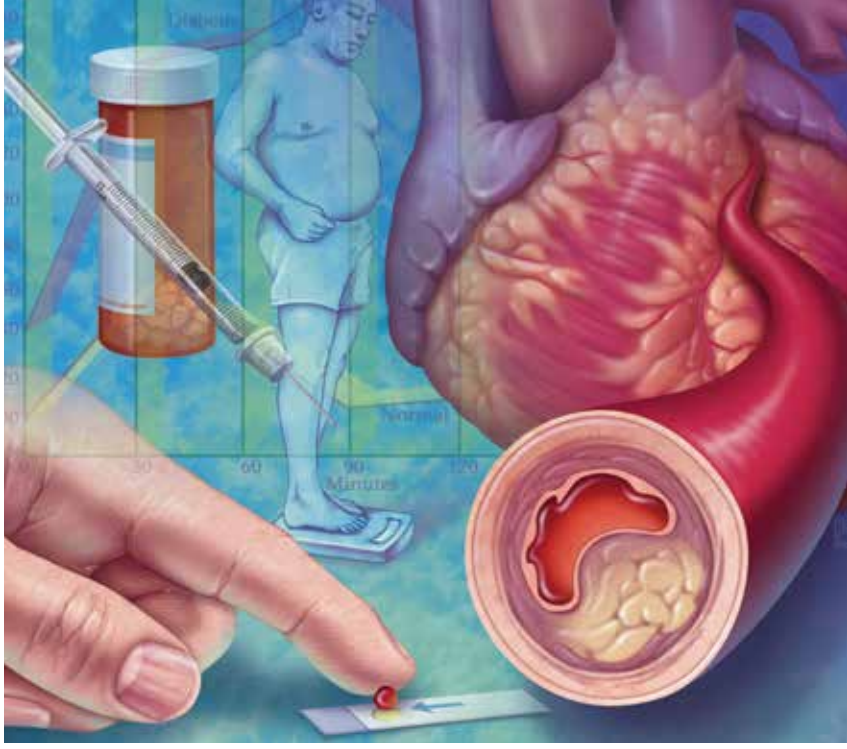
# New therapies for diabetes

## Has the regulatory program gone too far?



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*New therapies with additional benefits beyond glucose lowering are being developed to improve the management of diabetes. This article describes the changes to the regulatory framework that have demanded large cardiovascular safety studies for novel diabetes drugs and discusses new agents that may have a role in the management of patients with diabetes now and in the future.*

**Key points**

- **Cardiovascular diseases (CVDs) are the most common complications in people with type 2 diabetes.**
- **Poor glycaemic control is associated with higher rates of CVD.**
- **Current therapies that improve glycaemic control do not decrease the rate of CVD events.**
- **Improved glycaemic control with CVD benefit is the goal of new diabetes therapies.**



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The management of diabetes following the discovery of insulin in 1922 was relatively simple and straight forward for the first 75 years. Available therapeutic agents were insulins of different duration of action and different origins (human, beef, pig and later analogue insulins) and two classes of oral agents: biguanides and sulfonylureas. Following the negative findings of the University Group Diabetes Program (UGDP) in the 1960s,[1] the management of type 2 diabetes was primarily aimed at simply controlling symptoms of hyperglycaemia; this was very effectively achieved with the available agents. There was no great impetus to develop new glucose-lowering drugs given this conservative clinical goal. The therapeutic aim of achieving near normalisation of blood glucose levels (BGLs) to minimise or eliminate complications of hyperglycaemia was not considered at that time.

