Addition of insulin to oral therapy for type 2 diabetes

Roger Gadsby, GP and Associate Clinical Professor, Warwick Medical School, Warwick University.

There has been an increasing use of insulin therapy in people with type 2 diabetes in recent years.

Twenty or so years ago the usual way to initiate insulin in people with type 2 diabetes was to stop oral therapy and use twice-daily premixed insulin. Since then there has been a gradual realisation that continuing on oral agent therapy when initiating insulin is of value, in reducing the total dose of insulin needed, reducing weight gain and reducing hypoglycaemia.

There is a continuing debate as to whether once-daily long acting insulin or twice-daily premixed insulin is the best regimen to use, and there have been a few head-to-head studies comparing them.

The study reported in this paper is a multicentre, controlled, open label study of 708 people with type 2 diabetes with suboptimal glycaemic control on maximally tolerated doses of metformin plus sulphonylurea.

They were randomly assigned to receive twice-daily premixed insulin, once-daily long acting analogue insulin or thrice-daily rapid acting insulin with meals. Outcome measures at one year were HbA_{1c}, weight gain and hypoglycaemia.

At year one the average HbA_{1c} was 7.3% in both twice- and thrice-daily insulin regimens and 7.6% in the once-daily. There were more hypoglycaemic episodes and more weight gain in the thrice-daily regimen than the twice-daily regimen. The once-daily had the lowest weight gain and lowest number of hypoglycaemic episodes.

Most commentators on the study conclude that once-daily insulin gives the best balance of HbA_{1c} lowering, with reduced weight gain and hypoglycaemia.

The study is being continued for another 2 years. It may then be able to show which regimen is best at maintaining glycaemic control.

NEJM

Control varies across more simple insulin regimens

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

1 This paper reports on the data from the first year of the Treating to Target in Type 2 Diabetes (4-T) trial.

2 The 4-T trial is a 3-year, open-label, multicentre, randomised, controlled clinical trial examining the safety and efficacy of adding analogue insulin (biphasic, prandial or basal) to the treatment regimen of people with type 2 diabetes.

3 Recruitment occurred between November 1 2004 and July 31 2006. Inclusion criteria were: over 18 years of age; at least 12 months duration of diabetes; HbA_{1c} 7.0–10.0%; insulin naïve; and BMI ≤ 40 kg/m^2.

4 Of the 936 individuals who underwent screening, 708 met the inclusion criteria and were randomly assigned to either biphasic insulin aspart bd (235), prandial insulin aspart tds (239) or basal insulin detemir regimens od unless required bd (234).

5 The primary outcome for this paper was HbA_{1c} level 1 year from baseline.

6 The authors found that after 1 year, the maximum reduction in mean HbA_{1c} occurred at 24 weeks and stabilised therafter. Mean HbA_{1c} levels were similar in the biphasic group (7.3%) and the prandial group (7.2%; $P=0.08$) but higher in the basal group compared with both other groups (7.6%; $P<0.001$).

7 In conclusion, the addition of insulin to metformin and sulphonylurea therapy in type 2 diabetes is associated with clinically relevant and sustainable reductions in HbA_{1c}. The final 2 years of the trial will examine the use of complex insulin regimens in people with type 2 diabetes.

Holman RR et al (2007) Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes *NEJM* **357**: 1716–30

'This trial suggests that it is possible to sustain glycaemic control when substituting exenetide for insulin, but warns that this therapy substitution may not be suitable for all people with T2D. More investigation is required.'

JAMA

Rosiglitazone increases cardiovascular risk

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

1 Recent reports suggest that the risks associated with rosiglitazone may be too great to justify its use for treatment of type 2 diabetes.

2 The aim of this meta-analysis was to systematically review the current evidence of the risks of MI, heart failure, and cardiovascular mortality with long-term rosiglitazone use.

3 Data was searched up until May 2007. Data sources were: MEDLINE, the GlaxoSmithKline clinical trials register, US FDA website and product information sheets.

