



## Spotlight on clinical trials in diabetes & **HEART DISEASE**

Diabetes is one of a number of factors that increase a person's risk of heart disease.

People with both Type 1 and Type 2 diabetes are two to three times more likely to develop heart disease, and it is the most common cause of death among them.

Therefore, it is crucial that healthcare professionals are able to both reduce cardiovascular risk and treat diabetes effectively and safely. **Dr Maria Tennant** reviews the latest clinical trials whose outcomes will help inform treatment choices

**A**s well as reducing blood glucose, diabetes treatments target the 'treatable' cardiovascular risk factors – reducing weight, cholesterol and blood pressure. "We have made great strides in reducing microvascular complications of diabetes, like those that affect the kidneys and eyes, by using diabetes treatments to lower blood sugar and HbA1c," says Professor Angelyn Bethel, Deputy Director of the Diabetes Trials Unit (DTU) at the University of Oxford. "But, cardiovascular mortality remains high, so we need to find new ways to reduce cardiovascular risk."

Many clinical trials over several years have shaped diabetes treatments used in the clinic today. A number of exciting trials are now taking place that could help to shape the treatments of the future.

### Lowering cholesterol

Lipid management is an important way to reduce cardiovascular disease (CVD) risk. People over 40 years old with diabetes, and established cardiovascular risk factors or CVD, are usually prescribed a statin. Several outcome trials of lipid-lowering drugs, particularly statins, have provided overwhelming evidence they reduce cardiovascular risk, so they are commonly used in higher-risk patients, including people with diabetes. One of these trials was the Heart Protection Study<sup>1</sup>, which tested simvastatin in a range of 'at-risk' people, including 6,000 people with diabetes.

There have been some more recent developments in the area of cholesterol lowering. In 2015, the US Food and Drug Administration (FDA) approved two new monoclonal antibodies, alirocumab and evolocumab, to lower low-density lipoprotein cholesterol. Both of them belong to the drug class known as PCSK9 inhibitors, whose mode of action differs from that of statins. "These drugs offer an alternative for those who either cannot or won't take statins," says Jane Armitage, Professor of Clinical Trials and Epidemiology at the University of Oxford. Exploratory trials suggest these drugs can benefit cardiovascular health, and there are currently several large outcome trials taking place, whose findings will help guide treatment choices.



## Cardiovascular outcome trials

Over the years, there have been many trials testing drugs for the treatment of hyperglycaemia in diabetes which have also looked at whether they reduce cardiovascular risk. These include the UK Prospective Diabetes Study (UKPDS<sup>2</sup>), a landmark study that found intensive blood glucose reduction in newly diagnosed Type 2 diabetes patients reduced the long-term microvascular complications and macrovascular endpoints associated with diabetes, compared with conventional care. In the follow-up study, 10 years later, a reduction in heart attacks was still seen, and a sub-study found metformin may improve cardiovascular outcomes, by reducing heart attacks<sup>3</sup>. The PROactive trial also demonstrated cardiovascular benefits – the drug pioglitazone reduced myocardial infarction, stroke and cardiovascular mortality<sup>4</sup>. But, since then, a number of trials, including ACCORD, ADVANCE, VADT and ORIGIN, failed to show any significant cardiovascular benefit with glucose lowering. And, in 2007, a meta-analysis raised concerns over a group of drugs called thiazolidinediones, with the possibility that rosiglitazone could increase the risk of heart attack<sup>5</sup>.

As a result of this, the FDA announced a change in regulatory requirements. To license a drug, they now need proof from post-marketing cardiovascular outcome studies that a glucose-lowering drug does not cause cardiovascular harm. Studies have to last for at least two years, must include high-risk people, and assess several cardiovascular endpoints, including death from CVD and non-fatal myocardial infarction. The FDA requirement has now been adopted internationally and has led to several large outcome trials.

“At first, there was a concern among researchers that this regulatory requirement might stifle innovation,” says Prof Bethel. “By their very nature these trials are large and need to run for a long time. Fortunately, that does not seem to be the case and we are continuing to see new drug classes emerge.”

Many of these post-marketing trials

have a non-inferiority design – in other words, they aim to show that the drug being tested is not worse than the comparator drug by more than a pre-specified amount. “I think there is a perception that when these outcome trials show no difference between treatments, they have failed, but that is not true,” says Prof Bethel. “In this case, no difference between treatment groups is good, because it means the drugs do not show cardiovascular harm.”

