Diabetes and its cardiovascular complications are a major cause of morbidity and mortality in men. Over recent years a plethora of new drugs with novel modes of action have been introduced and tested in clinical trials. In this article the authors look at the results of these trials and discuss how the drugs might help in the battle against diabetes in men.

In 2015, 6.7% of men had doctor-diagnosed diabetes compared to 5.1% of women. The recent report ‘One in ten: the male diabetes crisis’, published by the Men’s Health Forum charity last year, demonstrated that one in ten men in the UK now have either type 1 or type 2 diabetes mellitus (T2DM), and the incidence is predicted to triple over the next 30 years. Men are more likely to be overweight and to develop T2DM than women, and they do so at younger ages and lower average weights. Men are also more likely to suffer diabetic complications. The data showed that 59.6% of those who see a healthcare professional with a foot ulcer are men and that they are twice as likely as women to require amputation. More men die, and die prematurely, as a result of diabetes.

Cardiovascular (CV) disease is the major threat to people with diabetes. It accounts for more than 50% of deaths in this population and leads to a 12-year reduction in the life expectancy of a 60-year-old male patient with T2DM and CV disease, compared with the general population.

Until now, attempts to lower CV risk by means of glucose-lowering treatment alone have proved disappointing. Early trials suggested that this was possible, but subsequent research was unable to verify the original observations and concerns arose that some glucose-lowering drugs could actually cause cardiovascular harm. This led to demands for mandatory CV outcome trials, a large number of which have now been performed or are ongoing. Some of the key findings of these trials include some surprising and highly rewarding benefits of the sodium glucose transporter 2 (SGLT2) inhibitors and the glucagon-like peptide-1 (GLP-1) agonists.

However, we must not forget that metformin, a guanidine derivative that was found in the French lilac Galega officinalis more than 50 years ago, remains the most widely used drug for the treatment of T2DM, and continues to be recommended by major clinical guidelines as first-line therapy and in combination with any other blood glucose-lowering drugs.

Metformin’s hypoglycaemic effect stems from an insulin-sensitising action on both the liver, resulting in decreased glucose release, and to a lesser extent on the peripheral tissues, where it increases glucose uptake. A recent paper looks at the effect of metformin on epigenomics, microRNA levels and subsequent...
gene expression in diabetes and its potential clinical implications. A recent review of metformin's effects on the heart and the CV system concluded that the overall evidence accumulated from both clinical trials and real-world registry favours a protective effect of metformin relating to both coronary events and progression to heart failure. In light of this potential, its efficacy, safety and low cost, metformin should remain the mainstay of T2DM therapy.

Second-line antidiabetic therapy
The effect of novel second-line antidiabetic therapy on CV risk has been examined in many trials, but it is important to appreciate that:

- Most of these trials were designed to demonstrate non-inferiority and did not therefore have the statistical power to reliably detect potentially significant benefit.
- All these trials used a composite primary endpoint (eg CV death, non-fatal myocardial infarction and non-fatal stroke). While this approach improves the statistical power of the study, it has many drawbacks. For example, it is possible that intervention may increase one element of a composite endpoint and reduce another, producing a null effect overall. Equally, it is self-evident that some elements of a composite endpoint, most notably death, should carry more weight than others (eg hospitalisation for heart failure).
- Almost all of these trials were placebo-controlled and do not therefore directly address the question of which drug to select from the many options once metformin monotherapy and optimum CV risk factor reduction (blood pressure control, statin therapy, etc) have been initiated. Indeed, only direct comparisons of equipotent drug regimens can do this.
- The inclusion criteria differed greatly. Most trials only included patients with T2DM who either had or were deemed to be at high risk of developing CV disease. The results cannot therefore be easily extrapolated to lower-risk subjects.
- The drugs being evaluated have numerous pleiotropic effects, so it should not be assumed that any changes in CV outcome are mediated by lowering blood sugar. On the other hand, a specific cardiovascular effect can only be inferred if both arms of a study produce equally good diabetic control. It may also be difficult to determine if the observed effects apply to all drugs in the same class.

Obviously, CV outcomes are not the only consideration in choosing a diabetes drug and differences in blood glucose-lowering, side-effect profiles, and cost and convenience must all be factored into decision-making. Nevertheless, in spite of these reservations, it seems clear that there are important differences in the likely impact of common diabetes therapies on cardiovascular risk that should influence therapeutic choices.

Sulfonylureas
The sulfonylureas (eg glipizide, glibenclamide) are the most commonly prescribed class of oral agents after metformin and offer a well-tolerated means of lowering blood glucose concentrations.

Some randomised controlled trials have reported that sulfonylurea treatment is associated with higher rates of CV events when compared to metformin. However, it is not clear if this reflects the hazards of sulfonylurea therapy or the specific benefits of metformin.

The sulfonylureas lower blood glucose by stimulating pancreatic beta cell insulin secretion. It is conceivable that they may promote CV events by inducing recurrent hypoglycaemia with secondary increases in heart rate, vascular inflammation, platelet aggregation and pro-arrhythmia.

