Cardiovascular impact of new drugs (GLP-1 and gliflozins): the ABCD position statement

ANSU BASU,[1] DIPESH PATEL,[2] PETER WINOCOUR,[3] ROBERT EJ RYDER[1]

Abstract

The glucose intolerance of diabetes aggravates atherosclerosis indirectly through its effect on lipids and endothelial function. The cardiovascular (CV) impact of this metabolic disturbance is seen in the worsening of atherosclerotic vascular disease predominantly manifest as progression of coronary and cerebrovascular disease. The microvascular changes induced by prolonged glucose intolerance lead to ultrastructural changes in the glomerular basement membrane and renal mesangium which alters intrarenal haemodynamics, which may become evident initially as proteinuria and later lead to a decline in glomerular filtration rate. As the kidney plays a central role in blood pressure control, these changes have far-reaching CV consequences in patients with diabetes.

Despite this, glucose lowering has been shown to have only a modest impact on CV outcomes in diabetes. The new antidiabetic medications have been studied in clinical trials designed to assure safety as grounded in the FDA guidance of 2008. Whilst a direct comparison of results from these trials is not possible in view of heterogeneity in trial design, the individual CV outcome measures have broadly re-defined their role in terms of equivalence (non-inferiority) and/or benefit (superiority). The composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke (major adverse cardiovascular events, MACE) may be perceived as surrogate markers for atherosclerotic cardiovascular disease (ASCVD). This has been universally accepted as the primary endpoint in these cardiovascular outcome trials (CVOTs) and has been helpful in understanding the possible CV impact these drugs may have on patients with diabetes.

The dipeptidyl peptidase 4 (DPP-IV) inhibitors (sitagliptin, alogliptin, saxagliptin, linagliptin), two sodium-glucose co-transporter 2 (SGLT2) inhibitors (dapagliflozin and ertugliflozin) and two glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1 RA) drugs (lixisenatide and extended-release exenatide) have demonstrated non-inferiority on MACE outcomes with comparators – that is, they have assured CV safety when used in conjunction with other glucose-lowering treatment to improve glycaemic control. Four GLP-1 agonists (liraglutide, albiglutide, semaglutide and dulaglutide) and two SGLT2 inhibitors (empagliflozin and canagliflozin) have demonstrated CV benefit on MACE outcomes; such demonstration of superiority may be seen as evidence for benefit. The SGLT2 inhibitors canagliflozin, empagliflozin, dapagliflozin and ertugliflozin have all demonstrated a significant benefit in reducing the risk of hospitalisation due to heart failure (HHF) as a secondary/exploratory outcome measure in their CVOTs. Further confirmation of benefit in heart failure (HF) independent of the presence of glucose intolerance has been demonstrated with dapagliflozin and empagliflozin in HF patients with or without diabetes. Dapagliflozin remains the only SGLT2 inhibitor that has shown benefit both in patients with established HF with reduced ejection fraction (HFrEF) and in those with CKD and proteinuria, even in the absence of diabetes in separately designed CV outcome trials. However, a comparable benefit in heart failure has not so far been seen in studies with the DPP-IV inhibitors or GLP-1 receptor agonists. Albiglutide is not available in the UK and may have little relevance to the practising clinician other than through the information it contributes about the possible mechanisms of action of GLP-1 RA medications.

Br J Diabetes 2021;**21**:132-148

Key words: CVOT, cardiovascular outcome trials, cardiovascular disease, type 2 diabetes, position statement

[1] Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK
[2] Royal Free NHS Foundation Trust, London, UK
[3] East & North Hertfordshire NHS Trust, Welwyn Garden City, UK

Address for correspondence: Dr Ansu Basu
Diabetes and Endocrine Unit, City Hospital, Dudley Road, Birmingham B18 7QH, UK
E-mail: ansu.basu@nhs.net

https://doi.org/10.15277/bjd.2021.283

Recommendations

DPP-IV inhibitors

- Saxagliptin has a neutral effect on CV risk; it increases the risk of heart failure (HF), which precludes its use in those at increased risk of HF [SAVOR-TIMI 53].
- Alogliptin had a numerically higher number of patients hospitalised with heart failure (HHF), but did not demonstrate an increased risk of HF in the post hoc analysis. The drug SPC advises caution in patients with NYHA III and IV stages of HF and is therefore best avoided in such situations. Importantly though, alogliptin is the only DPP-IV inhibitor to have demonstrated safety in patients after an acute coronary syndrome (EXAMINE).
- There is no restriction with the use of sitagliptin in patients with HF and, given its extensive clinical trial information including a prolongation of the time to insulin dependence, it appears to be a safe and reliable DPP-IV inhibitor (TECOS). Similarly, linagliptin may be used to improve glycaemic control without

concerns for CV safety or HF (CARMELINA, CAROLINA); it is also licensed regardless of the state of renal function.
- A systematic review of clinical trials and observational studies suggest that there is an overall excess risk of HF with DPP-IV inhibitors in individuals with pre-existing cardiovascular disease (CVD), although this meta-analysis was largely driven by the increased incidence of HF seen in SAVOR-TIMI 53.
- **The ABCD position is to exercise caution in patients with HF as other therapeutic agents such as SGLT2 inhibitors have clearly demonstrated benefit. Sitagliptin, alogliptin and linagliptin are all safe in patients with pre-existing CVD – alogliptin particularly so in patients after acute coronary syndrome and linagliptin in patients with renal impairment.**

GLP-1 RA
- All the GLP-1 RAs can be used safely to improve glycaemic control without having any adverse effect on CVD or HF.
- Lixisenatide is safe to use in patients following acute coronary syndrome but is unlikely to provide additional CV benefit in this situation.
- The evidence supports CVD benefit for liraglutide in patients with pre-existing CVD and also those with high risk for CVD. A dose of 1.8 mg once daily should be used to get the full benefit of such an effect.
- Semaglutide offers benefit by reducing the risk of CVD in patients with pre-existing CVD and also those with high risk for CVD, but given uncertainty regarding the yet unknown risk of worsening retinopathy in association with rapid improvement in glucose control, caution must be exercised in patients with significant diabetic retinopathy.
- Prolonged release exenatide is safe to prescribe in patients with pre-existing CVD but lacks definitive clinical trial evidence that it can offer cardioprotection from future CVD events.
- Dulaglutide reduces CV outcomes to a similar degree in patients with established CVD and those at high risk.
- Dulaglutide and semaglutide both offer reduction in non-fatal stroke.
- The increase in heart rate associated with trials with GLP-1 RA is still not clearly understood.
- Currently, albiglutide is not available in the UK
- **The ABCD position based on existing data is to consider the use of a long-acting GLP-1 RA – in particular, semaglutide 1 mg once weekly, dulaglutide 1.5 mg once weekly or liraglutide 1.8 mg daily – in patients with pre-existing CVD or CVD risk if tolerated by the patient. Lixisenatide and prolonged-release exenatide are both safe in patients with pre-existing CVD and lixisenatide in patients following acute coronary syndrome. These two drugs will help lower HbA_{1c} and promote weight loss but may not confer additional CVD benefits.**

SGLT2 inhibitors
- Canagliflozin and empagliflozin offer CV benefit; additionally, empagliflozin offers reduction in CV death and all-cause mortality. Evidence of which has not been demonstrated with canagliflozin or dapagliflozin. The latter may be due to trial design with a reduced number of patients with pre-existing CVD.
- Both dapagliflozin 10 mg daily and canagliflozin 100 mg daily have been shown to provide reno-protection by reducing the composite endpoints of decline in glomerular filtration rate, progression to end-stage renal disease or death from renal or CV causes in patients with established chronic kidney disease. The two drugs also reduced the incidence of HHF in such patients.
- Ertugliflozin, alongside the other SGLT2 inhibitors canagliflozin, dapagliflozin and empagliflozin, will reduce the risk of incipient HF.
- Whether a reduction in bone density is a class effect among SGLT2 inhibitors remains to be seen; a putative mechanism for bone loss and fracture risk needs to be ascertained. We suggest exercising caution in the elderly.
- Additionally, both dapagliflozin and empagliflozin have shown benefit in patients with established HF even in the absence of diabetes. NICE has recently issued support for the use of dapagliflozin as an add on in this situation and is considering the same for empagliflozin.
- **The ABCD position is to use canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin in patients with pre-existing CVD and type 2 diabetes.**
  - **In patients with established CVD either canagliflozin, dapagliflozin or empagliflozin should be considered after metformin.**
  - **In the presence of chronic kidney disease, the first choice should be dapagliflozin 10 mg once daily which has shown benefit in patients with CKD and macroalbuminuria with or without diabetes; canagliflozin 100 mg has proven benefit in patients with type 2 diabetes. SGLT2 inhibitors should not be used in patients with CKD and type 1 diabetes.**
  - **Dapagliflozin and empagliflozin have shown significant benefits in patients with established heart failure (HFrEF, NYHA II-IV), independent of the presence of diabetes**.

Introduction

Type 2 diabetes is a form of atherosclerotic cardiovascular disease (ASCVD) where vascular dysfunction is aggravated by glucose intolerance and concomitant secondary dyslipidaemia. The manifestations of ASCVD such as myocardial infarction and stroke remain the major cause of morbidity and mortality in patients with diabetes.[1,2] Hypertension and dyslipidaemia are the major determinants of the macrovascular changes seen in ASCVD; additionally, diabetes with the inevitable changes in the microvasculature is in itself an independent risk factor for the development of ASCVD.[3]

Cardiovascular (CV) events such as myocardial infarction and stroke linked to glucose intolerance may precede the onset of type 2 diabetes by several years,[4] but tends to occur after long-standing disease in individuals with type 1 diabetes.[5] The contri-

bution of glucose-lowering strategies to reduce CV events in patients with diabetes is only modest compared to lipid lowering with statins and the control of blood pressure.[6] Despite this, improvement in glycaemic control is still necessary to improve CV outcomes; a meta-analysis of 13 prospective cohort studies including UKPDS showed that, for every 1 percentage point increase in HbA_{1c}, the relative risk for any CV event was 1.18 (95% CI 1.10 to 1.26).[7] Further, the benefits of intensive glucose lowering in improving microvascular endpoints remains consistent across a wide variety of clinical trials.

HF is a clinical syndrome that may occur with preserved ejection fraction (LVEF ≥50%) or with reduced ejection fraction (LVEF <40%). In both states, symptoms of HF are present. In individuals with HF and preserved ejection fraction (HFpEF), left ventricular volumes are normal but there is evidence of diastolic dysfunction – an abnormal pattern of left ventricular filling with elevated filling pressures; this is also referred to as diastolic HF.[8] In HFrEF, the LVEF is reduced and left ventricular volume is increased; this is also referred to as systolic HF. Importantly, though, HF in an individual with diabetes may be completely independent of the presence of coronary heart disease.[9] Diabetic cardiomyopathy, which is manifest as left ventricular systolic and/or diastolic dysfunction in the absence of a recognised cause such as coronary heart disease or hypertension,[10] is believed to be due to a myriad of reasons such as microcirculatory dysfunction, accumulation of advanced glycation end products which increases ventricular muscle stiffness, altered intermediary metabolism in cardiac muscle due to decreased insulin sensitivity and/or availability, upregulation of the renin-angiotensin system and autonomic dysregulation.[8]

The prevalence of HF increases with age[11] and is higher in patients with diabetes than in those without the disease.[12] In patients with stable coronary heart disease, diabetes and glycaemic control appear to be independent risk factors for new-onset HF.[13] Despite this, it appears that HF as a CVD outcome is often ignored in diabetes.[14]

Chronic kidney disease (CKD) is an independent risk factor for CVD; there is a graded relationship between declining glomerular filtration rate (GFR) and the risk of death, CV events and hospitalisation for heart failure (HHF), independent of the presence of diabetes.[15–17] Increased albumin excretion, as measured by an elevated albumin-creatinine ratio (ACR) and a decline in GFR, together multiplicatively increase mortality.[18] These changes in GFR and ACR become particularly relevant in the context of diabetes as CKD remains a common complication in both type 1[19] and type 2 diabetes.[20,21]

Background to the design of cardiovascular outcome trials (CVOTs) for the use of antidiabetic drugs

In December 2008 the FDA (Food and Drug Administration, Rockville, Maryland) issued guidance to the pharmaceutical industry focusing on the CV safety of the development of antidiabetic drugs in the future.[22] This was against a backdrop of questionable safety of previous drugs, particularly the thiazolidinedione rosiglitazone.[23] Further, at the time, the CV safety of antidiabetic drugs had not been clearly established. Subsequently, similar expectations were also placed by the EMEA (European Medicines Agency, London, UK).[24]

Most pharmaceutical agents have traditionally been evaluated in a superiority setting, where an experimental treatment or drug has been shown to be superior to the control or placebo treatment. In such a randomised clinical trial (RCT) design it is easy to determine if the experimental drug or treatment is better than control when the results are found to be statistically significant. If the results are, however, not statistically significant, the experimental drug can no longer claim better performance; it can neither claim equivalence nor non-inferiority. In a clinical setting this means we are trying to establish whether one agent is more efficacious than the other. Superiority of one drug over another might not always be the case, especially if the drugs being compared belong to the same class or bear structural homology. Additionally, a statistically insignificant result may be misinterpreted as lack of evidence.

