapy versus dual oral therapy alone.

5 The HbA_{1c} levels were lowered by 1.67% (95% confidence interval [CI], -1.90 to -1.44%; *P*<0.001) and 1.18% (95% CI -1.41 to -0.95%; *P*<0.001) in the inhaled insulin plus dual oral therapy group and the inhaled insulin alone group, respectively, compared with dual oral therapy alone. HbA_{1c} levels of <7% were achieved by 32% of the inhaled plus oral regimen group compared with 1% of the oral agents-only group. Pulmonary function was normal in all groups.

6 The authors conclude that inhaled insulin improves overall glycaemic control when added to or substituted for dual oral therapy, although larger and longer trials need to be conducted.

Rosenstock J, Zinman B, Murphy LJ et al (2005) Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. *Annals of Internal Medicine* **143**(8): 549–58

CLINICAL THERAPEUTICS

Rosiglitazone/metformin combination versus metformin alone

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Fixed-dose combination therapy of rosiglitazone/metformin (RSG/MET; 4mg/2g per day, which was increased to 8mg/2g per day at week 8 of the study) was compared with high-dose metformin (MET; 3g per day) in order to assess the benefits of RSG/MET in people with type 2 diabetes in this 24-week, multicentre, randomised, double-blind, parallel-group study.

2 The safety group consisted of 568 (MET, 280; RSG/MET, 288) and the intent-to-treat group of 551 (MET, 272; RSG/MET, 279) participants. Baseline characteristics were comparable across all participants.

3 Fifty-four per cent of participants treated with RSG/MET achieved HbA_{1c} levels <7.0% compared with 36% treated with MET alone (odds ratio 2.42; *P*<0.001). RSG/MET was relatively well tolerated, with most of the adverse events reported being mild to moderate. Serious adverse events were reported in 3% of the RSG/MET treatment group and 2% of the MET-alone group.

4 Participants in the RSG/MET group reported improvements in treatment satisfaction compared with the MET-alone group, as assessed by the Diabetes Treatment Satisfaction Questionnaire.

5 The authors conclude that RSG/MET combination is effective, is well tolerated and enables more people with type 2 diabetes to reach glycaemic targets.

Bailey CJ, Bagdonas A, Rubes J et al (2005) 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. *Clinical Therapeutics* **27**(10): 1548–61

BRITISH MEDICAL JOURNAL

Care of people with chronic conditions in English GP practices has improved

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 A longitudinal cohort study was conducted across 42 general practices in England in order to measure changes in the quality of care for three major chronic conditions – coronary heart disease (CHD), asthma and type 2 diabetes – from 1998 to 2003.

2 Medical record data for 2300 patients from 1998 and 1495 patients from 2003 were assessed against predefined evidence-based review criteria.

3 Substantial improvements were observed in the quality of care of the three conditions between 1998 and 2003, which were most marked for CHD.

4 In terms of maximum possible scores on the review criteria, the quality of care improved from 60.5% to 78.1% for CHD (change=17.6%, 95% confidence interval 13.9–21.4%, *P*<0.001); from 60.1% to 70.3% for asthma (10.2%, 4.6–15.8%, *P*=0.001); and from 70.4% to 77.7% for type 2 diabetes (7.3%, 3.5–11.1%, *P*=0.001).

5 The authors believe that with financial incentives now in place, further improvements in quality of care will be seen.

Campbell SM, Roland MO, Middleton E, Reeves D (2005) Improvements in quality of primary care in English general practice 1998–2003: longitudinal observational study. *British Medical Journal* **331**(7525): 1121–5

'Different combination treatment approaches could provide better results with regard to the characteristics of type 2 diabetes and the metabolic syndrome.'

INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Burdens of type 2 diabetes alleviated by early lifestyle and drug intervention

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The onset and progression of the complications of type 2 diabetes is significantly delayed by improving glycaemic control. However, the authors state that the proportion of people with type 2 diabetes reaching, achieving and sustaining recommended targets is unacceptably low.