The Diabetes Control and Complications Trial (DCCT) was the first study to show benefits of improved glycaemic control albeit in patients with type 1 diabetes.[2] Subjects were randomised to an intensive insulin management strategy compared with a conservative approach. There was a significant improvement in glycaemic control associated with highly significant and relevant reductions in microvascular complications in the intensive insulin management group. This was at the expense of higher rates of hypoglycaemia. In 1997 the results of the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated benefits for people with type 2 diabetes.[3] In this trial, patients with new-onset type 2 diabetes were randomised to an intensive management protocol with either sulfonylureas or insulin versus a conservative but contemporarily appropriate management protocol. A small sustained difference of 0.9% in glycated haemoglobin ($HbA_{1c}$; with an average $HbA_{1c}$ in the intensive group of 7.0%) was associated with significant reductions in microvascular complications.[3] A small nonsignificant 14% reduction in myocardial infarction was observed. A substudy of 342 obese patients with a BMI of 32 kg/m$^2$ or above treated with metformin did demonstrate cardiovascular disease (CVD) benefits, although it took at least seven years to become evident and was not observed in combination with a sulfonylurea.[3] This CVD benefit of metformin, together with its associated weight loss, has led to it being recommended as first-line therapy for the pharmacological management of patients with type 2 diabetes. When it is considered that the evidence base for a CVD protection effect of metformin is derived from outcomes in 342 subjects when current cardiovascular safety studies have

**Table 1. Current cardiovascular safety studies**

| Trial name | Drug | Number of subjects | Study length (years) |
|---|---|---|---|
| EXAMINE | Alogliptin | 5400 | 2* |
| CAROLINA | Linagliptin | 6000 | 7 |
| TECOS | Sitagliptin | 14,000 | 5 |
| SAVOR | Saxagliptin | 16,500 | 2* |
| EXCEL | Exenatide long-acting release | 12,000 | 5.5 |
| LEADER | Liraglutide | 9000 | 5 |
| ELIXA | Lixisenatide | 6000 | 5 |
| DECLARE | Dapagliflozin | 17,000 | 5 |
| CASCADE | Empagliflozin | 7000 | 4–8 |
| CANVAS | Canagliflozin | 4500 | 4 |
| ALECARDIO | Aleglitazar | 6000 | 4.5 |

* Completed.

enrolled up to 17,000 patients, some interesting questions regarding the validity and reproducibility of this observation arise.

The positive results of the above two studies confirmed the benefit of improved glycaemic control to minimise diabetes-specific complications. However, there were problems associated with the more intensive therapeutic management strategies, including weight gain and increased rates of hypoglycaemia. Subsequently, the benefit of normalising glycaemic control in type 2 diabetes was assessed in the glycaemic control arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.[4] The intensively managed cohort had an increased rate of cardiovascular death associated with but not necessarily caused by hypoglycaemia.

Alpha-glucosidase inhibitors were introduced into clinical practice approximately 20 years ago but have had little impact on management strategies, at least in Australia. The first new class of glucose-lowering drugs to have a significant impact on the management of diabetes was the thiazolidinediones. These were introduced into clinical practice in the 1990s with the promise of addressing the perceived key pathophysiological abnormality of diabetes and the metabolic syndrome – insulin resistance. Disappointingly, studies failed to show a reduction in the primary CVD end points in two trials using pioglitazone and rosiglitazone – Efficacy of Pioglitazone on Macrovascular Outcome in Patients With Type 2 Diabetes (PROACTIVE) trial[5] and Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial.[6]

Furthermore, an analysis of data submitted by the Federal Drug Administration (FDA) suggested that rosiglitazone was associated with an increased rate of CVD events.[7] As a result, the FDA mandated that all new diabetes therapies had to demonstrate CVD safety.[8] In practice, what this means is that pharmaceutical companies wishing to market diabetes drugs in the USA must undertake large CVD safety studies to prove that these new therapies not only lower BGLs but that they are also safe to use. There are a large number of these trials currently enrolling over 100,000 patients at a estimated cost of US$20,000 to 40,000 per patient (Table 1).[9] The total cost of these studies to date is probably in excess of US$10 billion and rising. Thus the development costs of new diabetes therapies has substantially increased, putting pressure on the affordability of new medications for the population at large, particularly when compared with existing therapies, such as metformin, sulfonylureas and insulin, which are inexpensive, with oral agents having become generic therapies many years ago. Although these therapies are safe and effective with proven outcome data[2,3] and have many years of safety data, these old agents are not without problems. Weight gain and hypoglycaemia are well-recognised adverse consequences of these drugs. It is also the case that many people with type 2 diabetes remain 'resistant' to these therapies with suboptimal responses. There is a need for improved therapies that are more effective and also safe. But how much better do these agents need to be? Many newer therapies have only marginally improved clinical characteristics. How significant does the impact on hypoglycaemia and weight have to be? Although desirable benefits, does addressing these two problems impact on healthcare costs? How much is society prepared to pay to avoid these unwanted effects? Is the price premium sufficient to allow the pharmaceutical industry to maintain a substantial research and development program?

