



# 'New therapies for type 2 diabetes have added little to improve glycaemic control compared to conventional therapies'

## FOR

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### Definition of 'not new' and date of introduction

- Insulin 1922
- Sulphonylureas 1955
- Metformin 1979
- Lifestyle 1977 (or earlier)
- Bariatric surgery 1966

### Old evidence about old drugs

The UK Prospective Diabetes Study (UKPDS) remains the best source of evidence that the old drugs are effective. After 10 years in the randomised trial, insulin, metformin and two different sulphonylureas (SUs) led to improved HbA<sub>1c</sub> and a significant reduction in microvascular complications.<sup>1</sup> In the UKPDS, randomisation to treatment group only took place if the fasting blood glucose was >6mmol/L after a three-month period on diet (carbohydrate 50% and reduced total energy). During this period, fasting blood glucose fell from 11.4 to 8.1mmol/L, which demonstrates the effectiveness of this simple, cheap and well-tried process that has been available to people with diabetes for decades.<sup>2</sup> The UKPDS also showed that insulin and SUs were equally effective in reducing the risk of microvascular complications, while metformin had the additional benefit of reducing the risk of myocardial infarction (MI).<sup>3</sup> For this reason, metformin has become the recommended treatment for people newly diagnosed with type 2 diabetes.<sup>4</sup>

### New evidence about old drugs

The UKPDS effect persisted for at least 10 years after the randomised study itself had closed. Once the constraints of randomisation were removed, the difference in metabolic control between intensive and conventional groups was lost but a legacy effect of tight control was demonstrated. The protective effect of insulin and SUs on microvascular disease persisted. Risk reduction from MI, which was not quite statistically significant at the end of the study, became highly significant 10 years on in the group originally randomised to intensive control. Moreover, the metformin effect in preventing MI became even more significant 10 years after the study (p=0.005).<sup>5</sup>

The ADVANCE study<sup>6</sup> is really the UKPDS with the wrinkles ironed out. The numbers are greater and the target HbA<sub>1c</sub> was achieved throughout the study with no increase in body weight. (See Table 1.)

By the end of the ADVANCE study, the mean HbA<sub>1c</sub> values were 6.5% in the intensive control group and 7.3% in the standard control group. This improvement in metabolic control led to a reduction in major microvascular events of 14% (p=0.015), but there was no reduction in risk of macrovascular events after five years. The majority of patients in the intensive group were on metformin and SUs and 40% were on insulin. Only 17% were taking glitazones and this study demonstrates the effectiveness of conventional therapies.

Bariatric surgery was first applied as treatment for obesity and, in a large meta-analysis, there was a cure rate for type 2 diabetes of 76.8% and an improvement in 86%.<sup>7</sup> No other form of treatment can approach these figures.

### New evidence about new drugs

The ACCORD study<sup>8</sup> was superficially similar to ADVANCE and also set out to investigate the effect of very tight metabolic control (target HbA<sub>1c</sub> <6%) on prevention of cardiovascular disease. The study was stopped prematurely at 3.5 years as there was greater mortality in the intensive control group. There were important differences in the design of ACCORD and ADVANCE. Nearly all patients in the ACCORD intensive group were on triple oral therapy (metformin, SU and a glitazone)

**Table 1.** Differences between ADVANCE and UKPDS. The therapeutic information refers to the groups randomised to intensive therapy

ADVANCE study (n=11 140)	UKPDS (n=5102)
Median duration of diabetes =8 years	Newly diagnosed
Previous macrovascular event in 32%	Active cardiac problem an exclusion
Target HbA <sub>1c</sub> =6.5%	Target fasting glucose 6mmol/L
HbA <sub>1c</sub> fell from 7.0 to 6.5% over 5 years	HbA <sub>1c</sub> increased from 6.2 to 7.8% over 10 years
Polypharmacy – 75% on SU and metformin, 40% on insulin	Monotherapy – insulin or SU with metformin added in 28%
No increase in weight over 5 years	Weight increase 5kg over 10 years



and more than 50% were also on basal bolus insulin. Although the evidence is circumstantial, it is likely that the excess deaths were indirectly related to hypoglycaemia. In ADVANCE only 17% of the intensive control group were on a glitazone, while the percentage in ACCORD was 92%.

