Management & prevention of type 2 diabetes

LANCET

Pioglitazone reduces specific vascular events in T2D

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

1 It is well established that people with type 2 diabetes (T2D) are at high risk of myocardial infarction (MI) and stroke.

2 Pioglitazone is used in the treatment of T2D. Several of its metabolic effects suggest that it may reduce the macrovascular risk associated with the condition.

3 This prospective, multicentre, randomised controlled trial assigned 5238 people with T2D and evidence of established macrovascular disease to receive either pioglitazone (maximum of 45 mg/day, titrated up from 15 mg/day; n=2605) or placebo (n=2633) on top of existing medications.

4 The primary end point was the time from randomisation to a composite of all-cause mortality, non-fatal MI, stroke, acute coronary syndrome, or endovascular and surgical interventions.

5 The main secondary end point was the time to the composite of all-cause mortality, stroke or non-fatal MI.

6 The proportion of participants who reached the primary end point was not significantly different between groups.

7 The proportion of patients reaching the main secondary end point was significantly lower in the pioglitazone group (n=301/2605) than the placebo group (n=358/2633; *P*=0.027).

8 The authors concluded that, in patients with T2D who are at high risk of cardiovascular events, pioglitazone treatment can reduce the composite of all-cause mortality, non-fatal MI or stroke.

Dormandy JA, Charbonnel B, Eckland DJ et al (2005) Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* **366**(9493): 1279–89

More prescribing action for pioglitazone following the PROactive study

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The therapeutics of type 2 diabetes is increasingly congested with lots of effective therapies vying for supremacy. In terms of oral hypoglycaemic agents, following the findings of the UK Prospective Diabetes Study Group (1998), metformin deservedly assumed first place in most people's practice because of a number of significant benefits. For equivalent hypoglycaemic effect, the symptomatic improvement, the additional anorectic effect limiting weight gain, the lower incidence of hypoglycaemia, the lower cost and the hint of macrovascular benefit in overweight patients were sufficient to see metformin emerge ahead of the pack.

The sulphonylureas, also effective glucose-lowering agents, and the metaglinides, essentially similar to the sulphonylureas, assumed second-line position. The early promise of the thiazolidinediones was stalled when troglitazone proved to have unacceptable hepatoxicity (Isley, 2003), and appropriate caution was generally applied. The emerging consensus was that the newcomers needed to be as good as, if not better than, the established therapies, and I was certainly cautious about the use of thiazolidinediones in my own clinical practice, preferring to wait for more robust evidence.

The important PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study (see left), was a pragmatic attempt to answer the question and test whether the addition of thiazolidinediones to optimal current therapy (as defined by the treating physician) reduced macrovascular morbidity and mortality in high-risk patients with type 2 diabetes. This add-on therapeutic approach has broad and welcome appeal as a clinical trials design with considerable validity, allowing more direct extrapolation to current clinical practice.

There are problems, however, with the trial design. Perhaps most significantly, the primary end point (a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, or endovascular and surgical interventions) was too ambitious and open-ended. Coronary and peripheral revascularisation are soft as end points, with the decision to intervene based as much on local surgical and medical practice as on a standardised assessment of disease severity. The major anticipated side effect (oedema) was also poorly defined, quantified and characterised, and inadequately explained. There was an increased rate of peripheral oedema and heart failure, although mortality due to heart failure was not increased in the pioglitazone-treated patients.

Nonetheless, pioglitazone was well tolerated and was associated with a significant reduction in time to initiation of insulin and a significant reduction in the secondary end point (a composite of all-cause mortality, stroke or non-fatal myocardial infarction). The delay in time to start insulin is a major consideration for patients, and the additional cardiovascular end point reduction, while small, was seen despite good uptake of standard secondary protection agents.

Given the number of effective agents available and their benefits for cardiovascular event rate reduction when deployed together, it is unlikely that any single new agent will be hugely powerful in terms of event rate reduction. It is important that the threshold for new agents is as good as or better than currently available treatments, but we need to be careful not to set the threshold unrealistically high. For all these reasons, pioglitazone's modest contribution seems to be worth careful consideration.