For new agents to reach the market place there is now the expectation that they should have significant clinical benefits over and beyond glucose lowering. A successful clinical trial program demonstrating substantial benefit may justify the very high price that the pharmaceutical companies must charge to recover development costs. Without the latter, the financial incentive for companies to continue to develop the products that clinicians and patients demand will disappear. But has the regulatory program gone too far? It is interesting to contemplate what would have happened to existing agents if current regulatory practices were present years ago. If insulin had been marketed following metformin and considering its apparent CVD benefits demonstrated in the UKPDS,[3] would a CVD outcomes safety study comparing insulin with metformin have concluded that insulin caused CVD? Insulin may never have been approved for use in type 2 diabetes. If sulfonylureas had been discovered after dipeptidyl peptidase-4 (DPP-4) inhibitors, would sulfonylureas have come to the market given their higher rates of adverse events? Given that the role of sulfonylureas and insulin in the management of diabetes is accepted, it does question whether the current plethora of short term but large CVD outcomes studies are really relevant in type 2 diabetes (Table 1). Is this huge investment really leading to improved outcomes for patients with diabetes? The proven long-term benefits of improved glycaemic control on microvascular disease reduction are not under primary evaluation in any of these current studies. Reducing renal disease in diabetes has major benefits and is likely to have secondary macrovascular implications. Insulin, sulfonylureas and

metformin have proven microvasular disease benefits. At this stage, none of the newer therapies have been shown to reduce microvascular complications, although it is accepted that this will occur with improved glycaemic control. Only two DPP-4 inhibitors have demonstrated short-term cardiovascular safety to date.[9,10] Is it more relevant to confirm microvascular benefit before considering cardiovascular safety?

There is a difficult balance between the funding of new medical therapies with unproven microvascular and macrovascular benefits that have modest additional benefits so that pharmaceutical innovation continues to be rewarded. This is occurring at a time where the health-care system is seeking more cost-effective medical care in an ageing population with an increasing burden of chronic disease. These issues will intensify as increasing financial pressure is placed on research expenditure and the healthcare systems. It is possible that the development of new diabetes therapies may become prohibitively costly.

A brief discussion of new agents that may have a role in the management of patients with diabetes now and in the future is described below. The therapeutic class and year of introduction are also shown in Table 2.

## New therapeutic classes

### DPP-4 inhibitors

There are now five DPP-4 inhibitors available in Australia and this class could now be considered established. DPP-4 inhibitors have gained acceptance from both patients and their doctors because of the perceived benefits of being weight neutral with reduced rates of hypoglycaemia events compared with that of sulfonylureas. From an Australian perspective, there are some issues. All five agents have demonstrated up to 10-fold lower rates of hypoglycaemia compared with comparator sulfonylureas. However, these studies have predominantly been registration studies necessary for their approval by the FDA in the USA market. Consequently, the comparator sulfonylurea agents (glimepiride and glipizide) have been used in the USA, and very little in Australia. The study design of these trials may have exaggerated the risk of sulfonylurea-induced hypoglycaemia. There was forced dose escalation of the sulfonylureas with a secondary end point being achieved fasting BGLs, which may have exaggerated the rate of hypoglycaemia. Additionally, the sulfonylurea most commonly used in Australia is gliclazide, which is not marketed in the USA. Gliclazide has been shown to have 2.5-fold lower rate of hypoglycaemia compared with glimepiride while being equally efficacious in improving glycaemic control.[10] The only reported trial that compared a DPP-4 inhibitor with gliclazide was a study of vildagliptin.[11] Compared with gliclazide, the rate of all hypoglycaemic events was only two-fold lower, the $HbA_{1c}$ reduction was noninferior but the failure rate (unsatisfactory control) was higher in the vildagliptin group.[11] Thus, from a clinical perspective, the benefits of DPP-4 inhibitors over sulfonylureas (specifically gliclazide) is less impressive. However, from a patient perspective, the combination of a DPP-4 inhibitor with metformin in a single tablet offers financial benefits to the patient as well as a reduction in pill burden. No similar combination exists for gliclazide and metformin.

