Management and prevention of type 2 diabetes

The case for multifactorial interventions

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Single factor intervention strategies aimed at hyperglycaemia, hypertension, or dyslipidaemia have produced modest reductions in risk of cardiovascular events. Can bigger reductions be obtained by combining these?

Gaede and colleagues believe the answer is 'yes'. They conducted an open parallel trial of 160 people with type 2 diabetes and microalbuminuria, of whom 80 had conventional treatment in accordance with national guidelines from their GPs, with referral as necessary.

The remaining 80 had intensive treatment with stepwise implementation of behaviour modification and drug therapy that targeted: hyperglycaemia (HbA_{1c} <6.5%); hypertension (blood pressure <130/80 mmHg); and dyslipidaemia (triglycerides below 1.7, cholesterol below 4.5 mmol/l). All patients in both groups were given aspirin and ACE inhibitor. The intensive group were also given vitamin E, vitamin C, folic acid and chrome picolinate.

After a mean follow-up of 7.8 years, one or more cardiovascular events had occurred in 44% of the conventional group but in only 24% of the intensive group. Cardiovascular events were defined as death from cardiovascular causes, non-fatal stroke or myocardial infarct, coronary or peripheral revascularisation or amputation as a result of ischaemia. Rates of nephropathy, retinopathy and autonomic neuropathy were also markedly reduced in the intensive group.

The study was not designed to investigate which interventions or groups of interventions were responsible for the benefits. Gaede et al calculate that 5 patients need to be treated for 7.8 years to prevent one cardiovascular event. This is important information. It shows that multifactorial interventions can reduce macrovascular disease as well as microvascular disease in type 2 diabetes. The target levels for HbA_{1c} and hypertension were tough ones and were achieved by patients visiting the world famous Steno hospital every 3 months. It remains to be seen whether they can be achieved in ordinary clinical practice in the UK.

DIABETIC MEDICINE

IV insulin followed by SCII can improve glycaemic control

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

1 Despite high-dose subcutaneous insulin therapy, some people with type 2 diabetes have inadequate metabolic control, and do not respond to further increases in insulin dose.

2 This study investigated whether intravenous (IV) insulin directed at euglycaemia, followed by continuous subcutaneous (SC) insulin infusion (CSII) using insulin analogues, reduces the severity of hyperglycaemia-induced insulin resistance and improves metabolic control.

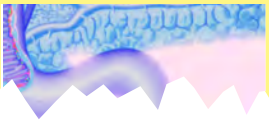
3 In this prospective observational study, 8 people with type 2 diabetes and severe insulin resistance were treated with IV insulin for 31±10 days aimed at euglycaemia, followed by CSII therapy for 12 months.

4 Euglycaemia was reached after 12±6 days of IV insulin treatment. The subsequent IV insulin dose needed to maintain euglycaemia decreased, whole body glucose uptake increased, HbA_{1c} decreased, lipid profile improved and plasminogen activator inhibitor type 1 levels decreased.

5 People who have severe insulin resistance and poorly controlled type 2 diabetes can achieve improved metabolic control by combining IV insulin followed by CSII.

Pouwels MJ et al (2003) Treatment with intravenous insulin followed by continuous subcutaneous insulin infusion improves glycaemic control in severely resistant type 2 diabetic patients. *Diabetic Medicine* **20**: 76–79

THE NEW ENGLAND JOURNAL OF MEDICINE



Intensive treatment cuts cardiovascular events by 50%

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

1 Cardiovascular morbidity is a major problem for people with type 2 diabetes.

2 The Steno-2 Study evaluated the effect of a targeted, intensive, multifactorial intervention comprising behaviour modification and polypharmacological therapy on modifiable risk factors in patients with type 2 diabetes and microalbuminuria.

3 Participants (mean age 55.1 years) were randomly assigned to either conventional treatment (80) or intensive treatment (80) that targeted hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria, along with secondary prevention of cardiovascular disease with aspirin, and followed up for a mean of 7.8 years.

4 Glycosylated haemoglobin, blood pressure, serum cholesterol and triglyceride levels measured after an overnight fast, and urinary albumin excretion, were all significantly reduced in the intensive therapy group.

5 Patients in this group also had a significantly lower risk of cardiovascular disease, nephropathy, retinopathy and autonomic neuropathy than those on conventional treatment.

6 Intensive treatment targeted at multiple risk factors in patients with type 2 diabetes and microalbuminuria reduced the risk of cardiovascular and microvascular events by about 50%.