Prior to the FDA/EMEA mandate, antidiabetes medications were approved on the basis of glycaemic efficacy over a 6–12-month phase 2/3 RCT. These trials selected young patients with a short duration of diabetes resulting in a low CVD event rate. Pooled data from such trials are bound to generate inconsistency.

The standard statistical methods used in clinical trials cannot be used to test for non-inferiority trials. Despite this, demonstrating non-inferiority is very important if we want to know if one treatment is as good as another treatment, especially if the former had previously been shown to be an effective form of treatment. The intent therefore is to demonstrate that the drug or treatment being evaluated is not materially worse than the control. For this reason, a one-sided test at an alpha value of 0.025 is of interest in testing the non-inferiority hypothesis. To test for non-inferiority, the statistical tests for hypothesis are adapted and the confidence interval boundaries are often pre-specified by the FDA or EMEA as what would be an acceptable boundary value for a particular group of pharmaceutical products.

The concept around CVOTs was to evaluate CV safety as event-driven trials of the newer antidiabetic drugs and not to evaluate glycaemic efficacy as this had been previously established in short-term phase 2 and 3 RCTs. In line with this, the FDA and EMEA specified that the pre-specified upper limit of the 95% confidence interval for the hazard ratio for major adverse CV events (MACE) for new diabetes drug trials should be 1.3 to demonstrate non-inferiority and exclude unacceptable CV risk. It also specified that all MACE events should be adjudicated by an independent committee and the clinical trials should include patients with an acceptable CV risk. Once the non-inferiority hazard ratio (HR) threshold <1.3 is achieved, further sequential analyses were allowed to show superiority or any potential CV benefit.[25,26]

Cardiovascular impact of the older antidiabetic drugs

Earlier antidiabetic drugs were not subject to the rigorous scrutiny put forward by the FDA and EMEA in demonstrating CV safety, as has been the case with the newer agents; these are summarised below.

Metformin

Metformin does not appear to have an adverse CV profile and appears to decrease CVD events in certain populations. In the United Kingdom Prospective Study (UKPDS), 342 overweight subjects demonstrated a 39% (p=0.01) relative risk reduction compared with 411 controls for myocardial infarction, which was maintained over the post-interventional 10-year follow-up period.[27,28]

Sulfonylureas

Sulfonylureas are the most widely used drugs for the treatment of type 2 diabetes. They are inexpensive and are associated with modest weight gain. Their continued use as a cost-effective treatment option in type 2 diabetes has been ratified in the 2018 Joint ADA-EASD Consensus Report on the management of hyperglycaemia in type 2 diabetes.[29] The CV effects of sulfonylureas have previously been questioned in the absence of properly designed cardiovascular outcome trials (CVOTs).[30] The CVD concerns with sulfonylureas are likely to be due to glibenclamide; gliclazide and glimepiride have been shown to carry a low risk of all-cause and CV mortality.[31] The safety of gliclazide has been shown in the ADVANCE trial where there was no evidence of excess mortality or adverse CV outcomes,[32] and that of glimepiride in the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA) trial where patients on 4 mg glimepiride did not demonstrate excess CV mortality or any increase in all-cause mortality compared with linagliptin which had previously demonstrated CV safety.[33]

Meglitinides

There are no long-term studies of the meglitinides repaglinide or nateglinide to assess CV outcomes or mortality in patients with type 2 diabetes.

Acarbose

Analysis of the CVD events in the STOP-NIDDM trial of patients with impaired glucose tolerance showed 49% relative risk reduction in the incidence of the composite of any CV event with acarbose (HR 0.51, 95% CI 0.28 to 0.95; p=0.03).[34] Similarly, the Acarbose Cardiovascular Evaluation (ACE) trial conducted solely in China did not show any reduction in the 5-point MACE with acarbose in patients with impaired glucose tolerance (HR 0.98, 95% CI 0.86 to 1.11).[35]

Thiazolidinediones

A meta-analysis of rosiglitazone in 2007 by Nissen *et al* suggested a 43% increased risk of myocardial infarction and a 64% increased risk of CV death which was not statistically significant.[23] A subsequent study, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent combination therapy for type 2 Diabetes (RECORD),[36] designed to address the CV safety of the drug did not confirm the earlier findings and subsequently the FDA lifted its prescription restrictions on rosiglitazone. More recent evidence has also dismissed concerns about excess risks of myocardial infarction.[37,38] Pioglitazone has a more favourable lipid profile than rosiglitazone, with significantly greater reductions in triglyceride and LDL-cholesterol levels and an increase in HDL-cholesterol levels. It also produces a reduction in LDL particle size and LDL particle concentration.[39] In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) trial, the addition of pioglitazone to other glucose-lowering drugs demonstrated a significant reduction in the secondary endpoint of all-cause mortality, non-fatal myocardial infarction and stroke (HR 0.84, 95% CI 0.72 to 0.98; p=0.027). The primary composite endpoint of all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries and amputation above the ankle did not reach statistical significance (HR 0.90, 95% CI 0.80 to 1.02; p=0.095).[40] In support of the vascular effects of pioglitazone, a further two RCTs have suggested that pioglitazone slows down or may even reverse the atherosclerotic process.[41,42] It has been suggested that this effect of pioglitazone on the atherosclerotic process could have significantly impacted the amount of surgical intervention in coronary and leg arteries that was part of the primary composite endpoint in the PROactive clinical trial. This would have made the primary composite endpoint less robust in ascertaining whether pioglitazone did produce any CV benefit.[43,44] The secondary endpoint is similar to the 3-point MACE used in the majority of CVOTs and may therefore be a more reliable indicator of the true effect of the drug. Further analysis of the PROactive study demonstrated that pioglitazone significantly reduced the chances of patients who have had a myocardial infarction from having a further myocardial infarction (HR 0.72, 95% CI 0.52 to 0.99; p=0.045),[45] and that it significantly reduced the chances of patients who have had a stroke from having a further stroke (HR 0.53, 95% CI 0.34 to 0.85; p=0.0085).[46] In a meta-analysis of 19 RCTs, pioglitazone-treated patients had significantly lower rates of death, myocardial infarction and stroke compared with those receiving control therapy.[47] In the Insulin Resistance after Stroke (IRIS) trial, pioglitazone significantly reduced the risk of the primary composite outcome of fatal or non-fatal stroke or fatal or non-fatal myocardial infarction in patients with insulin resistance but without diabetes (HR 0.76 for pioglitazone, 95% CI 0.62 to 93; p=0.007). Pioglitazone also reduced the risk of developing diabetes from impaired glucose tolerance.[48] In a more recent pragmatic clinical trial, Effects on the Incidence of Cardiovascular Events of the Addition of Pioglitazone versus Sulfonylureas in patients with Type 2 diabetes inadequately controlled with metformin (TOSCA.IT), the incidence of CV events was similar with sulfonylureas (glimepiride 48%, gliclazide 50% and glibenclamide 2%) or pioglitazone as add-on to metformin in patients with type 2 diabetes inadequately controlled with metformin alone (HR 0.96, 95% CI 0.74 to 1.26; p=0.79). The rates of HF, bladder cancer and fractures were not found to be significantly different between the treatment groups.[49] Nevertheless, this was a pragmatic study and does not carry the level of evidence that would come from a RCT.

The accumulated evidence from clinical trials favours the use of pioglitazone as a drug with CV benefit.

Cardiovascular impact of the newer antidiabetic drugs based in cardiovascular outcome trials (CVOTs)

Design of CVOTs

To date, 17 CVOTs of the newer diabetes agents have been

published. It is worth considering the following points when results from these trials are critically appraised:

- The CVOTs were designed to rule out unacceptable CV risk through demonstration of non-inferiority in hazard, but some were powered to estimate for superiority by sequential testing after non-inferiority had been demonstrated. The requisite was to demonstrate non-inferiority in all cases. This necessitated that the upper limit of the two-sided confidence interval of <1.3 had been first achieved.
- The CVOTs were designed to achieve 'glycaemic equipoise' between treatment and placebo, although invariably a modest improvement in glycated haemoglobin was seen at the end of the trial in the treatment cohort.
- Some trials have recruited largely based on a secondary prevention strategy including 99–100% of subjects with established CVD, whilst other trials have included a substantial number of individuals with multiple risk factors without established CVD (primary prevention). Even within the latter group, the inclusion of patients with established CVD ranged from 41%[50] to 82%.[51] This variation in patient selection is likely to have impacted the final outcome and should be borne in mind when these results are generalised in clinical care. In trials where a large proportion of patients have established ASCVD, accrual of a sufficient number of events is likely to occur sooner as more participants would have already had a prior CV event and therefore are more likely to be followed by another one.[52]
- The 3-point MACE (Major Adverse Cardiovascular Event), which is a composite outcome measure for CV death, non-fatal myocardial infarction and non-fatal stroke has been used as a primary outcome measure for ASCVD in the intention-to-treat (ITT) population in all trials except in Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes (TECOS)[53] and Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome (ELIXA)[54] where a 4-point MACE was adopted with the inclusion of hospitalisation for unstable angina as an additional primary outcome measure.
- Statin usage has been more than 75% across the clinical studies. Similarly, aspirin usage ranged from 60% to 97%.
- Two trials, Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes (EXAMINE)[55] and Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome (ELIXA)[54] recruited patients between 15 and 90 days and within 180 days of acute coronary syndrome, respectively. Consequently, aspirin and statin usage were >90% in each of the trials, which was greater than in the other CVOTs. The target would be to identify individuals who could have another event soon after a recent coronary event. Whilst it can be argued that accrual of subsequent events would be easier in such a scenario, it is equally possible that a smaller number of events would become the reality given that most patients would have received some form of therapeutic percutaneous coronary intervention as part of standard care.
- HF is a critically important measure of CV outcome which is independent of ASCVD in patients with diabetes.[12] All the published CVOTs to date have included hospitalisation for heart failure (HHF) as a critical secondary endpoint to assure CV safety of the drug.
- Separately, two studies have evaluated the use of SGLT2 inihibitors in patients with established HF with or without diabetes.[56,57]
- Canagliflozin and dapagliflozin have CVOTs explicitly in patients with CKD and type 2 diabetes; more importantly the trial involving dapagliflozin also included patients without diabetes.[58,59]

Individual CVOTs

DPP-IV inhibitors

The DPP-IV inhibitors are structurally dissimilar – sitagliptin, saxagliptin and vildagliptin are classed as peptidomimetic agents while alogliptin and linagliptin are grouped as non-peptidomimetic drugs. There appears to be some structural homology between saxagliptin and vildagliptin.[60] DPP-IV inhibitors prevent the degradaton of endogenous GLP-1 by blocking the action of DPP-IV, thereby allowing GLP-1 to modulate postprandial insulin release and concomitant inhibition of glucagon release.[61]

The CVOTs on the DPP-IV inhibitors that have been completed to date are Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53),[62] Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE),[55] Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS),[53] A Study to Assess Cardiovascular Outcomes Following Treatment With Omarigliptin [MK-3102] in Participants With Type 2 Diabetes Mellitus [MK-3102-018] (OMNEON),[63] Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA)[64] and CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA).[33]

A summary of the completed CVD outcome trials with DPP-IV inhibitors is presented in Table 1.

Vildagliptin

There does not seem to be any specific CVD outcome study with vildagliptin. In a small clinical study, Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure: A Randomized Placebo-Controlled Trial (VIVIDD) involving 254 patients with type 2 diabetes and prior history of HF (NYHA I–III), vildagliptin was found to increase the left ventricular end diastolic and end systolic volumes but had no effect on left ventricular ejection fraction,[65] suggesting a possible risk of fluid retention with this drug.

