Review Article

Pharmacological treatment for Type 2 diabetes integrating findings from cardiovascular outcome trials: an expert consensus in the UK

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Abstract

In people with Type 2 diabetes, cardiovascular disease is a leading cause of morbidity and mortality. Thus, as well as controlling glucose, reducing the risk of cardiovascular events is a key goal. The results of cardiovascular outcome trials have led to updates for many national and international guidelines. England, Wales and Northern Ireland remain exceptions, with the most recent update to the National Institute for Health and Care Excellence (NICE) guidelines published in 2015. We reviewed current national and international guidelines and recommendations on the management of people with Type 2 diabetes. This article shares our consensus on clinical recommendations for the use of sodium-glucose co-transporter 2 inhibitors (SGLT-2is) and glucagon-like peptide 1 receptor agonists (GLP-1RAs) in people with Type 2 diabetes and established or at very high risk of cardiovascular disease in the UK. We also consider cost-effectiveness for these therapies. We recommend considering each person’s cardiovascular risk and using diabetes therapies with proven cardiovascular benefits when appropriate to improve long-term outcomes and cost-effectiveness.

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Introduction

The prevalence of Type 2 diabetes is rising rapidly in the UK and across the world, in part due to the increasing prevalence of obesity and the ageing population [1,2]. In people with Type 2 diabetes, cardiovascular disease remains the leading cause of morbidity and mortality [3]. Once cardiovascular disease is present in a person with Type 2 diabetes, the risk of all-cause mortality is increased threefold and the risk of cardiovascular death is increased fivefold [4]. Thus, in addition to controlling glucose, reducing the risk of cardiovascular events is a key goal in the management of people with Type 2 diabetes. Before the establishment of cardiovascular disease, treatment should aim to reduce the risk of cardiovascular disease developing; whereas, once it occurs, the goal needs to be limiting its progression and reducing the risk of further adverse cardiovascular events. Attaining good glycaemic control, by whatever means, is important within the first 5 years after diagnosis of Type 2 diabetes, and prior to the onset of micro- or macrovascular disease, because this decreases the risk of cardiovascular events [5]. However, prior to 2008, no individual anti-hyperglycaemic agent had demonstrated a benefit with regard to cardiovascular events beyond 5 years within a clinical trial setting [5].

As a result of safety concerns raised with the peroxisome proliferator-activated receptor gamma agonist rosiglitazone [6], the US Food and Drug Administration (FDA) published a Guidance for Industry document requiring evidence of the cardiovascular safety of new anti-hyperglycaemic agents [7]. Since then, data from several cardiovascular outcome trials of dipeptidyl peptidase-4 inhibitors (DPP-4is) [8–11], sodium–glucose co-transporter 2 inhibitors (SGLT-2is) [12–15] and glucagon-like peptide 1 receptor agonists (GLP-1RAs) [16–22] have been published (Table 1). To date, all these trials have met their primary endpoint of non-inferiority compared with placebo with respect to the composite cardiovascular endpoint of cardiovascular mortality, non-fatal myocardial infarction and stroke [3-point major adverse cardiovascular events (MACE)] or 4-point
What’s new?

- Following positive cardiovascular outcome trial results, many national and international guidelines on the management of people with Type 2 diabetes have been updated for those also at high risk of cardiovascular disease. However, not all countries have updated their guidelines, notably England, Wales and Northern Ireland.
- This review shares a consensus on clinical recommendations for use of glucagon-like peptide 1 receptor agonists and sodium–glucose co-transporter 2 inhibitors in people with Type 2 diabetes.
- Although some countries have not yet updated their guidelines, we recommend consideration of each person’s cardiovascular risk when selecting their diabetes therapy, to improve long-term outcomes and cost-effectiveness.

MACE, including hospitalization for unstable angina (Table 1). Trials of two SGLT-2is (EMPA-REG [15] with empagliflozin and CANVAS [12] with canagliflozin) and three GLP-1RAs (LEADER [20] with liraglutide, HARMONY Outcomes [16] with albiglutide and REWIND [17] with dulaglutide) have demonstrated the superiority of these drugs compared with standard of care (including targeted glycaemic equipoise) for reducing the risk of MACE. Additionally, a post hoc analysis of the SUSTAIN 6 [22] trial demonstrated the superiority of the GLP-1RA semaglutide to placebo, and results from DECLARE-TIMI 58 demonstrated that dapagliflozin was non-inferior compared with placebo with regard to incidence of MACE, but significantly reduced rates of cardiovascular death and hospitalization for heart failure [24]. In this review, we provide an overview of current national and international guidelines and recommendations for the management of people with Type 2 diabetes at high risk of cardiovascular disease, and share our consensus (from an endocrinology, cardiology and stroke perspective) on clinical recommendations and decision-making for these people in the UK.