Gaede P, Vedel P, Larsen N et al (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *New England Journal of Medicine* **348**: 383–93

DIABETIC MEDICINE

Triple oral therapy may be helpful in insulin resistance

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

1 Triple therapy, using a combination of sulphonylurea, metformin and glitazone, is not a licensed indication for the management of type 2 diabetes, but it is not a contraindication either.

2 This clinical practice question discusses the use of triple oral antidiabetic therapy in people with type 2 diabetes.

3 Triple therapy is a reasonable option in people just above the recommended target for HbA_{1c}, particularly those who are overweight and more likely to be insulin resistant, or are likely to refuse insulin treatment.

4 Seven practice points for health professionals on the use of triple therapy are provided. It is suggested that glitazones should be prescribed early in the disease process, and are particularly suitable in combination with metformin.

Barnett AH (2003) Triple oral anti-diabetic therapy in type 2 diabetes. *Diabetic Medicine* **20:** 14–16

AMERICAN JOURNAL OF CARDIOLOGY

Rosiglitazone and atorvastatin reduce LDL cholesterol

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

1 This study aimed to characterise the effects of rosiglitazone on lipid and lipoprotein changes, and to evaluate the efficacy and safety of rosiglitazone in combination with atorvastatin.

2 A total of 332 people with type 2 diabetes entered an 8-week open-label treatment phase with 8 mg/day rosiglitazone; 243 were randomised to a 16-week double-blind period of continued rosiglitazone plus placebo, 10 mg or 20 mg/day atorvastatin.

3 Rosigliazone alone resulted in a modest increase in LDL cholesterol, a shift in LDL phenotype from dense to large buoyant subfractions and an increase in total HDL cholesterol levels.

4 Rosiglitazone in combination with atorvastatin reduced LDL cholesterol to <100 mg/dl and removed small dense LDL.

Freed MI, Ratner R, Marcovina SM et al (2002) Effects of rosiglitazone alone and in combination with atorvastin on the metabolic abnormalities in type 2 diabetes mellitus. *American Journal of Cardiology* **90**: 947–52

DIABETES CARE

Metformin and lifestyle interventions incur modest costs

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

1 Detailed descriptions of the costs of implementing new treatments can help translate the results of studies into efficient practice.

2 This article describes the costs associated with the primary prevention of type 2 diabetes in the Diabetes Prevention Programme (DPP).

3 The direct medical cost of laboratory tests to identify one person with impaired glucose tolerance (IGT) was $139.

4 Over 3 years, the direct medical costs of the DPP interventions were: $79 per person in the placebo group; $2542 in the metformin group; and $2780 in the lifestyle group.

5 Direct medical costs of care outside the DPP compared with the placebo group were $272 less per person in the metformin group and $432 less in the lifestyle group.

6 Direct non-medical costs were $9 less per person in the metformin group and $1445 greater in the lifestyle group, compared with the placebo group.

7 Indirect costs were $230 greater per person in the metformin group and $174 less in the lifestyle group, compared with the placebo group.

8 In terms of a health system, the cost of metformin intervention relative to the placebo intervention was $2191 per person, and the cost of the lifestyle intervention was $2269 per person over 3 years.

9 Metformin and lifestyle interventions are associated with modest costs compared with the placebo intervention.

The Diabetes Prevention Program Research Group (2003) Costs associated with the primary prevention of type 2 diabetes mellitus in the Diabetes Prevention Program *Diabetes Care* **26**: 36-47

'Metformin should be withdrawn during periods of suspected tissue hypoxia, or 2 days before general anaesthesia, and only be reinstated when renal function is stable.'

DIABETES CARE

Sibutramine can be effective adjunct to metformin therapy

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

1 This study investigated the effects of sibutramine on weight, metabolic control and blood pressure in obese metformin-treated people with type 2 diabetes.

2 A total of 195 people with type 2 diabetes and a BMI >27 took part in this 12-month randomised prospective placebo-controlled double-blind study.

3 Sibutramine induced significant weight loss with both 15mg/day and 20mg/day, compared with placebo.

4 Glycaemic control improved in parallel with weight loss, and people who lost ±10% weight showed significant decreases in HbA_{1c} and fasting plasma glucose.

5 HDL cholesterol increased slightly with the higher dose; plasma triglycerides fell with both doses.

6 Sibutramine can be an effective addition to metformin treatment in selected obese people with type 2 diabetes, and improves metabolic control in those who lose weight.

McNulty SJ, Ur E, Williams G (2003) A randomized trial of sibutramine in the management of obese type 2 diabetic patients treated with metformin. *Diabetes Care* **26**: 125–31

'Sibutramine can be an effective addition to metformin treatment in selected obese people with type 2 diabetes, and improves metabolic control in those who lose weight.'