Saxagliptin

In the SAVOR-TIMI 53 trial, 16,492 patients with type 2 diabetes and either a history of CVD or multiple risk factors for vascular disease were randomly assigned to saxagliptin or placebo; 78.4% of patients had established ASCVD at baseline. The trial demonstrated a similar proportion of patients achieving the 3-point MACE between saxagliptin and placebo (7.3% and 7.2% in the saxagliptin and placebo groups, respectively; HR 1.00, 95% CI

Table 1 Comparison of the CVD outcome studies with DPP-IV inhibitors

	Sitagliptin TECOS	**Saxagliptin SAVOR-TIMI 53**	**Alogliptin EXAMINE**	**Linagliptin CARMELINA**
Design	N=14,671 patients with T2D and CVD Prior ASCVD 100% patients Sitagliptin: n=7,332 Placebo: n=7,339 Primary composite outcome: CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina (4-point MACE) Secondary composite outcome: CV death, non-fatal myocardial infarction, or non-fatal stroke. The occurrence of the individual components of the primary CV outcome, fatal and non-fatal MI, fatal and non-fatal stroke, all-cause mortality, and hospitalisation for heart failure.	N=16,492 patients with T2D and CVD or CVD risk Prior ASCVD 78.4% patients Saxagliptin: n=8,280 Placebo: n=8,212 Primary composite endpoint: CV death, non-fatal MI, or non-fatal ischaemic stroke (3-point MACE) Secondary: CV death, non-fatal MI, non-fatal ischemic stroke, HHF, coronary revascularisation, or unstable angina	N=5,380 patients with T2D and ACS Prior ASCVD 100% patients Alogliptin: n=2,701 Placebo: n=2,679 Primary composite endpoint: CV death, non-fatal MI, or non-fatal stroke (3-point MACE) Secondary: CV death, non-fatal MI, non-fatal stroke, urgent revascularisation for unstable angina within 24 hours	N=6,979 patients with T2D and CV risk and high renal risk Prior ASCVD 57% patients Linagliptin: n=3,494 Placebo: n=3,485 Primary composite endpoint: CV death, non-fatal MI, or non-fatal stroke (3-point MACE) Secondary: composite of ESRD, renal death, or a 40% decrease in GFR Tertiary: all-cause mortality, HHF, renal death or ESRD. Albuminuria and its progression, sustained ESRD, sustained decrease of at least 50% in eGFR, death due to renal failure, and major ocular events
	Median follow-up: 3.0 years	Median follow-up: 2.1 years	Median follow-up: 18 months	Median follow-up: 2.2 years
Key Results	Least squares mean difference in HbA_{1c}: –0.29% (95% CI –0.32 to –0.27) for sitagliptin vs placebo CV outcomes Primary outcome: MACE + hospitalisation for unstable angina (HR: 0.98 (0.88-1.09); p<0.001 for non-inferiority; (HR: 0.98 (0.89-1.08); p=0.65 for superiority) No increased risk of HHF with sitagliptin: HR: 1.00 95% CI 0.83 to 1.20); p=0.98) No difference between sitagliptin and placebo in incidence of infections, cancer, renal failure, hypoglycaemia, or non-CV death	End of trial HbA_{1c} Saxagliptin: 7.7% ± 1.4% Placebo: 7.9% ± 1.5% (p<0.001 vs placebo) CV outcomes Primary outcome: MACE (HR: 1.00 (0.89-1.12); p=0.99 for superiority; p<0.001 for non-inferiority Higher incidence of HHF in saxagliptin group (HR 1.27; 95% CI 1.07 to 1.51; p=0.007) No difference between groups in incidence of acute or chronic pancreatitis; fewer cases of pancreatic cancer in saxagliptin group; more cases of non-fatal angioedema in saxagliptin group (8 vs 1)	Least squares mean difference in HbA_{1c}: –0.36% (95% CI –0.43 to –0.28; p<0.001) for alogliptin vs placebo CV outcomes Primary outcome: MACE (HR: 0.96 (≤1.16); p=0.32 for superiority; p<0.001 for non-inferiority) Numerically higher number of HHF in alogliptin group (3.1% vs 2.9%; HR 1.07, 95% CI 0.79–1.46) No difference between alogliptin and placebo in incidence of acute and chronic pancreatitis, cancer, renal impairment, angioedema, or severe hypoglycaemia	Least squares mean difference in HbA_{1c}: –0.36% (95% CI –0.42 to –0.29) for linagliptin vs placebo CV outcomes Primary outcome: MACE (HR 1.02 (0.89 to 1.17); p=0.74 for superiority p<0.001 for non-inferiority. No increase in HHF in linagliptin group Numerically higher numbers of pancreatitis; lower incidence of hypoglyceamia and malignancies.

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CI confidence interval; CV, cardiovascular; CVD, cardiovascular disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HHF, hospitalisation for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; T2D, type 2 diabetes.

0.89 to 1.12; p=0.99). However, significantly more patients in the saxagliptin group were hospitalised for HF (3.5% vs 2.8%; HR 1.27, 95% CI 1.07 to 1.51; p=0.007).[62]

Alogliptin

In the EXAMINE trial, 5,380 patients with type 2 diabetes were enrolled 15–90 days following an acute coronary event – acute myocardial infarction or unstable angina. In this respect, the trial was somewhat unique and all patients entering the trial had pre-existing CVD. The primary endpoint of a 3-point MACE occurred in a similar proportion of patients (11.3% and 11.8% in the alogliptin and placebo groups, respectively; HR 0.96, upper boundary of the one-sided CI 1.16) after a median follow-up period of 18 months. There was a numerically higher number of cases of HHF in the treatment arm (3.1% with alogliptin vs 2.9% with placebo).[55] A post hoc analysis of the data, however, showed no significant difference in the rate of HHF (HR 1.07, 95% CI 0.79 to 1.46).[66]

Sitagliptin

In the TECOS trial, 14,671 patients with type 2 diabetes and established CVD were randomised to receive 100 mg sitagliptin or placebo. The primary endpoint of 4-point MACE including hospitalisation due to unstable angina occurred in 11.4% and 11.6% in the sitagliptin and placebo groups, respectively (HR 0.98, 95% CI 0.89 to 1.08) after a median follow-up period of 3 years. It demonstrated evidence of non-inferiority across all primary and secondary CVD outcome measures and similar rates of HHF in both the sitagliptin and placebo groups. A slightly lower estimated GFR of –1.34 mL/min/1.73 m^2 (95% CI –1.76 to –0.91, p<0.0001) persisted in the sitagliptin group throughout the study period.[53]

Omarigliptin

The once-weekly DPP-IV inhibitor omarigliptin is not currently available in the UK. The trial, conducted solely in Japan, assigned

4,202 patients with type 2 diabetes with established CVD to omarigliptin 25 mg once weekly or matching placebo. After a median follow-up of 96 weeks (range 1.1–178.6 weeks), the study was terminated as a business decision. As a result of early termination it was not possible to test the primary hypothesis of non-inferiority in the 3-point MACE due a decrease in power.[63]

Linagliptin

In a pooled analysis of 19 phase 3 RCTs which included a total of 9,459 patients, there were a lower number of composite events (CV death, non-fatal stroke, non-fatal myocardial infarction and hospitalisation due to unstable angina) compared with the pooled comparator, suggesting CV safety with linagliptin (HR 0.78, 95% CI 0.55 to 1.12).[67]

The CARMELINA outcome trial included 6,979 patients with type 2 diabetes with associated CV and renal risk randomised to 5 mg linagliptin or matching placebo. After a median follow-up period of 2.2 years, the 3-point MACE occurred in a similar proportion of patients on linagliptin and placebo (12.4% and 12.1% in the linagliptin and placebo groups, respectively (HR 1.02, 95% CI 0.89 to 1.17; p<0.001 for non-inferiority and 0.74 for superiority) in the intention-to-treat population. There was no increased risk of HHF due to linagliptin (HR 0.90, 95% CI 0.74 to 1.08; p=0.26). Linagliptin was also associated with a statistically significant reduction in albuminuria progression (HR 0.86, 95% CI 0.78 to 0.95; p=0.003) and no increased risk of ocular events among the microvascular endpoints studied. The difference in glycated haemoglobin at study end was lower in the linagliptin group without an excess of hypoglycaemia but no differences in weight, systolic and diastolic blood pressure or lipid parameters were witnessed at the end of the study.[64]

In the subsequent trial of linagliptin versus active comparator glimepiride (CAROLINA), the 3-point MACE occurred in 11.8% of patients on linagliptin and 12% of glimepiride-treated patients (HR 0.98, 95% CI 0.84 to 1.14; p<0.001 for non-inferiority and 0.76 for superiority) in the intention-to-treat population. There was a reduction in weight in the linagliptin group at study end but no difference in glycated haemoglobin between the groups.[33]

The DPP-IV inhibitors have thus demonstrated safety on MACE endpoints but do not appear to have any effect on overall mortality. There was evidence for incident HF with saxagliptin and a trend towards one with alogliptin; this earned a safety warning for both these drugs in patients with kidney disease and HF. No such adverse effect was noticed with sitagliptin or linagliptin. There is a clear lack of data with vildagliptin. In a meta-analysis that compared RCTs, non-RCTs, cohort and case–control studies of DPP-IV inhibitors versus placebo, the overall risk of incident HF with these drugs remained uncertain due to a paucity of good quality evidence. There was, however, a suggestion that DPP-IV inhibitors may increase the risk of HHF.[68] In a systematic review and meta-analysis of 189 trials there was no difference in all-cause mortality between any incretin drug versus control.[69]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs)

The GLP-1RAs act by directly binding to the GLP-1 receptor resulting in meal-mediated insulin release with suppression of glucagon. They promote satiety and have a variable effect on weight loss which is greater than that seen with the DPP-IV inhibitors.[61] The pharmacokinetic properties of these drugs differ, which accounts for their differing efficacy. Exenatide is the synthetic version of exendin-4 extracted from the salivary gland of the Gila monster. It has partial sequence identity with human GLP-1. Lixisenatide is also an exendin-4 derived drug. Liraglutide, semaglutide and albiglutide have strong structural homology to the human GLP-1 molecule and are not derived from exendin-4.[61]

The seven trials published to date are the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA),[54] Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER),[51] Semaglutide and Cardiovascular Outcomes in Type 2 Diabetes (SUSTAIN-6),[70] Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes (EXSCEL),[71] Albiglutide and CV outcomes in patients with type 2 diabetes and CV disease (HARMONY Outcomes),[72] The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND)[68,69] and the Peptide Innovation for Early Diabetes Treatment (PIONEER-6) trial.[67]

The key findings from these trials are presented in Table 2.