4 Inclusion criteria were: randomised controlled trials of rosiglitazone with at least 12 months follow-up, monitored cardiovascular adverse events, provided numerical data. Four studies were included after detailed screening.

5 A fixed-effects meta-analysis was used to estimate the relative risks (RR) of myocardial infarction, heart failure, and cardiovascular mortality (n=14 291, including 6421 receiving rosiglitazone and 7870 receiving control therapy, with a duration of 1–4 years).

6 Rosiglitazone significantly increased the risk of myocardial infarction (RR 1.42; 95% CI 1.06–1.91; *P*=0.02) and heart failure (RR 2.09; 95% CI, 1.52–2.88; P<0.001) without a significant increase in risk of cardiovascular mortality (RR 0.90; 95% CI, 0.63–1.26; P=0.53).

5 The authors concluded that treatment with rosiglitazone should be avoided in people with T2D who are at risk of cardiovascular events, especially as safer treatments are available.

Singh S et al (2007) Long-term Risk of Cardiovascular Events With Rosiglitazone. *JAMA* **298**: 1189–95

DIABETES CARE

Does lifestyle counselling work?

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

1 The Good Ageing in Lahti Region (GOAL) Lifestyle Implementation Trial was designed for the primary healthcare setting.

2 Its focus is the prevention of T2 diabetes through lifestyle counselling.

3 Three hundred and fifty-two middle-aged participants received six group counselling sessions delivered by public health nurses.

4 Self-reports analysed lifestyle outcomes, and study nurses measured clinical risk factors.

5 At 12 months 20% of participants acheived at least 4 out of 5 key lifestyle outcomes.

6 In conclusion, lifestyle couselling can be effective and is feasible in a real-world setting.

Absetz P et al (2007) Type 2 Diabetes Prevention in the "Real World". *Diabetes Care* **30**: 2465-70

DIABETES CARE

Safety of exenatide substitution

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

1 Forty-nine people with type 2 diabetes using insulin in combination with oral anti-diabetes agents took part in this trial, which aimed to assess the safety of substituting exenatide for insulin.

2 It was an exploratory, multicentre, two-arm, parallel-design, open-label trial, and was conducted over 16 weeks at 5 centres in the US.

3 The participants were randomised into two groups: substitute exenatide for insulin or remain on current insulin regimen.

4 A total of 62% (18 of 29) of the exenatide group maintained glycaemic control compared with 81% (13 of 16) of the insulin group.

5 The safety profile was consistent with previous exenatide trials.

6 To sum up, this trial suggests that it is possible to sustain glycaemic control when substituting exenetide for insulin, but warns that this therapy substitution may not be suitable for all people with T2D. More investigation is required.

Davis SN et al (2007) Exploring the Substitution of Exenetide for Insulin in Patients With Type 2 Diabetes Treated With Insulin in Combination With Oral Antidiabetes Agents. *Diabetes Care* **30**: 2767–72

JAGS

Insulin detemir benefits older and younger alike

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

1 This study is a comparison of the safety and efficacy of insulin detemir, with neutral protamine Hagedorn (NPH) in older (≥65 years) and younger (18–64 years) people with T2D.

2 There were 416 older and 880 younger participants.

3 Hypoglycaemic episodes were recorded by the participants in a diary.

4 The results of this analysis highlighted the benefits of insulin detemir: HbA_{1c} with insulin detemir was not inferior to NPH insulin for both age groups (older age group: 0.035%, 95% CI = -0.114–0.183; younger age group: 0.100%, 95% CI = -0.017–0.217).

5 Previously reported benefits of insulin detemir were the same for older and younger people at similar levels of HbA_{1c}.

Garber AJ et al (2007) Lower Risk of Hypoglycaemia with Insulin Detemir than with Neutral Protamine Hagedorn Insulin in Older Persons with Type 2 Diabetes: A Pooled Analysis of Phase III Trials, *The Journal of the American Geriatrics Society*, **55**: 1735–40