Recent updates to diabetes treatment guidelines and recommendations

Since publication of EMPA-REG [15], CANVAS [12], LEADER [20] and SUSTAIN 6 [22], a number of national and international guidelines and recommendations for the management of Type 2 diabetes have been updated to include cardiovascular risk reduction as a key consideration, and specifically the use of anti-hyperglycaemic agents that have demonstrated cardiovascular protection in those with Type 2 diabetes (Table 51). Indeed, some have explicitly named empagliflozin and liraglutide as appropriate choices for the management of people with Type 2 diabetes at high risk for cardiovascular disease [28–47].

Recent updates to international guidelines and recommendations

Several major international guidelines and recommendations on the management of Type 2 diabetes specifically cite EMPA-REG [15], CANVAS [12], LEADER [20] and SUSTAIN 6 [22], and recommend a hierarchical approach to drug selection dependent on the strength of this evidence [3,48–50]. The updated joint American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus statement emphasizes a stratification of people based on the presence of pre-existing atherosclerotic cardiovascular disease before considering which additional glucose-lowering agent to add as dual therapy (following metformin failure) [51]. In those with atherosclerotic cardiovascular disease, the ADA/EASD recommend the use of a SGLT-2i (with a preference for empagliflozin) for those with a diagnosis of congestive cardiac failure or chronic kidney disease, or a GLP-1RA (with a preference for liraglutide or semaglutide) for those with atherosclerotic disease, as these agents have been shown to reduce cardiovascular death and all-cause mortality (except semaglutide) when added to standard care [51].

Diabetes treatment guidelines in the UK

In 2015, the National Institute for Health and Care Excellence (NICE) of England (also followed in Wales and Northern Ireland) set up a ‘standing update committee for diabetes’ to enable faster updates of discrete areas of the guidelines when new and relevant data are published. Since then, a number of minor amendments have been made, including the addition of SGLT-2is to the initial drug treatment section [52]. However, as yet, no individual SGLT-2i has been recommended, and there is no mention of reducing cardiovascular risk in the algorithm. Similarly, guidelines relating to GLP-1RAs have not yet been updated, and they remain restricted to settings when triple oral therapy is not effective, not tolerated or contraindicated, and only if the person has a BMI ≥ 35 kg/m² (adjusted accordingly for ethnic groups), cannot tolerate insulin or weight loss would benefit other significant obesity-related comorbidities [52]. Moreover, the algorithm has no mention of the use of GLP-1RAs in people who cannot be treated with metformin.