Lixisenatide

In the ELIXA trial, 6,068 patients with type 2 diabetes were recruited 180 days following acute coronary syndrome. The primary endpoint, the 4-point MACE which in this study included hospitalisation for unstable angina, occurred in a similar proportion of patients in the lixisenatide and placebo groups (13.4% and 13.2%, respectively; HR 1.02, 95% CI 0.89 to 1.17), demonstrating non-inferiority of lixisenatide to placebo (p<0.001) but not superiority (p=0.81). There was no significant difference in the rate of HHF (approximately 4% in each group) or in the composite of the primary endpoint, HHF or coronary revascularisation. At study end there was a small reduction in glycated haemoglobin, weight and systolic blood pressure. A small but statistically significant increase in heart beat by 0.4 beats/min (95% CI 0.1 to 0.6; p=0.01) was observed across all visits in the lixisenatide group.[54]

Liraglutide

In the LEADER trial, 9,340 patients with type 2 diabetes (mean HbA_{1c} 8.7%) and at least one co-existing CV condition if aged ≥50 years or at least one CV risk factor if age ≥60 years were randomly assigned to receive liraglutide or placebo; 82.1% had established CVD at the time of trial entry and 81.3% at the end of the trial. The primary endpoint of time to first occurrence of the 3-point MACE occurred in fewer patients in the liraglutide group (13.0% vs 14.9%; HR 0.87, 95% CI 0.78 to 0.97; p<0.001 for non-inferiority and 0.01 for superiority) compared with placebo after a median follow-up period of 3.8 years. HHF occurred in fewer patients but this did not reach statistical sig-

Table 2 Comparison of the CVD outcome studies with glucagon-like peptide 1 receptor agonists (GLP-1RAs)

	Lixisenatide ELIXA	**Liraglutide LEADER**	**Exenatide once weekly EXCEL**	**Semaglutide once weekly SUSTAIN-6**	**Albiglutide once weekly HARMONY**	**Dulaglutide once weekly REWIND**
Design	N=6,068 patients with T2D and ACS within 180 days Prior ASCVD (100%) patients Lixisenatide: n=3,034 Placebo: n=3,034 Primary endpoint: composite of CV death, non-fatal MI, or non-fatal stroke, or hospitalisation for unstable angina Secondary endpoints: composite of the primary end point or HHF; a composite of the primary end point, HHF, or coronary revascularisation procedures. All-cause mortality	N=9,340 patients with T2D and high CV risk Prior ASCVD (81.3%) patients Liraglutide: n=4,668 Placebo: n=4,672 Primary endpoint: composite of CV death, non-fatal MI (including silent MI), or non-fatal stroke Secondary endpoints: composite of CV death, non-fatal MI (including silent MI), non-fatal stroke, coronary revascularisation, and hospitalisation for unstable angina or HHF; death from any cause, a composite renal and retinal microvascular outcome	N=14,752 patients with T2D and previous CVD Prior ASCVD (73.1%) patients Exenatide: n=7,356 Placebo: n=7,396 Primary endpoint: composite of CV death, non-fatal MI, or non-fatal stroke Secondary endpoints: all-cause mortality, CV death, fatal or non-fatal MI, fatal or non-fatal stroke, and hospitalisation for ACS or HHF	N=3,297 patients with T2D and previous CVD Prior ASCVD (83%) patients Semaglutide: n=1,648 Placebo: n=1,649 Primary endpoint: composite of CV death, non-fatal MI (including silent MI), or non-fatal stroke Secondary endpoints: expanded composite CV outcome (death from CV causes, non-fatal myocardial infarction, non-fatal stroke, revascularisation [coronary or peripheral], and hospitalisation for unstable angina or HHF), an additional composite outcome (death from all causes, non-fatal myocardial infarction, or non-fatal stroke), the individual components of the composite outcomes, retinopathy complications, and new or worsening nephropathy.	N=9,463 patients with T2D and previous CVD Prior ASCVD (100%) patients Albiglutide: n=4,731 Placebo: n=4,732 Primary endpoint: composite of CV death, non-fatal MI, or non-fatal stroke Secondary endpoint: 4-component composite (the primary composite, with the addition of urgent revascularisation for unstable angina), the individual components of the primary endpoint, and the composite of CV death or hospital admission because of HHF.	N=9,091 patients with T2D with high-risk for CVD and prior ASCVD (31.5%) patients Dulaglutide: n=4,949 Placebo: n=4,952 Primary endpoint: composite of CV death or unknown causes, non-fatal MI, or non-fatal stroke Secondary endpoint: composite microvascular – retinopathy or renal disease; hospitalisation for unstable angina; each component of the primary composite; death; HHF or urgent visit
	Median follow-up: 25 months	Median follow-up: 3.8 years	Median follow-up: 3.2 years	Median follow-up time: 2.1 years	Median follow-up time: 1.6 years	Median follow-up time: 5.4 years
Key Results	Difference from placebo: HbA_{1c}: –0.27% (95% CI, –0.31% to –0.22%; p<0.001) Weight: –0.7 kg (95% CI, –0.9 to –0.5 kg; p<0.001) **CV outcomes** Primary: HR 1.02 (95% CI 0.89 to 1.17); p=0.81 for superiority; p<0.001 for non-inferiority Secondary: All-cause mortality: HR 0.94 (95% CI 0.78 to 1.13), p=0.50 CV death: HR 0.98 (95% CI 0.78 to 1.22), p=0.85 Hospitalisation for HF: HR 0.96 (95% CI 0.75 to 1.23), p=0.75 Primary endpoint or HHF: HR 0.97 (95% CI 0.85 to 1.10), p=0.63 Primary endpoint, HF or coronary revascularisation: HR 1.00 (95% CI 0.90 to, 1.11), p=0.96	Difference from placebo (at 36 months): HbA_{1c}: –0.40% (95% CI, –0.45% to –0.34%) Weight: –2.3 kg (95% CI, –2.5 to –2.0 kg) **CV outcomes** Primary: HR 0.87 (95% CI 0.78 to 0.97); p=0.01 for superiority; p<0.001 for non-inferiority Secondary: Expanded composite HR: 0.88 (95% CI 0.81 to 0.96); P=0.005 for superiority All-cause mortality: HR 0.85 (95% CI 0.74 to, 0.97), p=0.02 CV death: HR 0.78 (95% CI 0.66 to, 0.93), p=0.007 Hospitalisation for HF: HR 0.87 (95% CI 0.73 to 1.05), p=0.14 Increased rates of gastrointestinal events in liraglutide-treated patients Lower numerical incidence of pancreatitis in liraglutide group (0.4% in liraglutide and 0.5% placebo for acute pancreatitis [not statistically significant])	Difference from placebo: HbA_{1c}: –0.53% (95% CI, –0.57% to –0.50%) Weight: –1.27 kg (95% CI, –1.40 to –1.13 kg) **CV outcomes** Primary: HR 0.91 (95% CI 0.83 to 1.00); p=0.061 for superiority; p<0.001 for non-inferiority Secondary: All-cause mortality: HR 0.86 (95% CI 0.77 to 0.97), p=0.016 CV death: HR 0.88 (95% CI 0.76 to 1.02), p=0.096 Hospitalisation for ACS: HR 1.05 (95% CI 0.94 to 1.18), p=0.402 Hospitalisation for HF: HR 0.94 (95% CI 0.78 to 1.13), p=0.485 Higher numerical incidence of pancreatitis in exenatide group (0.4% vs.0.3%) group (not statistically significant); Numerically higher number of papillary thyroid cancers in exenatide group (10 vs. 4) but not medullary thyroid cancers	Difference from placebo: HbA_{1c}: –0.66%; p<0.001 [0.5mg]. –1.05%; p<0.001 [1.0mg] Weight: –2.87 kg; p<0.001 [0.5mg]. –4.35 kg; p<0.001 [1.0mg] **CV outcomes** Primary: HR 0.74 (95% CI 0.58 to 0.95); p=0.02 for superiority; p<0.001 for non-inferiority Secondary HR: Expanded composite: HR 0.74 (95% CI 0.62 to 0.89), p=0.002 All-cause mortality: HR 1.05 (95% CI 0.74 to 1.50), p=0.79 CV death: HR 0.98 (95% CI 0.65 to 1.48), p=0.92 Hospitalisation for HF: HR 1.11 (95% CI 0.77 to 1.61), p=0.57 Retinopathy complications were higher in the semaglutide group HR 1.76 (95% CI 1.11 to 2.78), p=0.02	Difference from placebo (at 16 months): HbA_{1c}: -0.52% (95%CI –0.58% to –0.45%) Weight: –0.83 kg (95%CI –1.06 to –0.60) **CV outcomes** Primary: HR 0.78 (95% CI 0.68 to 0.90); p=0.0006 for superiority; p<0.0001 for non-inferiority Secondary: Expanded composite: HR 0.78 (95% CI 0.69 to 0.90); p=0.0005 All-cause mortality: HR 0.95 (95% CI 0.79 to 1.16), p=0.644 CV death: HR 0.93 (95% CI 0.73 to 1.19), p=0.578 Hospitalisation for HF: HR 0.85 (95% CI 0.70 to 1.04), p=0.113 More injection site reactions with albiglutide with limited effect on weight compared with pkacebo	Difference from placebo HbA_{1c}: –0.61% (95% CI, –0.65% to –0.58%) Weight: –1.46 kg (95% CI, –1.67 to –1.25kg) **CV outcomes** Primary: HR 0.88 (95% CI 0.79 to 0.99); p=0.026 for superiority; Secondary: Microvascular composite: HR 0.87 (95% CI 0.79 to 0.95); p=0.002 All-cause mortality: HR 0.90 (95% CI 0.80 to 1.0), p=0.067 CV death: HR 0.91 (95% CI 0.78 to 1.06), p=0.21 Hospitalisation for HF or urgent visit: HR 0.93 (95% CI 0.77 to 1.12), p=0.46; Hospitalisation for unstable angina: HR 1.14 (95% CI 0.84 to 1.54), p=0.41;

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CI confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HHF, hospitalisation for heart failure; HR, hazard ratio; MI, myocardial infarction; T2D, type 2 diabetes.

nificance (HR 0.87, 95% CI 0.73 to 1.05; p=0.14). There was a small reduction in glycated haemoglobin, a –2.3 kg (95% CI –2.5 to –2.0) difference in weight and a small reduction in systolic (–1.2 mmHg, 95% CI –1.9 to –0.5) and diastolic blood pressures (–0.6 mmHg, 95% CI –0.2 to –1.0) at study end. The heart rate was higher by 3.0 beats/min (95% CI 2.5 to 3.0) in the liraglutide group.[51]

In a small phase 2 trial of liraglutide versus placebo in 300 patients (59% with type 2 diabetes) with established HF and reduced LVEF, liraglutide did not demonstrate a significant effect on the primary composite outcome (time to death, time to rehospitalisation for HF and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide level).[73]

Exenatide extended-release

In the EXSCEL trial, 14,752 patients with type 2 diabetes (73.1% with previous CVD) were randomly assigned to receive subcutaneous injections of 2 mg extended-release exenatide or matching placebo once weekly. The primary endpoint of the 3-point MACE did not differ significantly between the two groups (11.4% vs 12.2% with placebo; HR 0.91, 95% CI 0.83 to 1.0; p=0.06 for superiority and p<0.001 for non-inferiority). HHF was not significantly different from placebo (HR 0.94, 95% CI 0.78 to 1.13; p=0.49). At study end there was a minimal reduction in glycated haemoglobin, a –1.27 kg (95% CI –1.40 to –1.13; p<0.001) difference in weight, a –1.57 mmHg (95% CI –1.92 to –1.21; p<0.001) difference in systolic blood pressure and a –0.25 mmHg (95% CI –0.04 to –0.47; p=0.02) difference in diastolic blood pressure. The heart rate was statistically higher by 2.51 beats/min (95% CI 2.28 to 2.74; p<0.001) in the exenatide group.[71]

Semaglutide

In the SUSTAIN-6 trial, 3,297 patients with type 2 diabetes, 83% of whom had established ASCVD, were randomised to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo. The risks for future CVD events were significantly lower in the semaglutide group as a whole (HR 0.74, 95% CI 0.58 to 0.95; p<0.001 for non-inferiority and p=0.02 for superiority). Among the secondary outcome measures, there was a statistically significant reduction in non-fatal stroke (HR 0.61, 95% CI 0.38 to 0.99; p=0.04). HHF was not significantly different between the groups (HR 1.11, 95% CI 0.77 to 1.61; p=0.57). Although there was no difference in CV death between the semaglutide group and placebo, there were significantly fewer revascularisation procedures in the semaglutide group (HR 0.65, 95% CI 0.5 to 0.86; p<0.05), raising the possibility of a favourable drug effect on CVD. Importantly, though, the rates of retinopathy complications (vitreous haemorrhage, blindness or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher (HR 1.76, 95% CI 1.11 to 2.78; p=0.02) in the semaglutide group. The higher incidence of retinopathy was attributed to the magnitude and rapidity of reduction in glycated haemoglobin during the first 16 weeks of treatment in patients who had pre-existing retinopathy and poor glycaemic control at baseline, and in those who were treated with insulin.[74] There was significant weight loss (estimated treatment difference, ETD) with –2.87 kg (95% CI –3.47 to –2.28; p<0.001) and –4.35 kg (95% CI –4.94 to –3.75; p<0.001) with the 0.5 mg and 1.0 mg dose of semaglutide, respectively. The ETD in glycated haemoglobin at study end were –0.66 (95% CI –0.80 to –0.52; p<0.001) and –1.05 percentage points (95% CI –1.19 to –0.91; p<0.001) lower for the 0.5 mg and 1.0 mg dose of semaglutide respectively. The mean systolic and diastolic blood pressures were lower with semaglutide for both doses, with a slight increase in heart rate (+2.02 beats/min with 0.5 mg and 2.47 beats/min with 1.0 mg) compared with placebo.[70]