The DTU is involved in several cardiovascular outcome trials, and has recently published the results of the TECOS trial – the Trial Evaluating Cardiovascular Outcomes with Sitagliptin<sup>6</sup>. TECOS recruited over 14,700 people with Type 2 diabetes and who have had a cardiovascular event, and followed them for up to three years. It found no evidence that sitagliptin, a DPP-4 inhibitor, was associated with a significant increase in cardiovascular events compared with placebo, confirming the cardiovascular safety of the drug.

“TECOS was particularly interesting to clinicians because it reported after two other DPP-4 drug trials revealed surprising findings,” says Prof Bethel. “The SAVOR-TIMI trial, with saxagliptin, showed no difference in major cardiovascular events, but showed higher rates of hospitalisation from heart failure. Another trial with alogliptin, EXAMINE, also showed no difference

people with Type 2 diabetes, revealed liraglutide not only showed non-inferiority, but also demonstrated superiority – by significantly reducing the risk of heart attack and stroke compared with standard of care<sup>7</sup>. The SUSTAIN-6 trial has also shown that semaglutide reduces cardiovascular risk<sup>8</sup>, while the FREEDOM-CVO trial found that ICTA 650, a GLP-receptor agonist, could give cardiovascular benefit<sup>9</sup>. Detailed results of these trials will be presented at the American Diabetes Association conference in June 2016.

The EMPA-REG trial<sup>10</sup> tested empagliflozin, a SGLT-2 inhibitor, which works in the kidney to increase glucose loss in the urine and lower blood glucose levels. Patients with Type 2 diabetes at high risk for cardiovascular events received either 10mg or 25mg empagliflozin, or placebo, once daily. This was a landmark trial, because it is the first time a diabetes drug has been shown to reduce the relative risk for both cardiovascular and all-cause mortality, when added to standard care. To underline the significance of this development, EMPA-REG actually resembles some of the statin trials in terms of reducing cardiovascular risk and mortality.

And later analysis of the impact on heart failure revealed empagliflozin also reduced heart failure hospitalisation and cardiovascular death<sup>11</sup>.

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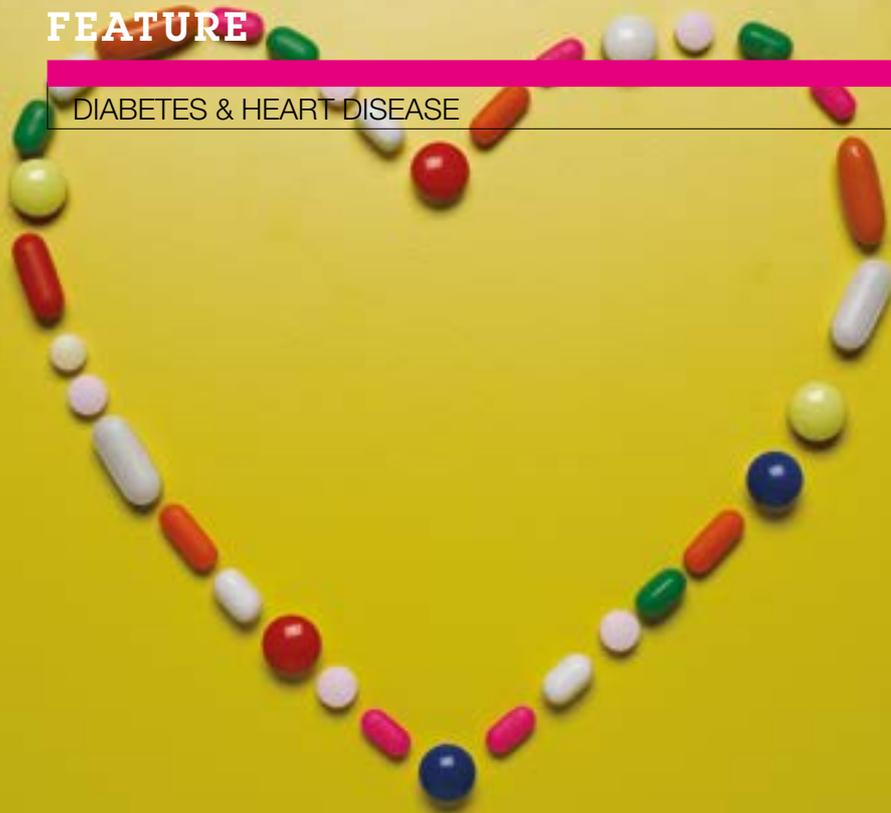
for major cardiovascular events, but showed a trend toward increased heart failure hospitalisations that was not statistically significant. For TECOS, no evidence of an increase in heart failure was shown. The reasons why these trials have different heart failure results is not clear.”