Isley WL (2003) Hepatotoxicity of thiazolidinediones. *Expert Opinion on Drug Safety* **2**(6): 581–6

UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* **352**(9131): 854–65

'For the secondary outcome measure – total cardiovascular disease events – there was a significant relative reduction of 11% with fenofibrate therapy.'

'In addition to a previously reported reduction in type 2 diabetes risk, intensive lifestyle intervention has been linked to improved fibrinolysis.'

LANCET

Fenofibrate therapy significantly reduces CVD events

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

1 Dyslipidaemia, which has a role in the increased risk of cardiovascular disease (CVD) seen in people with type 2 diabetes, can be improved using treatment with fibrates.

2 The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study looked at the impact of fenofibrate on CVD in type 2 diabetes.

3 The randomised controlled trial involved 9795 people aged 50–75 years with type 2 diabetes not taking statins at study entry, and assigned participants to micronised fenofibrate 200 mg/day (n=4895) or placebo (n=4900).

4 The primary outcome measure was coronary events over the study's 5 years (coronary heart disease or non-fatal myocardial infarction [MI]); the secondary outcome measure was total CVD events (CVD death, MI, stroke, or coronary or carotid revascularisation).

5 For the primary outcome measure, there was a non-significant relative reduction of 11% in the intervention group.

6 More participants on placebo than on fenofibrate started statins during the study, which could have masked a significant effect on the primary outcome measure.

7 For the secondary outcome measure – total CVD events – there was a significant relative reduction of 11% with fenofibrate therapy.

8 Fenofibrate had a good safety profile across concomitant therapy.

Keech A, Simes RJ, Barter P et al (2005) Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* **366**(9500): 1849–61

DIABETOLOGIA

Remission of nephrotic-range albuminuria improves survival

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

1 The impact of remission of nephrotic-range albuminuria (NRA; >2500 mg/day) on end-stage renal disease (ESRD) and mortality in type 2 diabetes was evaluated in 79 people.

2 Remission – defined as albuminuria <600 mg/day for 1 year or longer – was achieved with antihypertensives in 20 individuals .

3 The composite end point of ESRD or death was reached in six (30%) of those achieving remission and 39 (66%) of those not achieving it (P<0.01 for difference).

4 The risk reduction associated with remission for reaching this composite end point was 67%.

Rossing K, Christensen PK, Hovind P, Parving HH (2005) Remission of nephrotic-range albuminuria reduces risk of end-stage renal disease and improves survival in type 2 diabetic patients. *Diabetologia* **48**(11): 2241–7

DIABETOLOGIA

Intensive lifestyle intervention boosts fibrinolytic activity

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

1 It has been suggested that reduced fibrinolytic activity may contribute to cardiovascular disease in type 2 diabetes and the metabolic syndrome.

2 As part of the Finnish Diabetes Prevention Study, this investigation aimed to examine the effect of intensive lifestyle intervention (targeting weight, diet and exercise) on fibrinogen and plasminogen activator inhibitor (PAI)-1 levels.

3 All participants (163 in the intervention group and 158 controls) had impaired glucose tolerance (IGT).

4 After 1 year, a significantly greater reduction was seen in the intervention group for PAI-1 levels (P<0.0001) but not fibrinogen levels.

5 In addition to a previously reported association with reduced type 2 diabetes risk, intensive lifestyle intervention has thus been linked – through reductions in PAI-1 levels – to improved fibrinolysis.

Hamalainen H, Ronnemaa T, Virtanen A et al (2005) Improved fibrinolysis by an intensive lifestyle intervention in subjects with impaired glucose tolerance. The Finnish Diabetes Prevention Study. *Diabetologia* **48**(11): 2248–53

DIABETIC MEDICINE

Swedish patients are missing targets

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

1 Data from a Swedish diabetes register from 1996–2003 were used to investigate treatment patterns as well as whether or not targets are being met in people with type 2 diabetes.