Oral semaglutide, which has similar pharmacokinetic properties and clinical effects to the injectable preparation,[75] has been developed as a once-daily preparation. In the PIONEER 6 clinical trial, 3,183 patients were randomly assigned (in a 1:1 ratio) to receive once-daily oral semaglutide (1,591 patients, target dose 14 mg) or placebo (1,592 patients). After a median follow-up period of 15.9 months, the risk for future CVD events as the primary outcome in the intention-to-treat population was significantly reduced with oral semaglutide (HR 0.79, 95% CI 0.57 to 1.11; p<0.001 for non-inferiority and p=0.17 for superiority). It is noteworthy that, despite the fact that PIONEER 6 was a small trial of short duration, patients randomised to oral semaglutide experienced a reduction in CV death of approximately 50% (HR 0.49, 95% CI 0.27 to 0.92) and all-cause mortality (HR 0.51, 95% CI 0.31 to 0.84). HHF was not significantly different between the groups (HR 0.86, 95% CI 0.48 to 1.55). There was a slightly higher proportion of events related to diabetic retinopathy in the semaglutide group (7.1% vs 6.3%); most cases were due to non-proliferative retinopathy.[76]

Albiglutide

Whilst albiglutide is not yet available in the UK, the drug has demonstrated convincing evidence of reduction in CVD events in 9,463 participants with established ASCVD (HARMONY Outcomes). After a median follow-up period of 1.6 years, there was a 22% statistically significant relative-risk reduction in 3-point MACE with albiglutide compared with placebo (HR 0.78, 95% CI 0.68 to 0.90; p<0.0001 for non-inferiority and p<0.0006 for superiority). The secondary composite outcome of death from CV causes and HHF did not differ between the treatment arms (HR 0.85, 95% CI 0.70 to 1.04; p=0.113). There were minimal reductions in weight and systolic blood pressure and, as expected, a small reduction in glycated haemoglobin at study end. The heart rate was higher by 1.4 beats/min (95% CI 1.0 to 1.9) in the albiglutide group.[72]

Dulaglutide

The Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial enrolled 9,901 participants with newly diagnosed or established type 2 diabetes and multiple risk factors for CVD or established ASCVD (31.5%) to receive once-weekly 1.5 mg dulaglutide or matching placebo. The primary outcome was the first occurrence of the 3-point MACE (composite of CV death or non-fatal myocardial infarction or non-

fatal stroke). This was designed as a superiority trial.[77] After a median follow-up period of 5.4 years, a 12% relative risk reduction in MACE was observed in the intention-to-treat population compared with placebo (HR 0.88, 95% CI 0.79 to 0.99; p=0.026). Among the secondary outcome measures there was a statistically significant reduction in non-fatal stroke (HR 0.76, 95% CI 0.61 to 0.95; p=0.017) but no statistically significant difference was observed for CV death (HR 0.91, 95% CI 0.78 to 1.06; p=0.21) or for non-fatal MI (HR 0.96, 95% CI 0.79 to 1.16; p=0.65). There was no difference in hospital admission or in patients requiring urgent HHF (HR 0.93, 95% CI 0.77 to 1.12; p=0.46), hospitalisation from unstable angina (HR 1.14, 95% CI 0.84 to 1.54; p=0.41), all-cause mortality (HR 0.90, 95% CI 0.80 to 1.0; p=0.067) or any form of revascularisation procedures (p=0.37). The incidence of the microvascular composite endpoint of either eye or renal outcomes (HR 0.87, 95% CI 0.79 to 0.95; p=0.002) was significantly reduced, largely driven by fewer composite renal outcomes (HR 0.85, 95% CI 0.77 to 0.93; p=0.0004 for renal and HR 1.24, 95% CI 0.92 to 1.68; p=0.16 for eye). At study end there were minimal reductions in glycated haemoglobin and systolic blood pressure and a –1.46 kg (95% CI –1.25 to –1.67; p<0.0001) reduction in body weight. The heart rate was higher by 1.87 beats/min (95% CI 1.62 to 2.11; p<0.0001) among subjects in the dulaglutide group.[78]

Further analyses revealed that the renal component of the composite microvascular secondary outcome occurred in 17.1% of participants in the dulaglutide group compared with 19.6% of subjects in the placebo group, accounting for a lower incidence rate in the dulaglutide group by 0.6 per 100 person-years over the duration of the trial (HR 0.85; 95% CI 0.77 to 0.93; p=0.0004). The major benefits were noticed in the reduction of new-onset macroalbuminuria (HR 0.77, 95% CI 0.68 to 0.87; p<0.0001), sustained decline in eGFR of 30% or more (HR 0.89, 0.78 to 1.01; p=0·066) and the need for renal replacement therapy (HR 0.75, 95% CI 0.39 to 1.44; p=0.39); at baseline the proportions of subjects with micro- and macroalbuminuria were 27.1% and 8%, respectively.[79]

The GLP-1RA drugs have demonstrated CV safety. Additionally, liraglutide, albiglutide and semaglutide offer CV benefits.

The mechanistic reasons for the CV benefit are not known, but given the delayed separation of the survival curves for the primary outcome, it has been speculated to be due to the antiatherosclerotic effects of GLP-1.[80] In HARMONY Outcomes albiglutide was associated with CV benefit despite less impact on traditional CV risk factors than in the other trials with GLP-1RAs. This has raised the possibility that the many biological effects of GLP-1RAs, other than the effects on traditional CV risk factors, may be responsible for the CV benefits.[81] There appears to be a trend towards an increase in heart rate with the GLP-1RAs, with the lowest increase seen with lixisenatide.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

The SGLT2 inhibitors act by competitively inhibiting the reabsorption of filtered glucose in the proximal convoluted tubule. This promotes glucose loss in the urine and lowering of plasma glucose by an insulin-independent mechanism.[82]

The results from the four CVOTs Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME),[83] Canagliflozin Cardiovascular Assessment Study (CANVAS/CANVAS-R)[84] and Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction (DECLARE-TIMI 58)[50] are summarised in Table 3. More recently, the results of The Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease (VERTIS CV) has been published.[85] The CVOTs were not designed to monitor HbA_{1c} and patients were on guideline-directed standard care to achieve glycaemic equipoise.

Canagliflozin

The CANVAS program integrated data from two clinical trials – CANVAS and CANVAS-R. A total of 10,142 patients were followed up over a mean period of 3.6 years to demonstrate a 14% relative risk reduction in 3-point MACE (HR 0.86, 95% CI 0.75 to 0.97; p<0.001 for non-inferiority and p=0.02 for superiority); 65.6% of the participants had a previous history of ASCVD. There was a more marked reduction in HHF (HR 0.67, 95% CI 0.52 to 0.87) in patients on canagliflozin but no differences in all-cause mortality (HR 0.87, 95% CI 0.74 to 1.01). The CANVAS program also showed a regression in albuminuria which was more marked in those on canagliflozin than in those assigned to placebo (HR 0.73, 95% CI 0.67 to 0.79); these effects were greater in CANVAS-R. The composite outcome of a sustained 40% reduction in GFR, the need for renal replacement therapy or death from renal causes occurred less often in those on canagliflozin (HR 0.60, 95% CI 0.47 to 0.77); there was no heterogeneity between the two studies. Canagliflozin nearly doubled the risk of lower extremity atraumatic amputations predominantly in toe and mid-foot (71% of cases) among those patients with a prior history of amputation, peripheral vascular disease and neuropathy (6.3 vs 3.4 participants with amputation per 1000 patient-years; HR 1.97, 95% CI 1.41 to 2.75). The rate of all fractures was higher with canagliflozin than with placebo (15.4 vs 11.9 participants with fracture per 1000 patient-years; HR 1.26, 95% CI 1.04 to 1.52), and this appeared to be due to low-trauma fractures. The fracture data were significantly more evident in CANVAS than in CANVAS-R (p<0.005). There were minimal reductions in glycated haemoglobin at study end as expected, with a lower body weight (–1.60 kg; 95% CI –1.70 to –1.51) and lower systolic blood pressure (–3.93 mmHg; 95% CI –4.30 to –3.56) and diastolic blood pressure (–1.39 mmHg; 95% CI –1.61 to –1.17; p<0.001 for all comparisons). There was a rise in HDL- and LDL-cholesterol, so the ratio of LDL:HDL cholesterol remained unchanged.[84]

The trial of Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE)[58] was designed to specifically answer the question whether SGLT2 inhibition improved renal outcomes beyond that seen with exploratory analyses of the three major CVOTs.[50,83,84] The primary outcome was a composite of end-stage kidney disease (dialysis for at least 30 days, kidney transplantation or an estimated GFR of <15

Table 3 Comparison of the CVD outcome studies with SGLT-2 inhibitors

	Empagliflozin EMPA-REG OUTCOME	**Canagliflozin CANVAS/CANVAS-R**	**Dapagliflozin DECLARE TIMI-58**	**Ertugliflozin VERTIS-CV**
Design	N=7,020 patients with T2D; prior ASCVD 99.4% patients Empagliflozin: n=4,687 Placebo: n=2,333 Primary endpoint: composite of CV death, non-fatal MI (excluding silent MI), or non-fatal stroke Secondary endpoint: composite of CV death, non-fatal MI (excluding silent MI), non-fatal stroke, and hospitalisation for unstable angina	N=10,142 patients with T2D; prior ASCVD in 65.6% patients CANVAS + CANVAS-R: n=5,795; Placebo: n=4,347 Primary endpoint: composite of CV death, non-fatal MI, or non-fatal stroke Secondary endpoint: all-cause mortality, CV death, progression of albuminuria, and the composite of death from CV causes and HHF	N=17,160 patients with T2D; prior ASCVD in 40.6% patients Dapagliflozin: n=8,582 Placebo: n=8,578 Co-primary endpoint: CV death, non-fatal MI, or non-fatal stroke & composite of hospitalisation for HF and CV death Secondary endpoint: renal composite (≥40% decrease in eGFR to <60 ml/min/1.73 m^2 body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.	N=8,246 patients with T2D; prior ASCVD in 100% patients Ertugliflozin: n=5,499 Placebo: n=2,747 Primary endpoint: composite of CV death, non-fatal MI, or non-fatal stroke Secondary endpoint: composite of death from CV causes or HHF; death from CV causes; and a composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level
	Median follow-up: 3.1 years	Median follow-up: 2.4 years	Median follow-up: 4.2 years	Median follow-up: 3.0 years
Key Results	Week 206 HbA_{1c}, difference from placebo Empagliflozin 10 mg: –0.24% (95% CI, –0.40% to –0.08%) Empagliflozin 25 mg: –0.36% (95% CI, –0.51% to –0.20%) **CV outcomes (pooled analysis):** Primary: HR 0.86 (95% CI 0.74 to 0.99); p=0.04 for superiority; p<0.001 for non-inferiority Secondary HR: 0.89 (95% CI 0.78 to 1.01); p<0.001 for non-inferiority; p=0.08 for superiority Significantly lower rates of all-cause death, CV death, and HHF	Mean difference in HbA_{1c} between canagliflozin and placebo: –0.58% (95% CI, –0.61 to –0.56) **CV outcomes** Primary: HR 0.86 (95% CI 0.75 to 0.97); p=0.0158 for superiority; p<0.001 for non-inferiority Secondary: HHF: HR 0.67 (95% CI 0.52 to 0.87) CV death or HHF: HR 0.78 (95% CI 0.67 to 0.91) All-cause mortality HR 0.87 (95% CI 0.74 to 1.01)	Mean difference in HbA_{1c} between dapagliflozin and placebo: –0.42% (95% CI, –0.40 to –0.45) **CV outcomes** Co-Primary: MACE, HR 0.93 (95% CI 0.84 to 1.03); p=0.17 for superiority; p<0.001 for non-inferiority. HHF/CVD. HR 0.83 (95% CI 0.73 to 0.95); p=0.005 Secondary: 40% reduction in GFR or renal-replacement or renal or CV death: HR 0.76 (95% CI 0.67 to 0.87); All-cause mortality HR 0.93 (95% CI 0.82 to 1.04)	Mean difference in HbA_{1c} between ertugliflozin and placebo (at week 18): –0.50% **CV outcomes** Primary: HR 0.97 (95.6% CI 0.85 to 1.11; p<0.001 for non-inferiority Secondary: HHF: HR 0.70 (95% CI 0.54 to 0.90); Renal composite: HR 0.81 (95% CI 0.63 to 1.04); All-cause mortality HR 0.93 (95% CI 0.80 to 1.08)

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CI confidence interval; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; HR, hazard ratio; MI, myocardial infarction; T2D, type 2 diabetes.

mL/min/1.73 m^2 sustained for at least 30 days) and a doubling of the serum creatinine level from baseline sustained for at least 30 days or death from renal or cardiovascular causes. After a median follow-up of 2.62 years, 100 mg canagliflozin had lower event rates for the primary outcome compared with placebo (43.2 and 61.2 per 1000 patient-years, respectively; HR 0.70, 95% CI 0.59 to 0.82; p=0.00001). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level or death from renal causes was reduced by 34% (HR 0.66, 95% CI 0.53 to 0.81; p<0.001). Similarly, the relative risk of end-stage kidney disease was significantly lower in the canagliflozin group compared with placebo (HR 0.68, 95% CI 0.54 to 0.86; p=0.002). The canagliflozin group also had a lower risk of the 3-point MACE (CV death, non-fatal myocardial infarction or non-fatal stroke) by 20% (HR 0.80, 95% CI 0.67 to 0.95; p=0.01) as well as HHF (HR 0.61, 95% CI 0.47 to 0.80; p<0.001).[58] The amputation event rate was numerically higher with canagliflozin than with placebo, but this did not reach statistical significance (12.3 vs 11.2 per 1000 patient-years; HR 1.11, 95% CI 0.79 to 1.56). The rates for fracture were, however, numerically lower in the canagliflozin group, although the difference was not statistically significant (11.8 vs 12.1 per 1000 patient-years; HR 0.98, 95% CI 0.70 to 1.37).