## Cardiovascular benefit

Meanwhile, other trials are indicating that diabetes drugs could actually confer a cardiovascular benefit. Earlier this year, the LEADER trial, of 9,000 high-risk

## Current cardiovascular outcome trials

The DTU, together with the Duke Clinical Research Institute, is carrying out the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) clinical trial, which will find out if giving people with Type 2 diabetes a once-weekly preparation of the drug exenatide, alongside their usual diabetes care regime, can reduce their risk of heart disease<sup>12</sup>. In this trial, 14,000 people with Type 2 diabetes will receive an injection of study medication (exenatide or placebo) once a week. ▶



The results of this pragmatic trial, which aims to measure how beneficial a treatment would be in real clinical practice, are expected in 2018.

Meanwhile, a large comparative effectiveness trial aims to help doctors make the best clinical decisions when it comes to choosing from the array of glucose-lowering medications. The Glycemia Reduction Approaches in Diabetes (GRADE) trial will compare a range of outcomes, including glycaemic lowering of four commonly used classes of diabetes drugs alongside metformin in 5,000 volunteers, by following them for four to seven years<sup>13</sup>. The results of this trial are expected in 2020 and will shed light on which Type 2 diabetes drugs are best for glycaemic control.

### Aspirin – what's the story?

Aspirin works by inactivating platelets in the blood, reducing the chances of blood clots forming when a layer of atheroma in the wall of the blood vessel ruptures. But aspirin also has risks. For instance, it increases the chances of serious gastrointestinal bleeding. Currently, NICE advises that only people with existing CVD or at very high risk should take it regularly, because in these groups of people the benefits clearly outweigh the risks of taking the drug.

“In people at risk, such as those who have already had a heart attack or stroke, the benefits of aspirin are clear – their cardiovascular risk reduces by 20 per cent,” says Prof Armitage. “But there’s real uncertainty about whether aspirin could help people with diabetes who have not had a previous cardiovascular event.”

Prof Armitage is leading the ASCEND trial – A Study of Cardiovascular Events in Diabetes<sup>14</sup>, which aims to reduce this uncertainty. It will find out if aspirin, with or without fish oils, reduces the risk of heart disease, or cardiovascular events such as heart attacks or strokes, in people with Type 1 and Type 2 diabetes, and if the benefits outweigh the risks. Volunteers will take a daily 100mg dose of aspirin or a placebo, alongside a fish oil capsule or a placebo. Funded by the British Heart Foundation, the study is the largest trial of its kind, involving 15,480 people from around the UK for an average of 7.5 years.

For a trial such as ASCEND to prove efficacy against cardiovascular risk, it needs to have a certain number of cardiovascular events happening in the people taking part in the trial. “Our challenge is that the background rate of heart attacks and strokes is falling, and the rate in our volunteers was lower than expected, possibly because other cardiovascular disease risk factors are

being kept under control,” says Prof Armitage. “We had to increase the number of people recruited to the trial from 10,000 to 15,000, to ensure we had sufficient statistical power to answer our research question.”

But the hard work has paid off – the team is now in the finishing straight, and is hoping to have the results by early 2018. “This study will confirm if the benefits of aspirin outweigh the risks of bleeding in people with diabetes, and will ultimately help doctors decide if their patients could benefit from a regular dose of aspirin or fish oils,” says Prof Armitage. “We will drill down into our data to find out if certain people will benefit more than others, for example, older people or younger people. ASCEND could help to change clinical guidelines, but I anticipate it will still be about balancing the benefits and risks.”

Alongside cardiovascular disease, ASCEND will tell us if aspirin can also protect against cancer. “People with diabetes are also more likely to develop cancer than people without diabetes,” says Prof Armitage. “Studies suggest aspirin could protect against cancer, particularly in the bowel. But evidence so far is based on *post hoc* data – when data is revisited after the initial study findings have been reported. Because cancer is one of ASCEND’s outcomes, we can study cancer incidence in a prospective way – so we wait in anticipation of these results.”