**Table 2. Diabetes therapies and year of introduction**

| Class | Year of introduction |
|---|---|
| Animal insulin | 1922 |
| Insulin NPH | 1936 |
| Sulfonylureas | 1942 |
| Metformin | 1958 |
| Human recombinant insulin | 1982 |
| Alpha-glucosidase inhibitors | 1988 |
| Short-acting insulin analogues | 1996 |
| Thiazolidinediones | 1997 |
| Long-acting insulin analogues | 2000 |
| GLP-1 agonists | 2004 |
| DPP-4 inhibitors | 2006 |
| SGLT-2 inhibitors | 2013 |

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium glucose cotransporter-2.

### Glucagon-like peptide-1 agonists

Glucagon-like peptide-1 (GLP-1) agonists represent a significant advance in the management of type 2 diabetes with significantly greater reductions in $HbA_{1c}$ compared with sulfonylureas, decreases in weight and no increases in the rate of hypoglycaemia. Unfortunately, this class is associated with high adverse event rates with 10 to 25% of patients being unable to initially tolerate the medication and up to 50% of subjects discontinuing therapy within one year. However, some patients do achieve impressive improvements in glycaemic control with significant reductions in weight.

The only GLP-1 agonist currently subsidised though the pharmaceutical benefits scheme (PBS) is exenatide, which is taken twice a day by injection. Liraglutide is also available in Australia but is not available on the PBS. It is a longer-acting GLP-1 agonist compared with exenatide, only needing to be injected once a day. It is better tolerated and achieves greater reductions in $HbA_{1c}$ compared with exenatide or the long-acting form exenatide once weekly,[12] which is also available in Australia although not available on the PBS. Other preparations of GLP-1 agonists that can be administered once weekly are in development and may have a definite role in patient management, especially in difficult populations in whom daily injections may be problematic. The combination of a long-acting insulin with a GLP-1 agonist has significant theoretical advantages supported by impressive clinical trial data. Despite being an ideal regimen for patients with poorly controlled type 2 diabetes who fail therapy with oral hypoglycaemic agents, the use of GLP-1 agonists in combination with basal insulin therapy is not yet approved for reimbursement by the Pharmaceutical Benefit Advisory Committee (PBAC).

### Sodium glucose cotransporter-2 inhibitors

Sodium glucose cotransporter-2 (SGLT-2) inhibitors have actually been known for nearly two centuries, phlorizin having been discovered in 1835. The advent of specific inhibitors of the renal sodium glucose cotransporter has lead to renewed interest in this class. The mode of

action of these drugs is to increase glycosuria, which is in direct contrast to the classic approach to the management of diabetes in which the aim is to minimise this. The inhibition of the transporter increases renal glycosuria, resulting in the loss of approximately 70 g of glucose per day, equivalent to about 300 kcals/day. There is also a loss of some sodium. Clinically, reductions in $HbA_{1c}$ equivalent to those achieved with metformin are observed, associated with greater weight loss and small decreases in blood pressure, attributable to the naturesis.

Canagliflozin and dapagliflozin are currently PBS approved for use as dual therapy in combination with either metformin or a sulfonylurea in patients after failing to achieve inadequate control with other dual therapies. Given that the mode of action of this class is independent of circulating insulin, these drugs may have an important role in a variety of clinical situations. The most clinically relevant role may be in poorly controlled, overweight patients with type 2 diabetes who are taking large doses of insulin. Preliminary studies have shown improvements in $HbA_{1c}$, weight loss and reduced insulin requirements in patients randomised to SGLT-2 inhibitors, which are all very desirable outcomes.[13] Once again, the use of these drugs to improve the management of such problematic patients is not currently reimbursed by the PBS. Empagliflozin has been recommended for approval by the PBAC and a combination of SGLT-2 inhibitors with metformin in a single pill formulation is also being considered for approval by the PBAC.