Empagliflozin

In the EMPA-REG OUTCOME clinical trial, 7,020 participants were followed up over a mean period of 3.1 years, demonstrating a 14% relative risk reduction in the 3-point MACE (HR 0.86, 95% CI 0.74 to 0.99; p<0.001 for non-inferiority and p=0.04 for superiority). Although this was very similar to the results from the CANVAS program, the majority (99.4%) of the patients in the EMPA-REG OUTCOME had established ASCVD. This reduction was driven by a significant decrease in CV death (HR 0.62, 95% CI 0.49 to 0.77; p<0.001), Similarly, there was a statistically significant reduction in HHF (HR 0.65, 95% CI 0.50 to 0.85; p=0.002) and also for all-cause mortality (HR 0.68, 95% CI 0.57 to 0.82; p<0.001). At study end there was a small but statistically significant reduction in glycated haemoglobin of –0.30 percent-

age points, with approximately a 2 kg weight loss in the empagliflozin group compared with placebo.[83] Further analyses of the renal microvascular outcomes revealed a statistically significant reduction in incident or worsening nephropathy (HR 0.61, 95% CI 0.53 to 0.70; p<0.001), progression to macroalbuminuria (HR 0.62, 95% CI 0.54 to 0.72; p<0.001) and in the post hoc composite renal outcome of a doubling of serum creatinine, initiation of renal replacement therapy or death from renal disease (HR 0.54, 95% CI 0.40 to 0.75; p<0.001).[86]

The trial of empagliflozin in HF in patients with or without diabetes (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a reduced Ejection Fraction (EMPEROR-Reduced)) recruited patients with chronic HF (functional class II–IV) with a LVEF of ≤40%. After a median follow-up period of 16 months, the primary outcome of a composite of CV death or hospitalisation for worsening HF occurred in 361 patients (19.4%) in the empagliflozin (10 mg once daily) group and 462 patients (24.7%) in the placebo group (HR 0.75, 95% CI 0.65 to 0.86; p<0.001). The results were independent of the presence of diabetes.[57]

Dapagliflozin

In the DECLARE TIMI-58 clinical trial a large cohort of 17,160 patients received either dapagliflozin or placebo and were observed over a median follow-up period of 4.2 years. It demonstrated a 7% relative risk reduction in the primary safety outcome of a 3-point MACE which met the pre-specified criterion for non-inferiority (HR 0.93, 95% CI 0.84 to 1.03; p<0.001 for non-inferiority and p=0.17 for superiority). The two primary efficacy outcomes were MACE and a composite of CV death or hospitalisation for HF. Dapagliflozin had a lower rate of cardiovascular death or hospitalisation for HF than placebo (4.9% vs. 5.8%; HR 0.83; 95% CI 0.73 to 0.95; p=0.005) largely driven by a lower rate of hospitalisation for HF. In this trial, 40.6% had established ASCVD; the remainder had multiple risk factors without ASCVD. HHF as a secondary endpoint was reduced by 27% (HR 0.73, 95% CI 0.66 to 0.88). There were non-significant changes in CV death (HR 0.98, 95% CI 0.82 to 1.17) and in all-cause mortality (HR 0.93, 95% CI 0.82 to 1.04); the renal composite endpoint of 40% reduction in GFR or requirement for renal replacement or death due to renal causes was reduced (HR 0.53, 95% CI 0.43 to 0.66). At study end, the dapagliflozin group had a lower mean glycated haemoglobin, a reduction in mean weight by –1.8 kg (95% CI 1.7 to 2.0) and reduction is mean systolic (–2.7mmHg, 95% CI 2.4 to 3.0) and diastolic (–0.7 mmHg (95% CI 0.60 to 0.90) blood pressures.[50]

The trial of dapagliflozin in patients with heart failure DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF)) with or without diabetes, the primary composite endpoint of worsening HF (hospitalisation or an urgent visit resulting in intravenous therapy for HF) or death from CV causes occurred in 386 (16.3%) patients in the dapagliflozin group and in 502 (21.2%) patients in the placebo group (HR 0.74, 95% CI 0.65 to 0.85; p<0.001). The results were independent of the presence of diabetes.[56] As this position statement went to press it was announced that NICE recommended dapagliflozin as an option for treating symptomatic chronic heart failure with reduced ejection fraction in adults, only if used as an add-on to optimised standard care.[87]

The trial designed to specifically address the CV and renal outcome of patients with CKD and proteinuria (DAPA-CKD) showed a statistically significant benefit with a 39% reduction (HR 0.61; 95% CI 0.51 to 0.72; p<0.001) in the primary composite outcome of a 50% sustained decline in GFR, onset of ESRD or renal or CV death. There was a sustained decline in the eGFR of at least 50%, end-stage kidney disease or renal death (HR 0.56, 95% CI 0.45 to 0.68; p<0.001), and a similar improvement in the composite of death from CV causes or HHF (HR 0.71, 95% CI 0.55 to 0.92; p=0.009).[59] The DAPA-CKD study was uniquely in that it showed similar effects in patients with or without diabetes.

Ertugliflozin

The Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease (VERTIS CV).[88] A total of 8,246 patients were randomised to once-daily ertugliflozin either 5 or 15 mg. After a follow-up period of 6.1 years, the primary endpoint of a 3-point MACE achieved statistical significance for non-inferiority (HR 0.97, 95% CI 0.85 to 1.11; p<0.001 for non-inferiority). There was a 30% reduction in HHF (HR 0.70, 95% CI 0.54 to 0.90.[85] The renal composite endpoint (HR 0.81, 95% CI 0.63 to 1.04; p=0.08) did not reach statistical significance.[85]

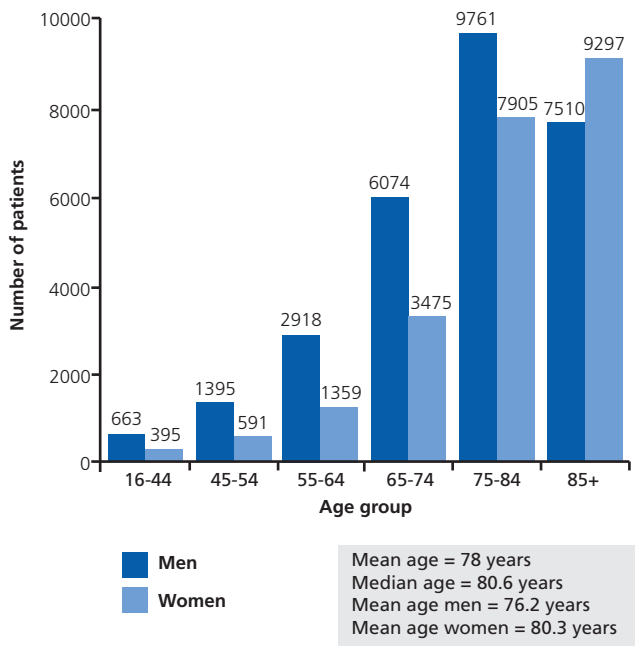
The key points observed among the SGLT2 inhibitor CVOTs were a strikingly early separation of the survival curves, suggesting a very early benefit with these drugs. All these drugs met their pre-specified criteria of non-inferiority in the primary outcome of a 3-pont MACE. There was significant improvement in HbA_{1c}, systolic and diastolic blood pressure, body weight and a reduction in the rate of HHF in all the SGLT2 inhibitor trials. The results from the VERTIS-CV TRIAL failed to demonstrate significant CV benefits of the drug although there was a reduction in HHF.[85]

The CV benefit seen with canagliflozin, dapagliflozin and empagliflozin was in patients with type 2 diabetes and pre-existing CVD. Whether these agents would reduce incident CVD (primary prevention) remains unknown. There was modest improvement in glycaemia in both trials. Further, there are no long-term safety data on the effects of prolonged glycosuria as can be expected when patients are put on these drugs. The information is limited to the maximum period of follow-up in these trials. It would become available in the future as real-world evidence data emerges.

Summary

Differences in study populations, baseline patient characteristics and designs make it difficult to compare results across these trials. The trials have focused on two important areas of clinical care – namely, atherosclerosis and HF in patients with type 2 diabetes. The composite endpoint of MACE appears as a reliable outcome measure for improvement in ASCVD, whilst HHF reflects a level of severity in left ventricular dysfunction that requires in-hospital care; both are critical to the management of type 2 diabetes.

Figure 1. Age and gender demographics at first admission: National Heart Failure Audit (April 2016–March 2017).[92]

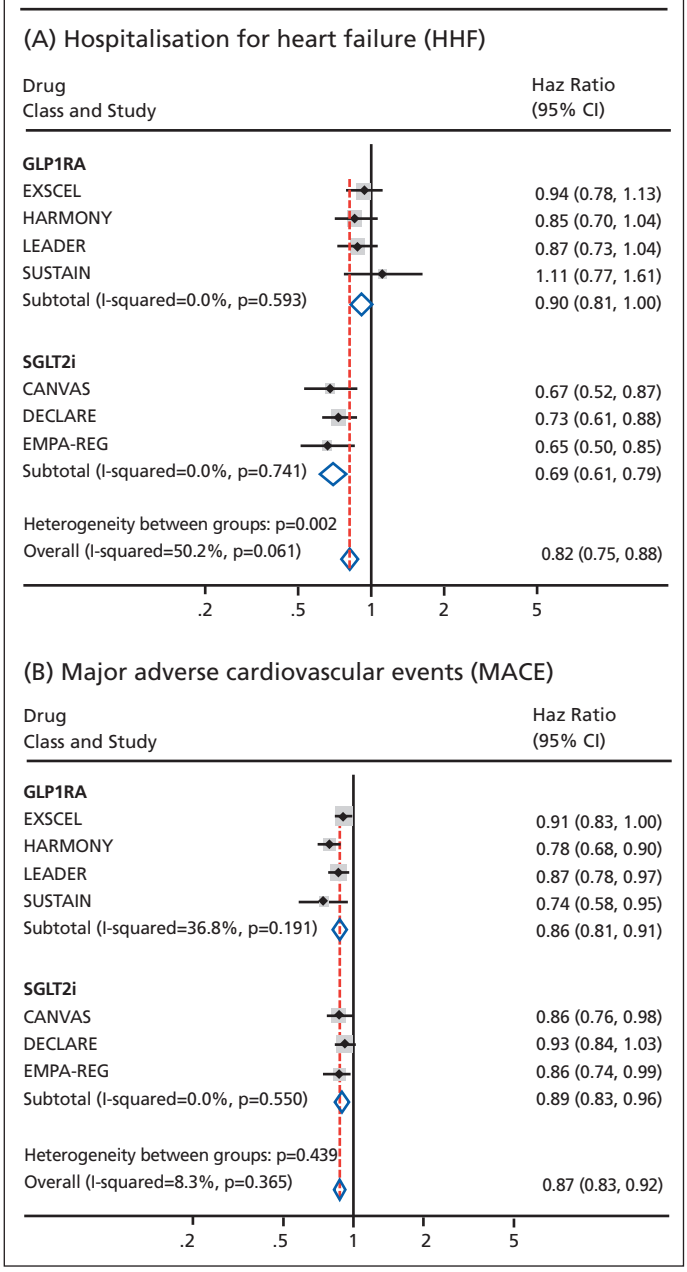


The DPP-IV inhibitors sitagliptin, alogliptin, saxagliptin, two SGLT2 inhibitors dapagliflozin and ertugliflozin and two GLP-1 RA drugs lixisenatide and extended-release exenatide have demonstrated non-inferiority on MACE outcomes with comparator – that is, they have assured CV safety when used in conjunction with other glucose-lowering treatment to improve glycaemic control. Four GLP-1 agonists (semaglutide, dulaglutide, liraglutide and albiglutide) and two SGLT-2 inhibitors (empagliflozin and canagliflozin) have demonstrated CV benefit on MACE outcomes.