Thiazolidinediones
Although these antidiabetic drugs were introduced in the late 1990s, fears that they may increase CV risk did not emerge until 2007 when a meta-analysis of 42 trials of rosiglitazone therapy reported higher rates of myocardial infarction (MI) (odds ratio [OR] 1.43; 95% confidence interval [CI] 1.03–1.98; \( p=0.03 \)) and CV death (OR 1.64; 95% CI, 0.98–2.74; \( p=0.06 \)). This triggered intense debate and prompted the FDA to introduce stringent proof of CV safety for new antidiabetic agents; it also led to a huge reduction in the use of rosiglitazone and numerous follow-up studies.

There is now no doubt that the PPAR-gamma agonists rosiglitazone and pioglitazone both substantially increase the risk of heart failure by promoting potentially reversible fluid retention. However, it is not clear if this has important adverse long-term consequences. Moreover, the impact of these drugs on other CV endpoints is not so clear.

In the RECORD trial, rosiglitazone increased the risk of heart failure but did not significantly increase the risk of death, MI or stroke. Unfortunately, the validity of these findings has been questioned because the overall event rate in this study was much lower than expected.

In contrast to rosiglitazone, pioglitazone, has never been reported to increase the risk of MI or other macrovascular adverse events. Indeed, a large CV outcome trial (PROactive) reported a borderline significant reduction in the composite of MI and stroke (hazard ratio [HR] 0.90, 95% CI 0.80–1.02), albeit with a substantial increase in...
severe heart failure events (HR 1.41; 95% CI 1.10–1.80; p<0.007).\textsuperscript{16}

Moreover, pioglitazone has numerous potentially beneficial effects on important CV risk factors (eg insulin sensitivity, blood pressure, triglycerides, HDL cholesterol, and markers of inflammation) in addition to lowering plasma glucose and, interestingly, was reported to reduce the composite risk of stroke and MI in a study of non-diabetic patients with a history of recent stroke or transient ischaemic attack.\textsuperscript{17}

**SGLT 2 inhibitors**

These drugs (empagliflozin, canagliflozin, and dapagliflozin) lower blood glucose by increasing urinary glucose excretion and have been reported to improve many CV risk factors, including blood pressure, body weight, visceral adiposity, hyperinsulinemia, albuminuria, serum uric acid and oxidative stress. Not surprisingly, the use of these drugs is also associated with higher rates of urinary and genital infection.

In the EMPA-REG trial, empagliflozin was reported to reduce CV death by 38% (3.7% versus 5.9%) (Figure 1) and all-cause death by 32% (5.7% versus 8.3%).\textsuperscript{18} Heart failure hospitalisations were significantly decreased by 35% (2.7% versus 4.1%). Treatment with empagliflozin was also associated with a marked reduction in incident or worsening nephropathy and modest reductions in weight and blood pressure, but there was no apparent effect on rates of lower limb amputation, MI or stroke.

Canagliflozin was found to have similar effects in the CANVAS trial, including a 14% reduction in the primary endpoint of CV death, non-fatal MI or non-fatal stroke, a 22% reduction in death from CV causes or hospitalisation for heart failure, and a 40% reduction in worsening nephropathy.\textsuperscript{19} In contrast to the EMPA-REG trial, amputation risk was increased in the canagliflozin cohort (6.3 versus 3.4 participants per 1000 patient-years; HR 1.97; 95% CI, 1.41–2.75). Treatment with empagliflozin was also associated with a marked reduction in incident or worsening nephropathy and modest reductions in weight and blood pressure, but there was no apparent effect on rates of lower limb amputation, MI or stroke.

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primary outcome of cardiovascular death, non-fatal MI and non-fatal stroke (HR 0.74; 95% CI 0.51–0.95). However, this result was largely driven by lower rates of non-fatal stroke and non-fatal MI with little or no effect on mortality.

Both of these studies reported a reduction in nephropathy events and little or no effect on heart failure events. Semaglutide but not liraglutide treatment was associated with an increase in incident retinopathy that merits further investigation. In contrast to these studies, a third large clinical trial of the GLP-1 agonist lixisenatide was negative. The mechanism of the potentially important CV benefits of GLP-1 agonists is not clear but is probably multifactorial. Moreover, it appears to be quite distinct from the action of the SGLT2 inhibitors: the event curves certainly take longer to diverge and most of the benefits appear to be associated with atheroma-related events as opposed to some form of myocardial protection. Weight loss is likely to be an important factor and there is growing interest in the potential to use these drugs to treat obesity.

**Dipeptidyl peptidase-4 (DPP-4) inhibitors**

The DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin and sitagliptin) prevent the breakdown of endogenous incretins and, like the GLP-1 agonists, increase insulin and decrease glucagon levels. They can, however, be given orally and do not inhibit gastric emptying.