Glitazones also carry a significant risk of heart failure<sup>9</sup> and fractures.<sup>10</sup>

The newest group of agents for treating diabetes are glucagon-like peptide-1 (GLP-1) agonists. These are costly and most funding bodies put severe restrictions on their use. GLP-1 agonists are as equally effective as an SU in reducing HbA<sub>1c</sub>.<sup>11</sup> Like glitazones, GLP-1 agonists have actions that are ill-understood, such as the cerebral effect of reducing appetite for food. We are still learning about them and we can only be reassured about their long-term safety after they have been in use for a long time. The main side effect of GLP-1 agonists is nausea, which may persist for up to 10 weeks with liraglutide and for six months with exenatide.<sup>12</sup>

Dipeptidyl-peptidase-4 (DPP-4) antagonists are sister drugs to GLP-1 agonists. They have the advantage of causing very few side effects but are not particularly potent in reducing blood glucose. The blood glucose

lowering effect of vildagliptin was shown to be similar to that of pioglitazone in a head to head study, in which one or the other was added to metformin in patients with poor control. Reduction in HbA<sub>1c</sub> was 0.68% in the group on vildagliptin and 0.57% with a glitazone.<sup>13</sup>

### Conclusion

Although the new agents for treating type 2 diabetes have caused a lot of excitement and raised hopes and expectations, no new agent has trial evidence to prove that it prevents diabetes complications. Health care professionals should not be seduced by the potential of these new agents and should not forget that the tried and tested agents have a solid research background to demonstrate their efficacy.

### Conflict of interest statement

Novo Nordisk and Lilly have sponsored me to give talks about GLP-1 agonists but may decide not to do so in the future.

### References

References are available online at [www.practicaldiabetesinternational.com](http://www.practicaldiabetesinternational.com).

## AGAINST

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### Expecting different results ...

It was Einstein who said: 'the definition of insanity is doing the same thing over and over again and expecting different results'. Since the end of World War 2 with the gradual increase, and now explosion, in cases of type 2 diabetes we have been limited, as far as our drug therapies are concerned, to: giving the beta cells a good kicking with sulphonylureas (SUs); preventing gluconeogenesis in the liver with metformin; contributing to social embarrassment with acarbose; and a whole host of bad things with insulin, such as serious weight gain, hypoglycaemia and all that accompanies these problems.

### The evidence

Nevertheless, there is some evidence that these agents, perhaps somewhat surprisingly, do have limited benefit and, if used aggressively in established disease, perhaps unsurprisingly, do potential harm.

The pivotal study that showed benefit from traditional agents – i.e. SUs, metformin, insulin and acarbose – is, of course, the UK Prospective Diabetes Study (UKPDS).<sup>1</sup> The main studies demonstrated clear benefits to the tight control group in terms of microvascular disease reduction – particularly in relation to retinopathy – but failed to show statistical benefit towards macrovascular disease, although there was a suggestion that there would be reduction in myocardial infarction (MI) and that the failure to reach significance was a statistical 'error'. The recent UKPDS 80 paper has shown that this is probably true as, after

long-term follow up of the UKPDS cohort, the reduction in MIs did reach significance.<sup>2</sup>

However, this is where the rub lies: the UKPDS was a study in newly-diagnosed diabetes; two recent studies into the effects of tight glycaemic control in established disease of eight to 10 years' duration, ACCORD<sup>3</sup> and ADVANCE,<sup>4</sup> have led to alarm bells ringing. In particular, ACCORD was stopped early due to a significantly higher death rate in the intervention group of 5% *vs* 4%; there was also significantly more severe hypoglycaemia in ACCORD of 3.1% *vs* 1%. ADVANCE used gliclazide-MR as its main antiglycaemic agent and, whilst no harm was demonstrated, neither was there benefit. Space does not permit detailed dissection of these two papers, but the messages are clear: aggressive therapies with traditional agents in type 2 diabetes of significant duration are not beneficial, and may be harmful.

### Squaring the circle

So, how are we to square the circle of UKPDS and ACCORD/ADVANCE? I propose that we should take advantage of the so-called metabolic memory demonstrated in the recent 80th UKPDS paper and treat early-stage type 2 diabetes aggressively with safe agents, while remaining cautious about aggressive glycaemic control in those with established disease and complications. Of course, life is not easy and, as about half of our diabetes cohorts are now diagnosed by other professionals such as cardiologists, podiatrists, stroke doctors, neurologists etc, we have a serious problem in defining exactly which patients are 'early' and which 'established'. I note that many newly-diagnosed patients when referred by other colleagues are, by definition, suffering from a complication at diagnosis, so 'early' and 'established' are clearly not dichotomous but rather a continuum.