It is worth recalling that clinical trials that have focused on glucose-lowering have shown improvement in microvascular endpoints with very limited impact on macrovascular events.[32,89,90] Lipid lowering and control of blood pressure remains the cornerstone of any treatment plan designed to reduce CVD events in patients with type 2 diabetes. The beneficial effect of glycaemic control in reducing CV events may take a long time to manifest, with a possible 'legacy' effect in patients receiving intensive treatment early on after diagnosis of both type 1 diabetes[91] and type 2 diabetes.[28]

The SGLT2 inhibitors canagliflozin, dapagliflozin, empagliflozin and ertugliflozin have a significant benefit in reducing the risk of HHF based on exploratory analyses of the four major outcome trials. The DAPA-HF clinical trial of HFrEF patients (NYHA II, III and IV) with and without diabetes and the similar trial with empagliflozin (EMPEROR-Reduced) reduced the risk of worsening HF or death from CV causes.[56] The reduced risk of incident and worsening HF may well be a class effect, as demonstrated in the large multicentre observational study (CVD-Real)

Figure 2. Effect sizes compared for the glucagon-like peptide 1 receptor agonist (GLP-1RA) and sodium-glucose co-transporter 2 inhibitor (SGLT2i) trials (excluding ELIXA)



trial involving 309,056 patients across six countries in the western world. There were clearly lower rates of HHF (HR 0.61, 95% CI 0.51 to 0.73; p<0.001), death (HR 0.49, 95% CI 0.41 to 0.57; p<0.001) and HHF or death (HR 0.54, 95% CI 0.48 to 0.60, p<0.001) among patients recently commenced on a SGLT2 inhibitor with no significant heterogeneity between nations (p=0.17).[92] HF in elderly diabetic patients may be more common than myocardial infarction.[14] The National Heart Failure Audit (2016/17) demonstrated an increasing trend with advancing years in all groups of patients (Figure 1).[93] The benefits derived

Key messages

- The newer oral hypoglycaemic drugs used in diabetes have demonstrated CV safety in all cases with evidence of benefit in a few
- There is significant heterogeneity in study design which makes meaningful comparison somewhat difficult; results of systematic reviews have indicated a common trend within drug classes. These effects are around atherosclerotic cardiovascular disease (ASCVD) using time to the first major cardiovascular event (MACE) as a primary endpoint and hospitalisation due to heart failure (HHF) as a co-primary, secondary or exploratory outcome measure
- Only two drugs – alogliptin and lixisenatide – have been trialled in patients after acute coronary syndrome demonstrating safety
- The DPP-IV inhibitors are safe to use in those with CVD, although caution must be exercised in the presence of HF. The GLP-1 inhibitors are similarly safe and, in some cases, offer benefit
- Dapagliflozin is the only SGLT2 inhibitor that is currently licensed for use in patients with HF independent of the presence of diabetes. There is no evidence for their use either for HF or reno-protection in patients with type 1 diabetes
- Clinical judgement should always be used to make specific therapeutic choices as results from clinical trials can sometimes be difficult to generalise to individual patients.
- From the foregoing, there appears to be a genuine need now to collect data from real-world evidence to confirm or challenge the findings from the clinical trials

from the use of SGLT2 inhibitors in patients with HF are complementary to the benefits seen on MACE outcome.

Canagliflozin, as well as empagliflozin, dapagliflozin, liraglutide and semaglutide, have demonstrated a reno-protective effect; as secondary/exploratory outcomes the SGLT2 inhibitors also reduce progression of albuminuria. Subsequently, specifically designed trials of CKD with proteinuria (DAPA-CKD and CREDENCE) have further shown the beneficial effects of these agents in CKD. Further, DAPA-CKD by including patients without diabetes have shown that the drug is effective independent of glucose intolerance. In the absence of similar trials in the non-diabetic population it is too early to generalise this effect across other SGLT2 inhibitors. For a more detailed understanding of the effects and the use of SGLT2 inhibitors in CKD, the reader is advised to refer to the ABCD position statement published jointly with the Renal Association.

The evidence for primary prevention with SGLT2 inhibitors is lacking, as evidenced in the CANVAS trial. When the effect sizes of the clinical trials with GLP-1RA and SGLT2 inhibitors are compared, there appears to be a clear benefit towards reduction in HF risk solely with the SGLT2 inhibitors and benefit with MACE across both groups of drugs (Figure 2).

The ultimate choice of a particular drug in treating patients with type 2 diabetes should be at the discretion of the individual clinician caring for the patient using sound clinical judgment and a comprehensive review of the clinical evidence available to date.

Position paper writing group

Governance process for this position statement: The writing group was Ansu Basu, Dipesh Patel, Peter Winocour and Bob Ryder. The final draft was sent to the ABCD position papers sub-committee (10 people) and the ABCD executive committee (5 people) and all 15 people were given a chance to review it. The comments from these reviews were incorporated and the resulting final document was approved by the ABCD executive as the current ABCD position on the subject in December 2020.

Conflict of interest AB received honoraria for delivering educational meetings from AstraZeneca, Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Takeda, Janssen and Sanofi. DP reports: Commercial: Received fees for lectures and advisory work from AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Napp Pharmaceuticals, Novo Nordisk, Sanofi. Educational Activities: Financial compensation in relation to training of health professionals or planning training packages: received conference attendance support from Napp, Novo Nordisk and Sanofi. Expert functions in health care and health guidance processes, e.g. Board member in a development project, member of health board in the municipality: Chair, Association of British Clinical Diabetologists (ABCD). PHW has received honoraria for delivering educational meetings and/or attending advisory boards for Abbott, AstraZeneca, Bayer, BI, Eli Lilly, MSD, Napp, Sanofi, Novo and Vifor Pharmaceuticals. REJR has received speaker fees and/or consultancy fees and/or educational sponsorships from AstraZeneca, BioQuest, GI Dynamics, Janssen, Novo Nordisk, Sanofi-Aventis and Takeda.

Funding None.

This position statement was updated 17 May, 2021

References

1. Selvin E, Coresh J, Golden SH, Boland LL, Brancati FL, Steffes MW. Glycemic control, atherosclerosis, and risk factors for cardiovascular disease in individuals with diabetes. The Atherosclerosis Risk in Communities study. *Diabetes Care* 2005;**28**(8):1965–73. https://doi.org/10.2337/diacare.28.8.1965
2. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;**375**(9733):2215–22. https://doi.org/10.1016/S0140-6736(10)60484-9
3. Kennel W, McGee D. Diabetes and cardiovascular risk factors: the Framingham Study. *Circulation* 1979;**59**(1):8–13. https://doi.org/10.1161/ 01.cir.59.1.8
4. Norhammar A, Tenerz A, Nilsson G, *et al*. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002;**359**(9324):2140–4. https://doi.org/10.1016/S0140-6736(02)09089-X
5. Nathan D, Cleary P, Backlund J, *et al*. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;**22**:2643–53. https://doi.org/10.1056/NEJMoa052187
6. Ray KK, Seshasai SRK, Wijesuriya S, *et al*. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009; **373**(9677):1765–72. https://doi.org/10.1016/S0140-6736(09)60697-8
7. Selvin E, Marinopoulos S, Berkenblit G, *et al*. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;**141**(6):421–31. https://doi.org/10.7326/0003-4819-141-6-200409210-00007
8. von Heerebeek L, Hamdani N, Handoko ML, *et al*. Diastolic stiffness of the failing diabetic heart. *Circulation* 2008;**11**7(1):43–51. https://doi.org/10.1161/CIRCULATIONAHA.107.728550
9. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Car-*

diol 1972;**30**(6):595–602. https://doi.org/10.1016/0002-9149(72)90595-4
10. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. *Circulation* 2007;**115**(25):3213–23. https://doi.org/10.1161/ CIRCULATIONAHA.106.679597
11. Yancy CW, Jessup M, Bozkurt B, *et al*. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary. *Circulation* 2013;**128**(16):1810–52. https://doi.org/10.1161/CIR.0b013e31829e8807
12. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes. An update. *Diabetes Care* 2004;**27**(8):1879–84. https://doi.org/10.2337/diacare.27.8.1879
13. van Melle JP, Bot M, de Jonge P, de Boer RA, van Veldhuisen DJ, Whooley MA. Diabetes, glycemic control, and new-onset heart failure in patients with stable coronary artery disease. Data from the Heart and Soul Study. *Diabetes Care* 2010;**33**(9):2084–9. https://doi.org/10.2337/dc10-0286
14. McMurray JJV, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. *Lancet Diabetes Endocrinol* 2014;**2**(10):843–51. https://doi.org/10.1016/S2213-8587(14)70031-2
15. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**(13):1296–305. https://doi.org/10.1056/NEJMoa041031
16. Kottgen A, Russell SD, Loehr LR, *et al*. Reduced kidney function as a risk factor for incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. *J Am Soc Nephrol* 2007;**18**(4):1307–15. https://doi.org/10.1681/ASN.2006101159
17. Manjunath G, Tighiouart H, Ibrahim H, *et al.* Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003;**41**(1):47–55. https://doi.org/10.1016/s0735-1097(02)02663-3
18. Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;**375**(9731):2073–81. https://doi.org/10.1016/S0140-6736(10)60674-5
19. Orchard TJ, Dorman JS, Maser RE, *et al*. Prevalence of complications in IDDM by sex and duration: Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 1990;**39**(9):1116–24. https://doi.org/10.2337/diab.39.9.1116
20. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. *N Engl J Med* 1999;**341**(15):1127–33. https://doi.org/10.1056/NEJM199910073411506
21. Adler AI, Stevens RJ, Manley SE, *et al*. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 2003;**63**(1):225–32. https://doi.org/10.1046/j.1523-1755.2003.00712.x
22. US Food and Drug Administration (FDA). Guidance for industry: diabetes mellitus evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. 2008. https://www.fda.gov/media/71297/download
23. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;**356**(24):2457–71. https://doi.org/10.1056/NEJMoa072761
24. European Medicines Agency (EMA). Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. 2012. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-prevention-diabetes-mellitus-revision_en.pdf
25. Lesaffre E. Superiority, equivalence, and non-inferiority trials. *Bull NYU Hosp Jt Dis* 2008;**66**(2):150–4.
26. Hirshberg B. Cardiovascular outcome studies with novel antidiabetes agents: scientific and operational considerations. *Diabetes Care* 2013;**36**(Suppl 2):S253–8. https://doi.org/10.2337/dcS13-2041
27. UK Prospective Diabetes Study. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;**352**:854–65.
28. Holman R, Paul S, Bethel M, Matthews D, Neil H. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;**359**:1577–89. https://doi.org/10.1056/NEJMoa0806470
29. Davies MJ, D'Alessio DA, Fradkin J, *et al*. Management of hyperglycemia in type 2 diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;**41**(12):2669–701. https://doi.org/10.2337/dci18-0033
30. Meinert C, Knatterud G, Prout T, Klimt C. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. *Diabetes* 1970;**19**(Suppl):789–830.
31. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol* 2015;**3**(1):43–51. https://doi.org/10.1016/S2213-8587(14)70213-X
32. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;**358**(24):2560–72. https://doi.org/10.1056/NEJMoa0802987
33. Rosenstock J, Kahn SE, Johansen OE, *et al.* Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *JAMA* 2019;**322**(12):1155–66. https://doi.org/10.1001/jama.2019.13772
34. Chiasson J, Josse RG, Gomis R, *et al.* Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: The STOP-NIDDM trial. *JAMA* 2003;**290**(4):486–94. https://doi.org/10.1001/jama.290.4.486
35. Holman RR, Coleman RL, Chan JCN, *et al*. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017;**5**(11):877–86. https://doi.org/10.1016/S2213-8587(17)30309-1
36. Home PD, Pocock SJ, Beck-Nielsen H, *et al*. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 2009;**373**(9681):2125–35. https://doi.org/10.1016/S0140-6736(09)60953-3
37. Stone JC, Furuya-Kanamori L, Barendregt JJ, Doi SA. Was there really any evidence that rosiglitazone increased the risk of myocardial infarction or death from cardiovascular causes? *Pharmacoepidemiol Drug Saf* 2015;**24**(3):223–7. https://doi.org/10.1002/pds.3736
38. Florez H, Reaven PD, Bahn G, *et al*. Rosiglitazone treatment and cardiovascular disease in the Veterans Affairs Diabetes Trial. *Diabetes Obes Metab* 2015;**17**(10):949–55. https://doi.org/10.1111/dom.12487
39. Goldberg RB, Kendall DM, Deeg MA, *et al*. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care* 2005;**28**(7):1547–54. https://doi.org/10.2337/diacare.28.7.1547
40. Dormandy JA, Charbonnel B, Eckland DJA, *et al*. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;**366**(9493):1279–89. https://doi.org/10.1016/S0140-6736(05)67528-9
41. Mazzone T, Meyer PM, Feinstein SB, *et al*. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes. A randomized trial. *JAMA* 2006;**296**(21):2572–81. https://doi.org/10.1001/jama.296.21.joc60158
42. Nissen SE, Nicholls SJ, Wolski K, *et al*. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA* 2008;**299**(13):1561–73. https://doi.org/10.1001/jama.299.13.1561
43. Ryder REJ. Pioglitazone has a dubious bladder cancer risk but an undoubted cardiovascular benefit. *Diabet Med* 2015;**32**(3):305–13. https://doi.org/10.1111/dme.12627
44. Ryder REJ, DeFronzo R. Rehabilitation of pioglitazone. *Br J Diabetes Vasc Dis* 2015;**15**:46–9. http://dx.doi.org/10.15277/bjdvd.2015.021
45. Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *J Am Coll Cardiol* 2007;**49**(17):1772–80. https://doi.org/10.1016/j.jacc.2006.12.048
46. Wilcox R, Bousser M-G, Betteridge DJ, *et al.* Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* 2007;**38**(3):865–73. https://doi.org/10.1161/01.STR.0000257974.06317.49
47. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. A meta-analysis