### New insulins

Despite insulin being the oldest therapeutic agent used in the management of diabetes, ongoing research has enabled the continued development of new insulin therapies. Insulin degludec is a very long-acting insulin, which has been shown to be similarly efficacious to insulin glargine when administered by injection every second day. When used once a day, it has been shown to be associated with slightly lower absolute rates of hypoglycaemia despite achieving similar $HbA_{1c}$ levels to insulin glargine in patients with type 2 diabetes. Very 'normal' fasting BGLs were targeted in the study designs of these insulins potentially exaggerating any difference between the two. However, higher rates of hypoglycaemia were seen at times in patients with type 1 diabetes using insulin degludec, as well as a trend to higher rates of major adverse cardiovascular events in the registration studies overall.[14] Despite the fact that insulin degludec is available in Europe and some parts of Asia, the FDA has called for further cardiovascular studies before approving use of this agent in the USA. This may delay its introduction into Australia. Given issues of price it is unclear when, if ever, this insulin may be reimbursed in Australia.

Pegylated lyspro insulin is an innovative product that targets the liver. The large size of the pegylated insulin complex means that its capacity to cross into peripheral tissues and the brain is limited whereas passage through the larger fenestrated pores in the capillaries of the liver is possible. Compared with insulin glargine, pegylated lyspro insulin is equally efficacious in lowering $HbA_{1c}$ levels but has reduced intraday variability, has lower rates of nocturnal hypoglycaemia and is associated with weight loss.[15] Preliminary studies have shown changes in lipid parameters and increases in abnormal liver function tests, which are being further evaluated. These safety issues may delay its introduction or prevent its long-term use in managing diabetes.

Insulin glargine U300 is a new preparation of insulin glargine. Although initially developed to meet the needs of profoundly insulin-resistant patients, its pharmacodynamic properties are improved with less variability and a longer duration of action. Clinically it is associated with lower rates of hypoglycaemia compared with regular insulin glargine.[16] It will be marketed under a new name with a different injection device to differentiate it from insulin glargine. As it is the same molecule as insulin glargine, it already has been demonstrated to have cardiovascular safety based on the findings of the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial.[17]

A game-changing innovative approach to insulin therapy will be the successful development of smart insulins. One program has developed an insulin complex that consists of insulin molecules aggregated together into a nanoparticle biological matrix.[18] The stability of the matrix is dependent on the ambient BGL. Thus when the BGL is low, the aggregates either reform or do not dissociate. In contrast, when the BGL rises, the aggregates dissociate releasing free short-acting insulin. Potentially this could revolutionise insulin therapy as the physicochemical characteristics of the matrix would essentially clamp the BGL at a certain predetermined level without the need for blood glucose monitoring. This approach has been shown to be successful in mice. There are many hurdles to overcome before this 'smart insulin' may be a management option for patients with diabetes.

## Summary

Over the past few years there has been increased research resulting in the development of many new therapies to improve the management of patients with diabetes. The new agents that have been introduced have additional benefits beyond glucose lowering. These could be considered to be of uncertain clinical, social and financial benefit at this stage. The ability of these agents to prevent or decrease microvascular and macrovascular complications has not been demonstrated in clinical trials although the significant glucose-lowering ability of these new drugs should produce similar benefits to other glucose-lowering drugs.

Changes to the regulatory framework demanding large cardiovascular safety studies are substantially increasing costs of new drug development. Is the investment in studies of cardiovascular safety providing cost-effective answers that clinicians and patients need? Could that money be better spent to improve the care of people with diabetes? Would improved pharmacovigilance provide a better solution to long-term safety issues? Better use of existing therapies would overcome many of the perceived problems that the new therapies seek to address. **ET**

### References

A list of references is included in the website version (www.medicinetoday.com.au).

COMPETING INTERESTS: Associate Professor d'Emden has served on advisory boards, received honoraria for presentations and received support to attend international meetings from Eli Lilly, Boehringer Ingelheim, Bristol Myers Squibb, Novartis, Takeda, Merck Sharp and Dohme, Astra Zeneca and Novo Nordisk.

# New therapies for diabetes

## Has the regulatory program gone too far?

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