## What next after metformin?

*Roger Gadsby, GP and Senior Lecturer, Centre for Primary Healthcare Studies, Warwick University*

Which blood glucose-lowering agent should be added, once metformin alone at maximally tolerated doses does not enable the individual to reach their individualised $HbA_{1c}$ target, is one of the most hotly debated issues in diabetes prescribing today. It is also the area into which a number of new therapies have been launched. NICE (2009) recommends that a sulphonylurea (SU) should be the usual addition, but in situations where there is a significant risk of hypoglycaemia (or its consequences) the guideline suggests that a dipeptidyl peptidase-4 (DPP-4) inhibitor or a thiazolidinedione (TZD) can be considered.

The article summarised alongside by Phung et al (2010) seeks to answer the question as to which blood glucose-lowering therapy, when added to full-dose metformin, has the best attested evidence for $HbA_{1c}$ reduction, weight change and hypoglycaemia.

The article is a systematic review and meta-analysis, which considers 27 randomised controlled trials in 11 198 people with type 2 diabetes. In 20 trials where there was a placebo arm, the active agent was SU in two trials, glinide in two, TZD in three, DPP–4 inhibitor in eight, glucagon-like peptide (GLP-1) receptor agonist in two, and alpha-glucosidase inhibitor (AGIs) in two. A mixed treatment comparison meta-analysis methodology was used to calculate the weighted mean differences for changes from baseline in $HbA_{1c}$, body weight and relative risk (RR) of hypoglycaemia.

The different classes of drug were associated with similar $HbA_{1c}$ reductions (range –0.64 to –0.97%). SUs, glinides and TZDs were associated with weight gain (1.77–2.08 kg), while GLP-1 receptor agonists, DPP-4 inhibitors and AGIs were associated with weight loss or no weight change. SUs and glinides were associated with higher rates of hypoglycaemia than placebo (RR range, 4.57–7.50).

The conclusion that all therapies added to metformin monotherapy give similar $HbA_{1c}$ reductions counteracts any marketing strategy of "my therapy is more powerful than yours". The therapies, however, do have very demonstrably different effects on weight and hypoglycaemia. When cost is added to the equation it makes the scramble to be the "best" therapy to be added to metformin a fascinating battleground and area for debate.

NICE (2009) *Type 2 Diabetes: The Management of Type 2 Diabetes.* NICE, London

LANCET

## Screening for T2D most cost-effective at ages 30–45 years

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

1 This USA-based study calculated the cost-effectiveness of eight sequential, simulated screening strategies for the detection of new cases of T2D in a simulated population of 325 000 people aged 30 years with no diabetes.

2 The screening strategies – which differed in terms of age at initiation and frequency of screening – were compared with a no-screening control.

3 Compared with no screening, all strategies reduced the incidence of myocardial infarction and diabetes-related microvascular complications, and increased the number of quality-adjusted life-years.

4 Most strategies prevented a significant number of simulated deaths (two to five events per 1000 people), but there was little or no effect on the incidence of stroke.

5 The authors concluded that screening for T2D is most cost-effective when started at ages 30–45 years, and repeated every 3–5 years.

Kahn R, Alperin P, Eddy D et al (2010) Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *Lancet* **375**: 1365–74

JAMA

## Effect of non-insulin antidiabetes drugs when in combination with metformin

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

1 A literature search was performed to evaluate the comparative efficacy of non-insulin antidiabetes drugs (NIADs) when used in addition to metformin on glycaemic control, weight gain and hypoglycaemia in people with T2D.

2 Trials were included in the analysis if they were randomised controlled trials (RCTs) of 12–52 weeks' duration comparing NIADs in combination with metformin in people inadequately controlled on metformin monotherapy.

3 A total of 27 RCTs were included ($n$=11 198; age range, 53–62 years; 23–75% male; baseline $HbA_{1c}$ range, 6.4–9.3% [46–78 mmol/mol]), with a mean trial duration of 32 weeks.

4 All classes of NIADs significantly reduced $HbA_{1c}$ levels (range, –0.64 to –0.97%) compared with placebo.

5 Compared with placebo, sulphonylurea (SUs), glinides and thiazolidinediones (TZDs) were associated with weight gain, and alpha-glucosidase inhibitors (AGIs), dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists were associated with weight loss or no weight change.

6 SUs and glinides were associated with an increased risk of hypoglycaema compared with placebo. TZDs, AGIs, DPP-4 inhibitors and GLP-1 receptor agonists did not increase the risk of hypoglycaemia.

7 It was concluded that, when added to maximal metformin therapy, all NIADs had similar effects on $HbA_{1c}$ reduction, yet had different effects on weight gain and risk of hypoglycaemia.