## Conventional vs new therapies in improving glycaemic control

Hypoglycaemia is a serious problem in type 2 diabetes: the incidence of severe hypoglycaemia in insulin-treated patients is similar to that in type 1 diabetes and hypoglycaemia secondary to SUs is becoming widely recognised.<sup>5</sup> Those of us working in the front line will have seen serious, as well as sometimes chronic, hypoglycaemia secondary to inappropriate excessive treatment with SUs leading to much harm such as hip fractures and acute confusion, even on occasion being misdiagnosed as dementia.

The National Institute for Health and Clinical Excellence (NICE) for England and Wales recommends a step-wise approach to the management of glycaemic control in type 2 diabetes,<sup>6</sup> starting with metformin, which has the advantage of being well established and safe; moreover, it possibly has some cardiovascular benefits.<sup>7</sup> Their suggestion of SUs as second-line therapy was based on the UKPDS evidence both in terms of microvascular complication reduction and also extrapolation from the observational 'epidemiological' UKPDS assumption of reduced HbA<sub>1c</sub> being a good thing.<sup>1</sup> However, NICE guidelines are, by their very nature, out of date the moment they are published on the website and are, of course, guidelines – not dogma.

### The glitazones

Today we have newish agents such as the glitazones (TZDs), of which pioglitazone will be off patent soon and will become cheaper (probably) and thus will transform into a 'traditional agent' almost overnight. This drug has some cardiovascular benefit<sup>8</sup> and its sister TZD rosiglitazone, despite being tarred by some for possible cardiovascular harm, appears to be safe.<sup>9</sup> Heart failure and distal fractures are issues with these agents, but experienced physicians are very capable of taking these issues into account when considering their use and, most importantly, they do not cause severe hypoglycaemia. For patients, their main downside is weight gain and, if it occurs, it can be a lot; being told by one's doctor or nurse that it is 'good fat' really, really, does not help!

### New therapies

The new agents are the dipeptidyl-peptidase-4 (DPP-4) inhibitors and the glucagon-like peptide-1 (GLP-1) agonists/mimetics. Both the GLP-1 injectables, exenatide and liraglutide, improve glycaemic control and lower weight without causing severe hypoglycaemia (unless combined with an SU or insulin);<sup>10-13</sup> transient nausea is

an issue but most tolerate it and it resolves in most. The DPP-4 drugs are orally active and enhance endogenous GLP-1 levels by preventing GLP-1 breakdown by DPP-4; they lower HbA<sub>1c</sub> levels by up to 1%;<sup>14-18</sup> they, too, do not cause hypoglycaemia and whilst there are suggestions of minimal weight loss most accept them to be weight neutral.

'Super-GLP-1' therapy has been available for some time but only recently widely available in the UK; I refer to by-pass bariatric surgery which leads to very high GLP-1 levels postoperatively.<sup>19</sup> The alternative procedure of gastric banding has also recently been shown to be a good treatment for diabetes in moderately overweight individuals and can lead to a cure and improve longevity.<sup>20</sup>

### Conclusion

Thus, the antedeluvian attitude that we should remain locked to treating diabetes with traditional agents will tie our hands behind our backs, deny our patients possible benefit and will lead to an increase in the health burden due to diabetes. Of course, there is a requirement for long-term studies into the GLP-1 and DPP-4 agents and these are on-going. I note that the ACCORD result of probable harm and the ADVANCE result of probable little benefit with traditional agents both arrived about 43 years after the safety of SUs was first raised.<sup>21</sup> It seems to me that the traditional agents have served us well, but are clearly imperfect and we should, of course, continue to strive to better our therapeutic armamentarium – which includes using the new agents in selected patients, both those recommended by NICE and in others when specialist skills and patient choice combine.

### Conflict of interest statement

I have attended advisory boards and given talks sponsored by: Eli Lilly, Novo Nordisk, GlaxoSmithKline, Takeda, Bristol-Myers Squibb and Astra Zeneca, as well as others over the years.

### References

References are available online at [www.practicaldiabetesinternational.com](http://www.practicaldiabetesinternational.com).

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#### CONFERENCE NOTICE

## International Society for Pediatric and Adolescent Diabetes (ISPAD) 2010

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