Consensus treatment recommendations for people with Type 2 diabetes

Therapy choices based on efficacy

Lifestyle interventions are a key part of Type 2 diabetes management and should be considered concurrently with...
| Drug     | Trial                      | Number randomized | Treatment interventions                                                                 | Primary endpoint | Primary outcome |
|----------|----------------------------|-------------------|-----------------------------------------------------------------------------------------|------------------|-----------------|
| DPP-4is  |                            |                   |                                                                                         |                  |                 |
| Alogliptin | EXAMINE [8] NCT00968708   | 5380              | 25, 12.5 or 6.25 mg OD (depending on eGFR) alogliptin vs. placebo                         | 3-point MACE     | Non-inferiority demonstrated HR 0.96, 95% CI 1.16*       |
|          | CAROLINA [9] NCT01243424  | 6051              | Linagliptin 5 mg OD vs. glimepiride 1–4 mg OD vs. placebo                               | 4-point MACE     | Non-inferiority demonstrated HR 1.02, 95% CI 0.89 to 1.17 |
|          | CARMELINA [23] NCT01897532 | 6979              | Linagliptin OD vs. placebo                                                             | 3-point MACE     | Non-inferiority demonstrated HR 1.00, 95% CI 0.89 to 1.12 |
| Saxagliptin | SAVOR-TIMI-53 [10] NCT01107886 | 16 492 | 5 mg OD (2.5 mg if eGFR < 50 ml/min) saxagliptin vs. placebo | 3-point MACE     | Non-inferiority demonstrated HR 0.98, 95% CI 0.88 to 1.09 |
| Sitagliptin | TECOS [11] NCT00790205   | 14 671            | 100 mg OD (50 mg if eGFR ≥ 30 to >50 ml/min 1.73 m² sitagliptin vs. placebo             | 4-point MACE     |                 |
| Vildagliptin | No ongoing trial n/a     | n/a               | n/a                                                                                     | n/a              |                 |
| SGLT-2is  |                            |                   |                                                                                         |                  |                 |
| Canagliflozin | CANVAS [12] NCT01032629 | 10 142            | 100 mg OD canagliflozin vs. 300 mg OD canagliflozin vs. placebo                        | 3-point MACE     | Superiority demonstrated HR 0.86, 95% CI 0.75 to 0.97   |
|          | CREDENCE [13] NCT02065791 | 4401              | 100 mg OD canagliflozin vs. placebo                                                    | Composite endpoint of end-stage kidney disease, doubling serum creatinine, and renal or CV death | Superiority demonstrated HR 0.70, 95% CI 0.59 to 0.82 |
| Dapagliflozin | DECLARE-TIMI 58 [14,24]  | 17 160            | 10 mg OD dapagliflozin vs. placebo                                                    | 3-point MACE; also CV death or hospitalisation for heart failure | Non-inferiority demonstrated Upper boundary of the 95% CI <1.3; P < 0.001 (Superiority demonstrated for co-primary endpoint of CV mortality and hospitalisations due to heart failure [HR 0.83, 95% CI 0.73 to 0.95]) (Trial ongoing) |
| Ertugliflozin | VERTIS CV [25] NCT01986881 | 8246              | 5 mg OD erthropilizine vs. 15 mg OD erthropilizine vs. placebo                       | 3-point MACE     |                 |
| Empagliflozin | EMPA-REG [15] NCT01131676 | 7028              | 10 or 25 mg empagliflozin OD vs. placebo                                              | 3-point MACE     | Superiority demonstrated HR 0.86, 95% CI 0.74 to 0.99   |
| GLP-1RAs  |                            |                   |                                                                                         |                  |                 |
| Albiglutide* | HARMONY Outcomes [16] NCT01522651 | 9463 | 30–50 mg OW albiglutide vs. placebo                                                   | Composite endpoint of cardiovascular death, myocardial infarction or stroke | Superiority demonstrated HR 0.78, 95% CI 0.68 to 0.90   |
| Dulaglutide | REWIND [26] NCT01394952   | 9901              | 1.5 mg OW dulaglutide vs. placebo                                                      | 3-point MACE     | Superiority demonstrated (press release) HR not reported |
| Exenatide  | EXSCEL [18] NCT01144338   | 14 752            | 2 mg OW exenatide vs. placebo                                                         | Composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke | Non-inferiority demonstrated HR 0.91, 95% CI 0.83 to 1.00 |
| ITCA 650   | FREEDOM-CVO [19] NCT01455857 | Not reported | 60 mcg/day ITCA 650 vs. placebo                                                      | 4-point MACE     | Non-inferiority demonstrated (press release) HR not reported |
| Liraglutide | LEADER [20] NCT01179048   | 9340              | 1.8 mg liraglutide OD vs. placebo                                                     | 3-point MACE     | Superiority demonstrated HR 0.87, 95% CI 0.78 to 0.97   |
Unless contraindicated, metformin remains the mainstay of first-line drug therapy in all people with Type 2 diabetes. We then recommend assessing cardiovascular disease risk to guide further therapy (Fig. 1). For those with established cardiovascular disease, use of empagliflozin, canagliflozin, liraglutide or semaglutide is recommended (based on recent cardiovascular outcome trials data and in keeping with updated national and international guidelines; Fig. 1). The specific drug choice may be further guided by the individual’s cardiovascular history and comorbidities. Given their favourable results in reducing hospitalization for heart failure, empagliflozin and canagliflozin are a

### Table 1 (Continued)

| Drug          | Trial                                      | Number randomized | Treatment interventions | Primary endpoint | Primary outcome          |
|---------------|--------------------------------------------|-------------------|-------------------------|------------------|--------------------------|
| Lixisenatide  | ELIXA [21] NCT01147250                     | 6068              | 10 μg (titrated up to 20 μg) OD lixisenatide vs. placebo | 4-point MACE    | Non-inferiority demonstrated HR 1.02, 95% CI 0.89 to 1.17 |
| Semaglutide   | SUSTAIN 6 (pre-approval) [22] NCT01720446  | 3297              | (OW injection) 0.5 or 1.0 mg semaglutide vs. placebo | 3-point MACE    | Non-inferiority demonstrated HR 0.74, 95% CI 0.58 to 0.95 (superiority demonstrated post hoc analysis) |
|               | PIONEER 6 (oral semaglutide) [27] NCT02692716 | 3183              | Oral semaglutide OD vs. placebo | 3-point MACE    | Non-inferiority demonstrated (press release) HR 0.79 |