Phung OJ, Scholle JM, Talwar M, Coleman CI (2010) Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA* **303**: 1410–8

NEJM

## Valsartan reduces diabetes incidence but not CV events

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

1 The NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) study aimed to evaluate whether valsartan reduces the risk of diabetes and CV disease (CVD) in people with impaired glucose tolerance (IGT) or CV risk factors.

2 People ($n$=9306) with IGT and CVD or CV risk factors were randomised to receive valsartan or placebo.

3 The cumulative incidence of diabetes was 33.1% in the valsartan group, compared with 36.8% in the placebo group ($P$<0.001).

4 Valsartan did not significantly reduce the incidence of either the extended CV outcome ($P$=0.43) or the core CV outcome ($P$=0.85).

5 In people with IGT and CVD or risk factors, valsartan led to a relative reduction in diabetes incidence but not the rate of CV events.

NAVIGATOR Study Group, McMurray JJ, Holman RR et al (2010) Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* **362**: 1477–90

BMJ

## Effect of invitation type on screening attendance uptake

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

1 This randomised controlled trial compared the effect of a standard invitation and a validated invitation promoting informed choice for screening on uptake of T2D screening.

2 The validated invitation provided details of costs and benefits of screening and treatment, whereas the standard invitation simply described diabetes as a serious potential problem.

3 Of the 1272 participants (age range, 40–69 years), 55.8% in the informed choice group attended screening, compared with 57.6% in the standard invitation group ($P$=0.51).

4 Attendance was lower in the more socially deprived group (most deprived third, 47.5% vs least deprived third, 64.3%; $P$<0.001), regardless of invitation type.

5 The authors concluded that willingness to alter behaviour was strong and unrelated to the type of invitation received.

Marteau TM, Mann E, Prevost AT et al (2010) Impact of an informed choice invitation on uptake of screening for diabetes in primary care (DICISION): randomised trial. *BMJ* **340**: 2138

JOURNAL OF THE AMERICAN GERIATRICS SOCIETY

## Increasing diabetes prevalence in USA nursing homes

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

1 This study examined data from all National Nursing Home Surveys conducted between 1995 and 2004 of residents aged 55 years and older to assess the incidence of diabetes in USA nursing homes.

2 The estimated prevalence of diabetes increased from approximately 16.9% in 1995 to 26.4% in 2004 in men and from 16.1% to 22.2% in women (all $P$<0.05).

3 In residents with diabetes, the incidence of cardiovascular disease increased from 59.6% in 1995 to 75.4% in 2004 for men and 68.1% to 78.7% for women (all $P$<0.05).

4 The authors concluded that the increasing burden of diabetes in USA nursing home residents warrants further study on care practices and more resources for high-quality care.

Zhang X, Decker FH, Luo H (2010) Trends in the prevalence and comorbidities of diabetes mellitus in nursing home residents in the United States: 1995–2004. *J Am Geriatr Soc* **58**: 724–30

LANCET

## Liraglutide superior to sitagliptin when used in combination with metformin

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

1 A 26-week, parallel-group, open-label trial was undertaken to assess the efficacy and tolerability of the human glucagon-like peptide-1 (GLP-1) analogue liraglutide compared with the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin, in combination with metformin, in people with T2D.

2 Participants aged 18–80 years with T2D and inadequate glycaemic control on metformin alone were randomised to once-daily, subcutaneous liraglutide 1.2 mg ($n$=225) or 1.8 mg ($n$=221), or once-daily, oral sitagliptin 100 mg ($n$=219) for 26 weeks.

3 The largest reduction in mean $HbA_{1c}$ levels was seen with 1.2 mg liraglutide (–1.24%; 95% confidence interval [CI], –1.37 to –1.11; $n$=221) and 1.8 mg liraglutide (–1.50%; 95% CI, –1.63 to –1.37; $n$=218), compared with sitagliptin (–0.90%; 95% CI, –1.03 to –0.77; $n$=219).

4 Mean weight loss was greater with 1.8 mg liraglutide (–3.38 kg; 95% CI, –3.91 to –2.84) and 1.2 mg liraglutide (–2.86 kg; 95% CI, –3.39 to –2.32) compared with sitagliptin (–0.96 kg; 95% CI, –1.50 to –0.42).

5 Both liraglutide doses were associated with significant improvements in beta-cell function, C-peptide concentration and pro-insulin-to-insulin ratio compared with sitagliptin.

6 More treatment-emergent adverse events were reported with liraglutide than with sitagliptin.

7 Liraglutide was found to provide superior glycaemic control to sitagliptin in people poorly controlled with metformin.

Pratley RE, Nauck M, Bailey T et al (2010) Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* **375**: 1447–56

> *"In people with impaired glucose tolerance and cardiovascular disease or risk factors, valsartan led to a relative reduction in diabetes incidence but not the rate of cardiovascular events."*