2 Type 2 diabetes was reported in 17 547 cases in 1996 and 57 119 cases in 2003.

3 Targets of HbA_{1c} <6.1%, blood pressure <130/80 mmHg and total cholesterol <4.5 mmol/l were achieved in 2003 by 16%, 13% and 28% of cases, respectively.

4 More aggressive treatment was thus called for (including aspirin, which was used by 36% of individuals in 2003), along with reductions in smoking.

Eliasson B, Cederholm J, Nilsson P et al (2005) The gap between guidelines and reality: Type 2 diabetes in a National Diabetes Register 1996–2003. *Diabetic Medicine* **22**(10): 1420–6

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Lactation may reduce risk of type 2 diabetes

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

1 Lactation has been linked to improved glucose metabolism, but no previous study had examined the relationship between lactation and the risk of type 2 diabetes.

2 Data were collected prospectively from a cohort of 83 585 parous women in the Nurses' Health Study (NHS) and retrospectively from a cohort of 73 418 parous women in the Nurses' Health Study II (NHS II).

3 For each additional year of lactation, women who had given birth in the previous 15 years had a decrease in the risk of type 2 diabetes of 15 % in the NHS cohort (P=0.02) and 14 % in the NHS II cohort (P<0.001).

4 The authors suggest the need for further clinical investigation to confirm their findings and to determine the physiological mechanism involved.

Stuebe AM, Rich-Edwards JW, Willett WC, Manson JE, Michels KB (2005) Duration of lactation and incidence of type 2 diabetes. *Journal of the American Medical Association* **294**(20): 2601–10

DIABETIC MEDICINE

Screening for diabetes does not induce significant anxiety

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

1 Type 2 diabetes has been shown to satisfy many of the criteria for screening, but some concerns have been raised about psychological costs.

2 Published research, although limited, suggests that there is little evidence for a negative psychological impact on emotional well-being.

3 In this study, 1339 people at high risk of developing diabetes completed an oral glucose tolerance test and a questionnaire.

4 Little to moderate amounts of anxiety associated with screening were reported by the participants.

5 The only factor found to have a significant association with anxiety was the emotional stability of patients.

Skinner TC, Davies MJ, Farooqi AM, Jarvis J, Tringham JR, Khunti K (2005) Diabetes screening anxiety and beliefs. *Diabetic Medicine* **22**(11): 1497–502

CHEST

Type 2 diabetes increases risks of pulmonary embolism and pulmonary hypertension

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

1 People with type 2 diabetes have a hypercoagulable state, possibly making them more susceptible to thromboembolism.

2 This study examined the incidence of pulmonary embolism (PE) and pulmonary hypertension (PHT) in people with type 2 diabetes, adjusting for congestive heart failure, coronary artery disease, hypertension and smoking.

3 Patient documents for hospital admissions (n=845 748), including discharge diagnosis, were used to obtain data for univariate and multivariate analyses.

4 PE was present in 0.7 % of patients with type 2 diabetes and 0.5 % of those without.

5 PHT was present in 1.1 % of patients with type 2 diabetes and 0.6 % of those without.

6 The odds ratios were 1.27 for PE (95 % confidence interval [CI], 1.19–1.35; P<0.001) and 1.53 for PHT (95 % CI, 1.45–1.60; P<0.001).

7 The pathogenesis of the association is not yet known.

Movahed MR, Hashemzadeh M, Jamal MM (2005) The prevalence of pulmonary embolism and pulmonary hypertension in patients with type II diabetes mellitus. *Chest* **128**(5): 3568–71

DIABETIC MEDICINE

Nurses are well placed to provide primary care support

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

1 This study explored the views of people with newly diagnosed type 2 diabetes on Scottish diabetes services.

2 Forty people with newly diagnosed type 2 diabetes from general practices and hospital clinics in Lothian, Scotland, were interviewed three times over 1 year.

