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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.

Diabet. Med. 36, 1063–1071 (2019)

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

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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 S1). 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

Table 1 Cardiovascular outcome trials of anti-hyperglycaemic agents

Drug	Trial	Cardiovascular outcome trial			
		Number randomized	Treatment interventions	Primary endpoint	Primary outcome
DPP-4is					
Alogliptin	EXAMINE [8] NCT00968708	5380	2.5, 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* (Trial ongoing)
Linagliptin	CAROLINA [9] NCT01243424	6051	Linagliptin 5 mg OD vs. glimepiride 1–4 mg OD	4-point MACE	
	CARMELINA [23] NCT01897532	6979	Linagliptin OD vs. placebo	3-point MACE	Non-inferiority demonstrated HR 1.02, 95% CI 0.89 to 1.17
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 1.00, 95% CI 0.89 to 1.12
Sitagliptin	TECOS [11] NCT00790205	14 671	100 mg OD (50 mg if eGFR ≥30 to >50 ml/min 1.73 m ²) sitagliptin vs. placebo	4-point MACE	Non-inferiority demonstrated HR 0.98, 95% CI 0.88 to 1.09
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
	CREDESCENCE [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] NCT01730534	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; <i>P</i> < 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 ertugliflozin vs. 15 mg OD ertugliflozin vs. placebo	3-point MACE	Superiority demonstrated HR 0.86, 95% CI 0.74 to 0.99
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	EXSCCEL [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

Table 1 (Continued)

Drug	Trial	Cardiovascular outcome 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 <i>post hoc</i> 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.

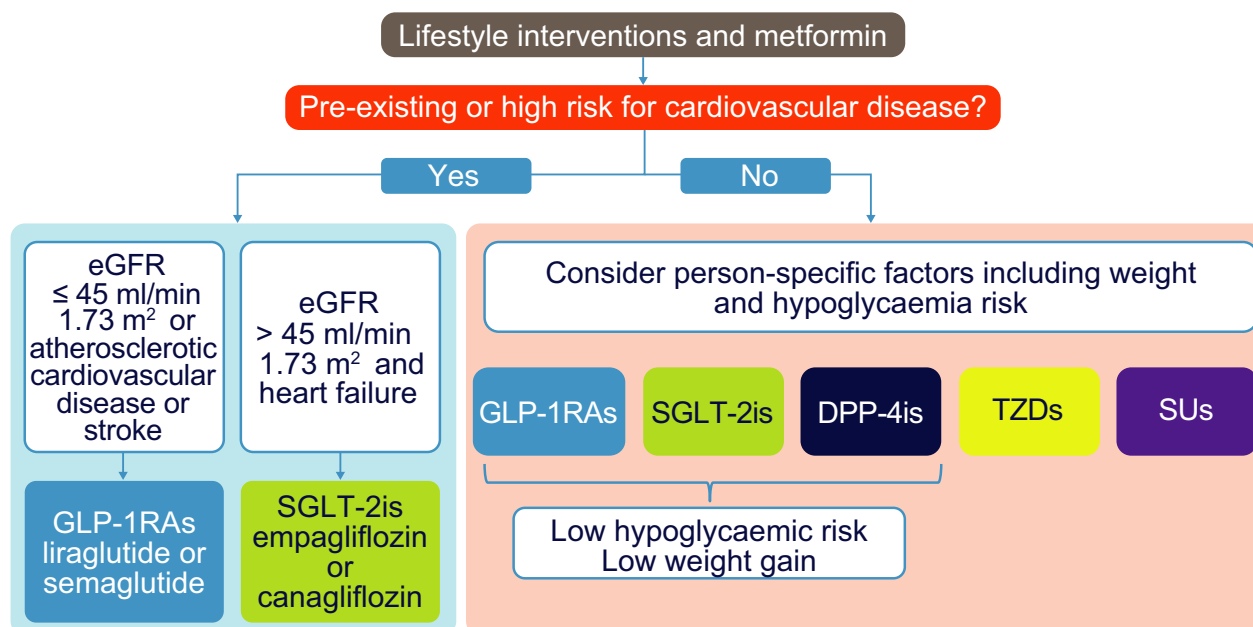


FIGURE 1 Initial therapy selection. Order does not denote any specific preference. *Metformin to be continued unless no longer tolerated.