*Upper boundary of the one-sided repeated confidence interval, at an alpha level of 0.01.
†Albiglutide is not currently available in the UK.
BID, twice daily; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular events; OD, once daily; OW, once weekly; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

### Lifestyle interventions and metformin

**Pre-existing or high risk for cardiovascular disease?**

- **Yes**
  - **eGFR ≤ 45 ml/min 1.73 m² or atherosclerotic cardiovascular disease or stroke**
    - GLP-1RAs liraglutide or semaglutide
  - **eGFR > 45 ml/min 1.73 m² and heart failure**
    - SGLT-2is empagliflozin or canagliflozin
- **No**
  - **Low hypoglycaemic risk Low weight gain**
    - GLP-1RAs SGLT-2is DPP-4is TZDs SUs

**Consider person-specific factors including weight and hypoglycaemia risk**

- **GLP-1RAs liraglutide or semaglutide**
- **SGLT-2is empagliflozin or canagliflozin**

**FIGURE 1** Initial therapy selection. Order does not denote any specific preference. *Metformin to be continued unless no longer tolerated.
†Individuals are considered a high risk if they have a history of cardiovascular disease or at least one risk factor (see Table S2 for further details). DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.
key consideration for those with heart failure, although the licences do not allow for initiation if eGFR is \( < 60 \text{ ml/ min } 1.73 \text{ m}^2 \) [12,15,53,54]. Empagliflozin and canagliflozin should be discontinued when eGFR is persistently below 45 ml/ min \( 1.73 \text{ m}^2 \) [53,54].

Significant reductions in MACE were reported with canagliflozin [12] and empagliflozin [15], and a numerical reduction with dapagliflozin [24]. However, notably, people with pre-existing cardiovascular disease should be made aware of the increased risk of lower leg amputations associated with canagliflozin [12,54], although no significant increase was seen in the CREDECE study [13]. A non-significant increase in risk of stroke was reported with empagliflozin despite a reduction in blood pressure [15], and dapagliflozin should be discussed before treatment in people with a history of stroke [55].

Liraglutide or semaglutide are recommended for people with atherosclerotic cardiovascular disease or stroke (or a cardiovascular risk factor and eGFR \( < 45 \text{ ml/ min } 1.73 \text{ m}^2 \); Fig. 1), although the use of semaglutide should be cautioned in those with active diabetic retinopathy, due to an increased risk of retinopathy events found in SUSTAIN 6 [22,56]. In LEADER, there was no significant difference in the risk of diabetic retinopathy associated with liraglutide vs. placebo [20]. If further treatment intensification is required to achieve glycaemic control, additional drugs (from another class) with proven cardiovascular safety are recommended, consistent with recent international recommendations [51]. Of interest will be the full results from REWIND, available June 2019, which evaluated dulaglutide in people with Type 2 diabetes, 69% of whom did not have a prior cardiovascular event at baseline. In this event-driven study, the press release stated that dulaglutide significantly reduced the risk of cardiovascular events [17]. Careful consideration of these data (once published) will be required when considering future guidelines to determine whether there was an effect on primary prevention, or whether the result was driven by the events occurring predominately in the 31% with prior cardiovascular disease [17].

For people without confirmed cardiovascular disease, cardiovascular risk factor modification is still important (including smoking cessation, hypertension management, and lipid-lowering and anti-platelet medication). The specific glucose-lowering drug or drug combination choice is best guided by individual factors, including consideration of weight and risk of hypoglycaemia (Fig. 1). Unlike the results from EMPA-REG for empagliflozin, the DECLARE-TIMI 58 trial did not achieve a reduction in 3-point MACE with dapagliflozin vs. placebo [24]. This dapagliflozin trial, however, showed a significant reduction in the co-primary outcome of cardiovascular mortality and hospitalizations due to heart failure, which were numerically similar in those with established disease and in the primary prevention population. Therefore, dapagliflozin may be considered for those without established cardiovascular disease but who are at high risk for heart failure with an eGFR \( \geq 60 \text{ ml/ min } 1.73 \text{ m}^2 \).

