Major journals

Glycaemic durability of rosiglitazone, metformin or glibenclamide monotherapy

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The UK Prospective Diabetes Study (UKPDS) demonstrated the relative deficiency of metformin and sulphonylurea therapy in maintaining durable blood glucose control. Since their development there has been considerable interest in the potential of the thiazolidinedione class of drugs to maintain glycaemic control. The study summarised to the right evaluated rosiglitazone, metformin and glibenclamide as initial therapy for recently diagnosed (<3 years) type 2 diabetes in a randomised, controlled trial. Involved were 4360 individuals treated for a median of 4 years. The primary outcome was time to monotherapy failure (defined as sustained fasting plasma glucose >10 mmol/l after maximal doses of either agent). Pre-specifed secondary end points included glycated haemoglobin, insulin sensitivity and β-cell function.

The cumulative incidence of monotherapy failure at 5 years was 15% for rosiglitazone, 21% for metformin and 34% for glibenclamide, representing a risk reduction of 32% for rosiglitazone compared with metformin and 63% compared with glibenclamide ($P<0.001$). β-cell function improved more in the glibenclamide group during the first 6 months (mean ratio of 6-month value to baseline: 1.45) than in the rosiglitazone (1.17) or metformin (1.16) group. Thereafter, β-cell function declined in all groups; the annual rate of decline after 6 months was greatest in the glibenclamide group (6.1%), intermediate in the metformin group (3.1%) and least in the rosiglitazone group (2.0%). The rates of β-cell function decline were significantly greater in the glibenclamide ($P<0.001$) and metformin groups ($P=0.02$) compared with rosiglitazone.

In addition, after 5 years, HbA_{1c} was significantly lower with rosiglitazone than metformin (absolute difference 0.13%, $P=0.002$) and significantly lower with rosiglitazone than glibenclamide (absolute difference 0.42%; $P<0.001$). Fasting plasma glucose was also significantly lower with rosiglitazone compared with both metformin (a difference of 9.8 mmol/l; $P<0.001$) and glibenclamide (a difference of 17.4 mmol/l, $P<0.001$).

No cardiovascular end points were assessed in this study. The proportion of individuals experiencing heart failure in the rosiglitazone group was 1.5% compared with 1.3% of those receiving metformin (P=NS) and 0.6% of those receiving glibenclamide ($P=0.05$). The incidence of heart failure in this study was again in line with that reported in previous trials and as indicated in the summary of product characteristics.

Rosiglitazone was associated with more weight gain and oedema than metformin or glibenclamide but fewer gastrointestinal events were reported than with metformin and with less hypoglycaemic events than glibenclamide. A higher rate of fractures was an unexpected observation in the group receiving rosiglitazone. This was confined to the female group and involved an increased incidence of fractures involving the humerus and hand and foot bones; however, there was no increase in the incidence of hip fractures. The mechanisms and clinical implications of these observations are unclear.

The data from this study demonstrated that thiazolidinedione therapy in the form of rosiglitazone was associated with the greatest durability of glycaemic control. However, even in the rosiglitazone group, only 23% of the initially randomised individuals compared with 22% in the metformin group and 16% in the glibenclamide group maintained glycaemic control with monotherapy alone. Thus, a major clinical implication of this study is that even in people who have a relatively short duration of type 2 diabetes, combination therapy is required to maintain optimal glycaemic control for the majority of individuals.

NEW ENGLAND JOURNAL OF MEDICINE

Rosiglitazone reduces risk of monotherapy failure in type 2 diabetes

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

1 This study was part of A Diabetes Outcome Progression Trial (ADOPT) and aimed to investigate the long-term effects on glycaemic control of a thiazolidinedione versus a biguanide and a sulphonylurea.

2 In total, 4360 treatment-naive people with type 2 diabetes were allocated either 4 mg rosiglitazone, 500 mg metformin or 2.5 mg glyburide.

3 The participants were monitored for time to monotherapy failure, which was set at >180 mg plasma glucose per decilitre (10 mmol/l) when fasting.

4 Versus metformin, rosiglitazone treatment resulted in a 32% risk reduction of monotherapy failure ($P<0.001$) and versus glyburide it inferred a 63% risk reduction ($P<0.001$).

5 Glyburide treatment showed a significantly reduced risk of cardiovascular events compared with rosiglitazone and metformin (1.8% versus 3.4% and 3.2%, respectively).

6 Weight gain and oedema were significantly more frequent in the rosiglitazone group ($P<0.001$ for both), while gastrointestinal side effects were less common ($P\leq0.01$).

7 This evidence suggests that rosiglitazone delays the progressive loss of glycaemic control associated with type 2 diabetes for longer than metformin and glyburide.

8 The authors recommend that physicians consider the risk–benefit profile of each drug, in part elucidated in this study, when selecting an oral glucose-lowering medication for individuals with type 2 diabetes.

Kahn SE, Haffner SM, Heise MA et al; ADOPT Study Group (2006) Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *New England Journal of Medicine* **355**: 2427–43

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Reclassifying women's cardiovascular risk in middle-age

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

1 A new algorithm for cardiovascular risk assessment for women was developed to include novel risk factors.

2 Women aged 45 years or older (n = 24 558) were followed for an average of 10.2 years. In total, 35 factors associated with cardiovascular complications were assessed, including myocardial infarction, ischaemic stroke, coronary revascularisation and death.