†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.

pharmacotherapy [52]. 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

key consideration for those with heart failure, although the licences do not allow for initiation if eGFR is < 60 ml/min 1.73 m² [12,15,53,54]. Empagliflozin and canagliflozin should be discontinued when eGFR is persistently below 45 ml/min 1.73 m² [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 CREDENCE 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 ml/min 1.73 m²; 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 predominantly 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 ≥ 60 ml/min 1.73 m².

Of note, the mean eGFR of participants in DECLARE-TIMI 58 (85.2 ml/min 1.73 m²) [24], was higher than in EMPA-REG (74.1 ml/min 1.73 m²) [15] and CANVAS (76.5 ml/min 1.73 m²) [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 CREDENCE 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

Table 2 Cost-effectiveness of all sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists assessed by National Institute for Health and Care Excellence

Drug	Most likely cost-effectiveness estimate (as an ICER)
SGLT-2is	
Canagliflozin	The committee concluded that the minor differences in costs and QALYs between canagliflozin (100 and 300 mg) and its key comparators showed that canagliflozin was a cost-effective use of NHS resources as dual therapy in combination with metformin, triple therapy in combination with metformin and either a sulphonylurea or a thiazolidinedione, and as an add-on treatment to insulin [57].
Dapagliflozin	<ul style="list-style-type: none"> For dapagliflozin as dual therapy in combination with metformin, the committee considered the DSU deterministic analysis and scenario analyses, which included convergence of differences in weight between treatment groups at the time of switching to the last line of treatment. It noted that these showed that DPP-4is were associated with higher costs and QALYs than dapagliflozin, but that these differences were small. It noted further that, in the DSU probabilistic sensitivity analysis, these differences were even smaller. For dapagliflozin as an add-on to insulin, the committee noted that, in all of the analyses conducted by the DSU, the estimate of the ICER for dapagliflozin, compared with DPP-4is, was below £20 000 per QALY [58].
Ertugliflozin	ICER not yet available.
Empagliflozin	The committee concluded that the minor differences in costs and QALYs between empagliflozin (10 and 25 mg) and its key comparators showed that empagliflozin was a cost-effective use of NHS resources as dual therapy in combination with metformin, triple therapy in combination with metformin and either a sulphonylurea or a thiazolidinedione, and as an add-on treatment to insulin [59].
GLP-1RAs	
Dulaglutide	ICER not yet available.
Exenatide	The committee noted that the ICERs presented in the manufacturer's submission were not specific to the place of weekly prolonged-release exenatide in triple- and dual-therapy regimens. The committee did, however, consider on the basis of the ICERs presented in the manufacturer's submission, that weekly prolonged-release exenatide is likely to be cost-effective when used in the same place in the treatment pathway as twice-daily exenatide and liraglutide 1.2 mg were currently recommended [60].
Liraglutide	<ul style="list-style-type: none"> There were many ICERs presented for different comparisons. For liraglutide vs. exenatide (triple therapy), the committee accepted the ICER of £10 100 per QALY gained (although the committee noted that this ICER related to liraglutide 1.8 mg). The committee did not consider the ICERs presented for other oral therapies in both dual- and triple-therapy regimens to be robust enough to allow them to recommend liraglutide as a cost-effective alternative. The committee noted the lack of clinical trial evidence showing a significant benefit from increasing the liraglutide dose from 1.2 to 1.8 mg, the widely varying ICERs and the uncertainty in the economic analysis. The committee concluded that liraglutide 1.8 mg would not be a cost-effective use of NHS resources, and therefore was not recommended (NICE 2010[61]; superseded by NG28)[52]. Note that, although there are no specific references to the cost-effectiveness of liraglutide 1.2 mg, it is recommended for use in very specific conditions in dual or triple therapy (see: NICE 2010) [52,61].
Lixisenatide	ICER not yet available.
Semaglutide	ICER not yet available.

DPP-4i, dipeptidyl peptidase-4 inhibitor; DSU, decision support unit; GLP-1RA, glucagon-like peptide-1 receptor agonist; ICER, incremental cost-effectiveness ratio; NICE, UK National Institute for Health and Care Excellence; NHS, UK National Health Service; NG28, NICE guideline 28; QALY, quality-adjusted life-year; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

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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Competing interests

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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.