of randomized trials. *JAMA* 2007;**298**(10):1180–8. https://doi.org/10.1001/jama.298.10.1180
48. Kernan WN, Viscoli CM, Furie KL, *et al.* Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med* 2016;**374**(14):1321–31. https://doi.org/10.1056/NEJMoa1506930
49. Vaccaro O, Masulli M, Nicolucci A, *et al*. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. *Lancet Diabetes Endocrinol* 2017;**5**(11):887–97. https://doi.org/10.1016/S2213-8587(17)30317-0
50. Wiviott SD, Raz I, Bonaca MP, *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**(4):347–57. https://doi.org/10.1056/NEJMoa1812389
51. Marso SP, Daniels GH, Brown-Frandsen K, *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**(4):311–22. https://doi.org/10.1056/NEJMoa1603827
52. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;**285**(19):2486–97. https://doi.org/10.1001/jama.285.19.2486
53. Green JB, Bethel MA, Armstrong PW, *et al*. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;**373**(3):232–42. https://doi.org/10.1056/NEJMoa1501352
54. Pfeffer MA, Claggett B, Diaz R, *et al*. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;**373**(23):2247–57. https://doi.org/10.1056/NEJMoa1509225
55. White WB, Cannon CP, Heller SR, *et al*. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;**369**(14):1327–35. https://doi.org/10.1056/NEJMoa1305889
56. McMurray JJV, Solomon SD, Inzucchi SE, *et al.* Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**(21):1995–2008. https://doi.org/10.1056/NEJMoa1911303
57. Packer M, Anker SD, Butler J, *et al*. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**(15):1413–24. https://doi.org/10.1056/NEJMoa2022190
58. Perkovic V, Jardine MJ, Neal B, *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**(24):2295–306. https://doi.org/10.1056/NEJMoa1811744
59. Heerspink HJL, Stefánsson BV, Correa-Rotter R, *et al*. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**(15):1436–46. https://doi.org/10.1056/NEJMoa2024816
60. Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab* 2011;**13**(1):7–18. https://doi.org/10.1111/j.1463-1326.2010.01306.x
61. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006;**368**(9548):1696–705. https://doi.org/10.1016/S0140-6736(06)69705-5
62. Scirica BM, Bhatt DL, Braunwald E, *et al*. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;**369**(14):1317–26. https://doi.org/10.1056/NEJMoa1307684
63. Gantz I, Chen M, Suryawanshi S, *et al.* A randomized, placebo-controlled study of the cardiovascular safety of the once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol* 2017;**16**:112–24. https://doi.org/10.1186/s12933-017-0593-8
64. Rosenstock J, Perkovic V, Johansen OE, *et al*. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA* 2019;**321**(1):69–79. https://doi.org/10.1001/jama.2018.18269
65. McMurray JJV, Ponikowski P, Bolli GB, *et al*. Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: a randomized placebo-controlled trial. *JACC Heart Fail* 2018;**6**(1):8–17. https://doi.org/10.1016/j.jchf.2017.08.004
66. Zannad F, Cannon CP, Cushman WC, *et al*. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet* 2015;**385**(9982):2067–76. https://doi.org/10.1016/S0140-6736(14)62225-X
67. Rosenstock J, Marx N, Neubacher D, *et al*. Cardiovascular safety of linagliptin in type 2 diabetes: a comprehensive patient-level pooled analysis of prospectively adjudicated cardiovascular events. *Cardiovasc Diabetol* 2015;**14**:1–15. https://doi.org/10.1186/s12933-014-0167-y
68. Li L, Li S, Deng K, *et al*. Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies. *BMJ* 2016;**352**:i610. https://doi.org/10.1136/bmj.i610
69. Liu J, Li L, Deng K, *et al*. Incretin based treatments and mortality in patients with type 2 diabetes: systematic review and meta-analysis. *BMJ* 2017;**357**:j2499. https://doi.org/10.1136/bmj.j2499
70. Marso SP, Bain SC, Consoli A, *et al*. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;**375**(19):1834–44. https://doi.org/10.1056/NEJMoa1607141
71. Holman RR, Bethel MA, Mentz RJ, *et al*. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;**377**(13):1228–39. https://doi.org/10.1056/NEJMoa1612917
72. Hernandez AF, Green JB, Janmohamed S, *et al*. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018;**392**(10157):1519–29. https://doi.org/10.1016/S0140-6736(18)32261-X
73. Margulies KB, Hernandez AF, Redfield MM, *et al*. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA* 2016;**316**(5):500–08. https://doi.org/10.1001/jama.2016.10260
74. Vilsbøll T, Bain SC, Leiter LA, *et al*. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. *Diabetes Obes Metab* 2018;**20**(4):889–97. https://doi.org/10.1111/dom.13172
75. Davies M, Pieber TR, Hartoft-Nielsen M-L, Hansen OKH, Jabbour S, Rosenstock J. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA* 2017;**318**(15):1460–70. https://doi.org/10.1001/jama.2017.14752
76. Husain M, Birkenfeld AL, Donsmark M, *et al*. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019;**381**(9):841–51. https://doi.org/10.1056/NEJMoa1901118
77. Gerstein HC, Colhoun HM, Dagenais GR, *et al.* Design and baseline characteristics of participants in the Researching cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial on the cardiovascular effects of dulaglutide. *Diabetes Obes Metab* 2018;**20**(1):42–9. https://doi.org/10.1111/dom.13028
78. Gerstein HC, Colhoun HM, Dagenais GR, *et al*. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;**394**(10193):121–30. https://doi.org/10.1016/S0140-6736(19)31149-3
79. Gerstein HC, Colhoun HM, Dagenais GR, *et al*. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* 2019;**394**(10193):131–8. https://doi.org/10.1016/S0140-6736(19)31150-X
80. Song X, Jia H, Jiang Y, *et al*. Anti-atherosclerotic effects of the glucagon-like peptide-1 (GLP-1) based therapies in patients with type 2 diabetes mellitus: a meta-analysis. *Scientific Reports* 2015;**5**:10202.
81. Ryder REJ, DeFronzo R. Diabetes medications with cardiovascular protection after HARMONY Outcomes and DECLARE-TIMI 58: could metformin, pioglitazone, SGLT2 inhibitors and long-acting GLP-1 receptor agonists complement each other to save lives by different mechanisms? *Br J Diabetes* 2019;**19**:1–5. https://doi.org/10.15277/bjd.2019.207
82. Jabbour SA, Goldstein BJ. Sodium glucose co-transporter 2 inhibitors: blocking renal tubular reabsorption of glucose to improve glycaemic control in patients with diabetes. *Int J Clin Pract* 2008;**62**(8):1279–84. https://doi.org/10.1111/j.1742-1241.2008.01829.x
83. Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**(22):2117–28. https://doi.org/10.1056/NEJMoa1504720
84. Neal B, Perkovic V, Mahaffey KW, *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**(7):644–57. https://doi.org/10.1056/NEJMoa1611925
85. Cannon CP, Pratley R, Dagogo-Jack S, *et al*. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020;**383**(15):1425–35. https://doi.org/10.1056/NEJMoa2004967

86. Wanner C, Inzucchi SE, Lachin JM, *et al*. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;**375**(4):323–34. https://doi.org/10.1056/NEJMoa1515920
87. Dapagliflozin for treating chronic heart failure with reduced ejection fraction. Technology appraisal guidance [TA679] Published date: 24 February 2021. See: https://www.nice.org.uk/guidance/TA679 (accessed 2 March 2021)
88. Cannon CP, McGuire DK, Pratley R, *et al*. Design and baseline characteristics of the eValuation of ERTugliflozin efflcacy and Safety CardioVascular outcomes trial (VERTIS-CV). *Am Heart J* 2018;**206**:11–23. https://doi.org/10.1016/j.ahj.2018.08.016
89. Duckworth W, Abraira C, Moritz T, *et al*. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;**360**(2):129–39. https://doi.org/10.1056/NEJMoa0808431
90. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**(24):2545–59. https://doi.org/10.1056/NEJMoa0802743
91. Nathan DM, Cleary PA, Backlund J-YC, *et al*. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;**353**(25):2643–53. https://doi.org/10.1056/NEJMoa052187
92. Kosiborod M, Cavender MA, Fu AZ, *et al*. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). *Circulation* 2017;**136**(3):249–59. https://doi.org/10.1161/CIRCULATIONAHA.117.029190
93. National Cardiac Audit Programme. National Heart Failure Audit 2016/17 Summary. 2018. https://www.nicor.org.uk/wp-content/uploads/2018/11/Heart-Failure-Summary-Report-2016-17.pdf

UPCOMING EVENTS

Association of British Clinical Diabetologists

For more information please visit **https://abcd.care/events**

ABCD Regional Meeting Yorkshire

Thursday, 17th June, 2021, VIRTUAL

This 3rd Yorkshire ABCD training day builds on our previous programmes to provide an excellent opportunity for up to date diabetes CPD and to network with colleagues in the region. This event is aimed at the MDT as a whole including primary care teams and hospital specialist teams treating people with diabetes

ABCD DTN-UK Annual Meeting 2021

Wednesday 13th October 2021, VIRTUAL

This is the premier UK meeting for healthcare professionals dedicated to diabetes technology and we look forward to seeing all clinicians interested or even slightly curious about the latest advances in diabetes technology.

ABCD Conference 2021

Thursday 14th October 2021, VIRTUAL

This conference offers professional education, update, development and networking for clinicians working in diabetes and endocrinology.

ABCD Regional Meeting South East

Thursday 2nd December 2021, VIRTUAL

An excellent opportunity for up to date diabetes CPD and to network with colleagues in the region. An event aimed at the MDT as a whole including primary care teams and hospital specialist teams treating people with diabetes.

ABCD Meeting to Commemorate the Centenary of the First Administration of Insulin into a Human

Tuesday 11th January 2022, Royal College of Physicians, London

On January 11th 1922 insulin was first used in the treatment of diabetes. Administered to a 14 year old, Leonard Thompson, who had diabetes and was dying at the Toronto General Hospital. In memory of this landmark moment in the history of diabetes, on January 11th 2022, exactly 100 years later, ABCD has planned a special event at the Royal College of Physicians in London to commemorate the occasion.