3 Data from two-thirds of the trial participants (randomly selected) were used to develop new algorithms. Observed and predicted outcomes were compared in the remaining women with models based on covariates from the National Cholesterol Education Program Adult Treatment Panel III score risk.

4 A best-fitting model and the Reynolds Risk Score, a clinically simplified model, had lower Bayes Information Criterion scores than the Adult Treatment Panel III models.

5 Both models had improved measures of fit, discrimination or calibration.

6 The best-fitting model reclassified 50 % of intermediate-risk women into higher- or lower-risk categories and similar effects were observed for the Reynolds Risk Score model.

Ridker PM, Buring JE, Rifai N, Cook NR (2007) Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *Journal of the American Medical Association* **297**: 611–9

LANCET

Link between antihyperintensive drugs and diabetes?

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

1 The authors conducted a network meta-analysis to assess how different antihyperintensive drugs affect incident diabetes.

2 The methods and results of this analysis have potential benefits in that they allow indirect comparisons of drug groups.

3 The analysis included 143 153 individuals without a diagnosis of diabetes at enrolment from 22 clinical trials.

4 The proportion of individuals who developed diabetes was calculated for the following initial drug therapy groups: ARB, ACE inhibitor, CCB, placebo, β-blocker or diuretic.

5 Compared with an initial diuretic, the degree of incoherence was small ($\omega = 0.000017$) across the network of drug trials.

6 ARBs and ACE inhibitors were found to have the lowest association with incident diabetes.

7 Calcium channel blockers, placebo, β-blockers and diuretics, in rank order, were more closely associated with incident diabetes.

Elliott WJ, Meyer PM (2007) Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* **369**: 201–7

Media Digest

ANNALS OF INTERNAL MEDICINE

Intra-operative insulin therapy in cardiac surgery

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

1 This study aimed to compare intensive intra-operative insulin therapy during cardiac surgery with conventional glucose management.

2 Adults with and without diabetes who were undergoing on-pump cardiac surgery were compared in a randomised, open-label, blinded-assessment, controlled trial.

3 In one group (n = 199), individuals' intra-operative glucose levels were maintained at 4.4–5.6 mmol/l by continuous insulin infusion. Controls (n = 201) received conventional treatment and were only administered insulin if their glucose levels were above 11.1 mmol/l.

4 Following surgery, the insulin-treated group had significantly lower blood glucose compared with controls (6.3 versus 8.7 mmol/l; $P < 0.001$)

5 Adverse events were reported in 82 of 185 (44 %) of people on intensive treatment and 86 of 186 (46 %) of controls ($P = 0.71$); however, more deaths (4 versus 0; $P = 0.061$) and strokes (8 versus 1; $P = 0.020$) were reported following intensive treatment than with conventional treatment.

6 Treatment group did not have an effect on the length of stay in intensive care or length of total hospital stay.

7 The authors concluded that intensive insulin administration during cardiac surgery did not reduce the risk of peri-operative complications or death and, in fact, was associated with a greater incidence of death and stroke.

8 Further studies should assess the effect of variables including diabetes type, duration of diabetes and risk factors for other diseases on these outcomes.

Gandhi GY, Nuttall GA, Abel MD et al (2007) Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. *Annals of Internal Medicine* **146**: 233–43

Weight loss with orlistat reduces cardiovascular risk factors

The weight loss medication orlistat (Xenical; Roche, Welwyn Garden City) significantly reduces weight, thereby decreasing cardiovascular risk factors.

Data pooled from five randomised, double-blind trials studying people with diabetes and hypertension showed that orlistat more than doubled weight loss when compared with the placebo group.

The analysis also demonstrated that weight loss was associated with significant improvements in systolic blood pressure, HbA_{1c}, insulin dose, fasting glucose and total cholesterol.

Improvements were more pronounced in early responders to treatment, defined as those who lost ≥5 % body weight in 3 months.

Media Press Release, 24 April 2007

Bleeding triples the risk of death at 1 year in people with acute coronary syndrome

The ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial has shown that people with acute coronary syndrome receiving bivalirudin (Angiox; Nycomed, Oxford) alone had similar rates of ischaemic clinical outcomes in comparison to more complicated standard therapy, confirming previous findings that bivalirudin shows similar ischaemia at 30 days and nearly 50 % fewer bleeding episodes.

Compared with controls, bivalirudin decreased the mortality rate (4.4 % versus 3.8 %).

A separate analysis found that in people with acute coronary syndrome, a major bleeding episode within 30 days following treatment nearly triples the risk of death within up to 1 year, making major bleeding a more powerful predictor of mortality than heart attack.

The Medicines Company, 18 April 2007

Elizabeth Arden joins the fight against cardiovascular disease

Elizabeth Arden, Inc., a global company specialising in beauty products, has signed a 3-year agreement with the World Heart Federation to globally support the *Go red for women* campaign.

Go red for women was created by the American Heart Association in 2004 and raises awareness of the risks of heart disease and stroke in women, spreading the message that cardiovascular disease kills 8.6 million women annually – more than HIV/AIDS, all cancers, malaria and tuberculosis combined – and emphasising the importance of preventative measures such as exercise.

Elizabeth Arden spokesperson and Oscar-winning actress Catherine Zeta-Jones commented: '*Go red for women* is an ongoing global programme, prompted by the World Heart Federation, to raise awareness of heart disease and stroke in women, helping women to be healthy and beautiful.'

World Heart Federation, 19 February 2007