3 General satisfaction with diabetes services was expressed, regardless of type of care, although the majority of interviewees wanted future care to be based in general practice (for reasons of convenience and accessibility).

4 A commonly held feeling was a lack of confidence or knowledge to manage diabetes in certain situations, and thus a need to have access to healthcare professionals who could quickly answer questions.

5 Another feeling expressed by interviewees was a desire for professionals working in primary care with diabetes expertise, but with more time than general practitioners.

6 Practice lead nurses for diabetes, where encountered, were spoken of positively.

7 Collating the findings, it seems that nurses with diabetes expertise are well placed to support patients in primary care.

8 It is recommended that practices operate as 'one-stop' diabetes clinics, providing structured care and offering easy access to podiatry, dietetics and retinal screening.

Lawton J, Parry O, Peel E, Douglas M (2005) Diabetes service provision: a qualitative study of newly diagnosed Type 2 diabetes patients' experiences and views. *Diabetic Medicine* **22**(9): 1246–51

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Antihypertensives recommended in prediabetes

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

1 This meta-analysis of randomised clinical trials was carried out to explore the role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in preventing the development of type 2 diabetes.

2 Twelve randomised clinical trials of ACE inhibitors or ARBs were identified by searching MEDLINE and reviewing meeting reports (CAPPP, STOP-2, HOPE, LIFE, ALLHAT, ANBP2, SCOPE, ALPINE, CHARM, SOLVD, VALUE and PEACE).

3 The pooled results comprised data from 72 333 individuals without diabetes at baseline (yielding roughly 340 000 person-years of follow-up).

4 The use of ACE inhibitors or ARBs was associated with a relative risk for developing type 2 diabetes of 0.75 (95 % confidence interval [CI], 0.69–0.82).

5 Subanalyses for ACE inhibitors and ARBs (used in seven and five of the trials, respectively) gave relative risks of 0.73 (95 % CI, 0.63–0.84) and 0.77 (95 % CI, 0.71–0.83), respectively.

6 Limitations of the meta-analysis included differing definitions of diabetes across the trials and the fact that the development of diabetes was a *post hoc* end point in ten of the twelve trials (only two trials prespecified it).

7 It is recommended that the use of ACE inhibitors and ARBs be considered in people with prediabetic conditions or a family history of diabetes.

Abuissa H, Jones PG, Marso SP, O'Keefe JH Jr (2005) Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *Journal of the American College of Cardiology* **46**(5): 821–6

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Muraglitazar linked to increase in death and major CV adverse events

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

1 An advisory committee for the US Food and Drug Administration recommended approval of the dual-peroxisome proliferator-activated receptor agonist muraglitazar in the control of blood glucose in people with type 2 diabetes.

2 This investigation determined the effect of muraglitazar, relative to controls, on a primary outcome of death, myocardial infarction or stroke and a more comprehensive outcome that also included congestive heart failure and transient ischaemic attack.

3 The authors reviewed prospective, randomised, double-blind trials that enrolled people who had type 2 diabetes and an HbA_{1c} of 7–10 %.

4 The primary outcome occurred in 35 of 2374 people (1.47 %) treated with muraglitazar and nine of 1351 people (0.67 %) people treated with placebo or pioglitazone (relative risk [RR], 2.23; 95 % confidence interval [CI], 1.07–4.66; P=0.03).

5 The more comprehensive outcome occurred in 50 of 2374 people (2.11 %) treated with muraglitazar and 11 of 1351 people (0.67 %) people treated with placebo or pioglitazone (RR, 2.62; 95 % CI, 1.36–5.05; P=0.004).

6 The authors state that muraglitazar should not be approved to treat diabetes until its safety has been shown in a dedicated cardiovascular end points trial.

Nissen SE, Wolski K, Topol EJ (2005) Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *Journal of the American Medical Association* **294**(20): 2581–6

'The authors state that muraglitazar should not be approved to treat diabetes until its safety has been shown in a dedicated cardiovascular end points trial.'

'It is recommended that the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers be considered in people with prediabetic conditions.'