Three large CV outcome trials among patients with T2DM and high CV risk have reported neutral effects on their primary composite endpoints (HR of 0.96, 1.00 and 0.98 for alogliptin, saxagliptin, and sitagliptin, respectively) (Table 1). There is, however, some evidence, most notably from the SAVOR-TIMI 53 trial, that these agents may increase the risk of hospitalisation for heart failure.

On the other hand, observational studies and meta-analyses have consistently suggested that DPP-4 inhibitors may produce better CV outcomes than sulfonylureas. The results of CAROLINA (a CV outcome trial comparing linagliptin with glimperide), due later this year, are therefore eagerly awaited.

**Conclusions**

In the past, the treatment of diabetes has focused on glycaemic control and the prevention of microvascular disease using treatment strategies designed to lower glycaated haemoglobin levels, minimise hyperglycaemia-related symptoms, such as polyuria, and reduce the risk of developing microvascular complications, namely retinopathy, nephropathy and neuropathy. In contrast, the prevention of macrovascular events has been addressed by targeting other CV risk factors, particularly hyperlipidaemia and hypertension, with a major emphasis on the use of ACE inhibitors, angiotensin-receptor blockers and statins.

The results of the CV outcome trials discussed in this article offer exciting new possibilities. At present, a combination of metformin, pioglitazone, an SGLT2 inhibitor and liraglutide appears to be the optimal cocktail of medications for improving both glycaemic control and CV outcomes for people with T2DM at high CV risk. Such a combination may not only prevent CV events, but may also save lives.

Nevertheless, treatment strategies must take account of many factors, including renal function, weight and side-effects, and will undoubtedly evolve as the results of new trials become available.

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**References**

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<th>Study (year published)</th>
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<tr>
<td>PROACTIVE (2005)(^{15})</td>
<td>Pioglitazone vs placebo</td>
<td>5238</td>
<td>No significant difference in the primary endpoint composite of all-cause mortality, non-fatal myocardial infarction (MI), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries (HR 0.90; 95% CI 0.80–1.02, (p=0.095)). Significant reduction in the secondary endpoint composite of all-cause mortality, non-fatal MI and stroke (HR 0.84; 95% CI 0.72–0.98; (p=0.027)). Significant increase in serious heart failure events (5.7% vs 4.1%; (p=0.007)) but no excess mortality among these heart failure patients.</td>
</tr>
<tr>
<td>RECORD (2009)(^{14})</td>
<td>Rosiglitazone + metformin/sulfonylurea vs metformin + sulfonylurea</td>
<td>4447</td>
<td>No difference in the primary endpoint of CV hospitalisation or CV death (non-inferiority margin 1.20). Higher rates of heart failure and fracture, lower rates of MI and stroke.</td>
</tr>
<tr>
<td>EMPA-REG (2015)(^{17})</td>
<td>Empagliflozin vs placebo</td>
<td>7020</td>
<td>CV death reduced by 38% (3.7% vs 5.9%) and all-cause death by 32% (5.7% vs 8.3%). Heart failure hospitalisations decreased by 35% and new onset or worsening nephropathy was reduced by 35%.</td>
</tr>
<tr>
<td>CANVAS (2017)(^{18})</td>
<td>Canagliflozin vs placebo</td>
<td>10 142</td>
<td>Composite of CV death, non-fatal MI and non-fatal stroke (MACE) reduced by 14% ((p&lt;0.001) for non-inferiority; (p=0.02) for superiority). 27% reduction in progression of albuminuria and 97% increase in amputations.</td>
</tr>
<tr>
<td>LEADER (2016)(^{23})</td>
<td>Liraglutide vs placebo</td>
<td>9540</td>
<td>Significant reductions in all-cause death (HR 0.85; 95% CI 0.74–0.97) and MACE (HR 0.87; 95% CI 0.66–0.93).</td>
</tr>
<tr>
<td>SUSTAIN 6 (2016)(^{24})</td>
<td>Semaglutide vs placebo</td>
<td>3297</td>
<td>Significant reduction in MACE (HR 0.74; 95% CI 0.51–0.95) but not all-cause or CV death alone.</td>
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<td>ELIXA (2015)(^{25})</td>
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<td>EXAMINE (2013)(^{26})</td>
<td>Alogliptin vs placebo</td>
<td>5380</td>
<td>No difference in major CV endpoints (MACE)</td>
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<td>SAVOR TIMI 53 (2013)(^{27})</td>
<td>Saxagliptin vs placebo</td>
<td>16 492</td>
<td>No difference in MACE. Increased hospitalisation for heart failure (3.5% vs 2.8%)</td>
</tr>
<tr>
<td>TECOS (2015)(^{28})</td>
<td>Sitagliptin vs placebo</td>
<td>14 671</td>
<td>No difference in MACE</td>
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</table>

Table 1. Major randomised placebo-controlled clinical trials reporting the effects of novel antidiabetic therapy on cardiovascular outcomes (CV) in type 2 diabetes mellitus