Of note, the mean eGFR of participants in DECLARE-TIMI 58 (85.2 ml/min 1.73 m\(^2\)) [24], was higher than in EMPA-REG (74.1 ml/min 1.73 m\(^2\)) [15] and CANVAS (76.5 ml/min 1.73 m\(^2\)) [12]. This differential in renal function and the observed differences in cardiovascular and mortality outcomes raise important questions around the mechanism of action of these drugs, in terms of cardiovascular effects as well as their optimal therapeutic positioning.

Furthermore, the results of the CREDECE study, which evaluated the renovascular outcomes associated with canagliflozin in people with Type 2 diabetes and chronic kidney disease, also require careful consideration. The study was discontinued early due to efficacy and outcome benefits in favour of canagliflozin, and future guidelines therefore need to take the trial results into consideration [13].

**Therapy choices based on cost-effectiveness analyses**

Cost-effectiveness analyses may be an additional consideration when choosing therapy. Assessments by NICE show that most SGLT-2is and GLP-1RAs are cost-effective at reducing hyperglycaemia with incremental cost-effectiveness ratios (ICERs) below the commonly accepted £20 000–30 000/ quality-adjusted life-year (QALY) threshold (Table 2). An early analysis concluded that liraglutide 1.2 mg was cost-effective but there was uncertainty regarding the 1.8 mg dose [61]; however, this has been superseded by new analyses in health technology assessments conducted as part of the NICE Type 2 diabetes clinical guidelines published in 2015 (and updated in 2017) [52], which make positive recommendations for GLP-1RAs as a drug class.

Empagliflozin and canagliflozin have both demonstrated cost-effectiveness vs. comparators in the UK [62–64]. Several studies of liraglutide in the UK have also concluded cost-effectiveness, despite increased acquisition cost, due to reduction in diabetes-related complications [65–67]. However, cost-effectiveness analyses evaluate drugs as glucose-lowering entities, and modelling is therefore based on traditional risk equations [68–71], which do not capture potential cardiovascular benefits [72]. Further analyses are now required to ensure that the additional benefit of reducing cardiovascular events is captured in cost-effectiveness evaluations in people with Type 2 diabetes, based on results from the respective cardiovascular outcome trials, and to incorporate these into updated ICER estimates.

The accepted technique for evaluating potential additional benefits beyond glycaemic control is termed marginal-effects analysis. This approach incorporates not just the traditional risk equation of improved glucose management, but also a fixed effect for reduction in cardiovascular events by implementing treatment strategies based around empagliflozin, canagliflozin, liraglutide or semaglutide in populations reflected by the study data. Evaluation of how the observed
event rate reductions in the respective trials affect healthcare resources and hospital bed occupancy is also necessary. This may be a more comprehensive way of looking at how implementing the strategies of cardiovascular outcome trials, impact on the budget and healthcare system compares with the more typically employed number-needed-to-treat analysis. These economic analyses will no doubt form the basis of future NICE technology appraisals and a guideline update. Meanwhile, we believe National Health Service (NHS) formularies should consider these international guidance updates to achieve earlier clinical and economic benefits or be rapidly responsive when NICE also evaluates these data. With an ever-growing diabetes and cardiovascular disease population, it is important make these therapies available without delaying for NICE updates, where the data are compelling.

Conclusions

Many people with Type 2 diabetes also have, or are at high risk of, concomitant cardiovascular disease and control of cardiovascular events remains a key goal for managing
outcomes. Given highly favourable results of cardiovascular outcome trials, many national and international guidelines and recommendations, including the consensus statement from the ADA and EASD, have been updated to include these results and therefore optimize treatment approaches. Although, in England, Wales and Northern Ireland, NICE postponed updating recommendations for SGLT-2i and GLP-1RA classes as some trials are still ongoing, the current evidence base of these agents has been evaluated by international guidelines groups recognizing their benefits. We therefore recommend evaluating individual’s cardiovascular risk factors before escalating diabetes therapy and considering anti-hyperglycaemics with proven cardiovascular benefit, to improve long-term outcomes, and reduce unplanned health resource use additionally. Formularies wishing to reduce the burden of care of diabetes should consider these latest guidelines as soon as possible to enable clinicians to maximize diabetes treatment.

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Supporting Information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. International and selected national guideline updates or recommendations since the publication of cardiovascular outcome trials.

Table S2. Definitions of high risk cardiovascular events according to trial.