### Prevention, and the rising diabetes problem around the world

As well as treating diabetes when it is established, treatments could help prevent or slow the development of diabetes and simultaneously reduce cardiovascular risk. The STOP-NIDDM trial suggested that in patients with impaired glucose tolerance, a drug called acarbose could reduce cardiovascular events<sup>15</sup>. With the University of Cambridge MRC Epidemiology Unit and the Leicester Diabetes Centre, the DTU are carrying out a feasibility study called the Glucose Lowering In Non-diabetic hyperglycaemia Trial<sup>1</sup> (GLINT). This trial will study the impact of metformin on

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### LIFESTYLE CHANGES AND LOSING WEIGHT

Lifestyle change is an important aspect of controlling Type 2 diabetes. This has been confirmed by a recent meta-analysis shows that lifestyle intervention can reduce the risk factors associated with CVD in people with the condition<sup>18</sup>. Weight loss is particularly important in this respect, and no round-up of clinical trials in diabetes and heart disease would be complete without mentioning the DiRECT trial, a study which is supported by the largest single research grant that Diabetes UK has ever awarded.

Previously, Professor Roy Taylor and his team at Newcastle University carried out a small study that showed that sticking to a very low calorie diet for eight weeks can reverse Type 2 diabetes<sup>19</sup>. “Weight loss allows individuals to keep fat where it’s meant to be, and not inside the internal organs, where it is harmful,” says Prof Taylor. “We found that in just eight weeks, liver fat and pancreas fat is reduced, and Type 2 diabetes can go into remission. All the volunteers stopped taking their anti-diabetes drugs on day one of the diet, and if remission persists in the long term, it could prevent or delay the long-term damage in different organs in the body.”

The team moved on to DiRECT, with Professor Mike Lean at the University of Glasgow. They are investigating whether substantial non-surgical weight loss using a low energy liquid diet, delivered and maintained within routine NHS care, can be a useful tool to put

Type 2 diabetes into remission, ultimately reducing the risk of cardiovascular disease<sup>20</sup>. “Diabetes is managed by staff in GP surgeries, so we need to find out if the low calorie diet approach is practical and feasible in routine clinical care,” says Prof Taylor.

In the DiRECT study, 280 people with Type 2 diabetes will be allocated to one of two groups – current guideline-based best possible diabetes treatment, or the weight loss intervention. The latter group will begin a low calorie liquid diet of around 800 calories per day for 12 weeks, with an option to continue this until 20 weeks, if they wish. After that, they will gradually return to normal eating, within an overall calorie intake. Both groups will be followed for two years, and some participants will have magnetic resonance scans and insulin secretion tests, to work out how glucose control is returning to normal.

“Recruitment has gone really well, and we hope to complete recruitment this summer,” says Prof Taylor. “This means our one year outcomes could be known as early as autumn 2017.” He hopes this study will provide evidence that weight loss support should be first-line therapy. “To effectively treat diabetes, I think we need 15 per cent weight loss in most people,” he says. “We need a tool for people to change their lifestyle and lose weight that really works in routine clinical practice. This study will reveal if low calorie diets could help more patients with Type 2 diabetes go into remission.”





Under investigation – can fish oils reduce heart risk in diabetes?

cardiovascular outcomes for people with non-diabetic dysglycaemia and who are at high cardiovascular risk in primary care<sup>16</sup>. Funded by the NIHR Health Technology Assessment programme, 250 volunteers will take part. If this is successful, they will recruit around 12,900 people to the full trial to be followed for five to seven years.

And, given that Type 2 diabetes has become a major problem in other countries, such as China, researchers from around the world are carrying out clinical trials in those countries. For example, DTU is carrying out the Acarbose Cardiovascular Evaluation (ACE) to find out if acarbose can replicate the effects of STOP-NIDDM in people with already established Type 2 diabetes<sup>17</sup>.

### An exciting future

It's clearly an exciting time for clinical trial research into diabetes and cardiovascular disease, particularly given that some drugs are now demonstrating superiority over standard care. Future results will help to shape clinical guidelines and advise clinicians how best to treat their patients with diabetes and ameliorate their cardiac risk.



The team at the Newcastle Magnetic Resonance Centre

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