2 This article focuses on and reviews trial-based evidence for early interventions that allow patients to reach target glycaemic levels, thus reducing related complications and delaying disease progression.

3 Intensive lifestyle therapy effectively lowers the rate of progression from impaired glucose intolerance (IGT) to type 2 diabetes over approximately 3 years in 60% of people with IGT. However, a significant proportion of people fail to sustain such a lifestyle and early pharmacotherapy must also be considered.

4 The authors suggest that, as monotherapy has been shown to be ineffective in a large proportion of people with type 2 diabetes in helping them reach target glycaemic levels, combination therapy must be considered as an early form of intervention.

5 Evidence shows that early intervention to lower blood pressure in people with type 2 diabetes is also beneficial in that strokes and major cardiovascular events can be prevented.

6 The authors conclude that there is a growing body of evidence to suggest early intensive intervention.

Bailey CJ, Del Prato S, Eddy D, Zinman B (2005) Earlier intervention in type 2 diabetes: the case for achieving early and sustained glycaemic control. *International Journal of Clinical Practice* **59**(11): 1309–16

ARCHIVES OF INTERNAL MEDICINE

MetS is a stronger predictor of diabetes than of CHD

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The metabolic syndrome (MetS; defined as the presence of three or more abnormalities based on modified National Cholesterol Education Program criteria) was compared with the Framingham Risk Score (FRS) with respect to predicting coronary heart disease (CHD), stroke and type 2 diabetes in this prospective study.

2 A total of 5128 men, aged 40–59 years from general practices across 24 UK towns and with no history of cardiovascular disease (CVD; defined as CHD or stroke) or type 2 diabetes, were observed for 20 years.

3 Men with MetS at baseline showed a significantly higher relative risk (RR) of developing CHD, stroke and type 2 diabetes (RR 1.64, 95% confidence interval [CI] 1.41–1.90; RR 1.61, 95% CI 1.26–2.06; RR 3.57, 95% CI 2.83–4.50; respectively).

4 The chances of developing CVD or type 2 diabetes over the 20 years increased from 11.9% to 31.2% for those with no abnormalities at baseline and to 40.8% in those with four or five abnormalities at baseline.

5 The FRS was found to be a better predictor of CHD and stroke than the MetS, which was better at predicting type 2 diabetes.

6 Presence of MetS is a significant predictor of CVD and type 2 diabetes. Compared with the FRS, MetS is a stronger predictor of type 2 diabetes than CHD. Although MetS does not predict CHD as well as the FRS, it is still a useful clinical tool in identifying people who are at risk of developing CVD or type 2 diabetes.

Wannamethee SG et al (2005) Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Archives of Internal Medicine* **165**(22): 2644–50

CLINICAL THERAPEUTICS

Rosiglitazone plus metformin associated with improved BP control

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 Few studies have compared the effect of different antihyperglycaemic treatments on blood pressure (BP) of people with type 2 diabetes.

2 The main aim of this study was to compare the effect of long-term combination treatment using glimepiride or rosiglitazone with metformin (G+M and R+M, respectively) on BP in people with type 2 diabetes and the metabolic syndrome. This was a 12-month, double-blind, randomised clinical trial composed of 95 people who completed.

3 Mean BP values were not significantly improved in the G+M group at any time point.

4 However, mean BP values were significantly improved in the R+M group ($P<0.05$ versus baseline and G+M).

5 Improvements in glycaemic control were observed at 9 months in the R+M group and at 12 months in the G+M group.

6 Both combination therapies were well tolerated.

7 The authors conclude that different combination treatment approaches could provide better results with regard to the characteristics of type 2 diabetes and the metabolic syndrome. They also say that larger studies are essential.

Derosa G, Cicero AF, Gaddi AV et al (2005) Long-term effects of glimepiride or rosiglitazone in combination with metformin on blood pressure control in type 2 diabetic patients affected by the metabolic syndrome: a 12-month, double-blind, randomized clinical trial. *Clinical Therapeutics* **27**(9): 1383–91