National Institute for Health and Care Excellence

Draft for consultation

Type 2 diabetes in adults: management

Pharmacological management of type 2 diabetes

Committee discussion

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1.1 Review questions

1.1.1 Report E, Initial therapy

For different population subgroups, which individual and/or combinations of pharmacological therapies are most clinically and cost-effective as initial treatment for the management of type 2 diabetes?

1.1.2 Report F, Subsequent therapy

Which pharmacological therapies are most clinically and cost-effective for the management of type 2 diabetes when current treatment has not given adequate response, including:

- medicines within the following classes biguanides, DPP-4 inhibitors, GLP-1 receptor agonists, insulin, sulfonylureas, SGLT-2 inhibitors, and thiazolidinediones (but not limited to these),
- approaches to optimise treatment (including combination treatment, switching to different therapies, de-escalation and stopping previous therapies), and
- consideration of different population subgroups?

1.2 Summary of significant recommendations

1.2.1 Standard release or modified release metformin

What is being recommended?	What is the evidence?	What is the quality of the evidence?	Why did the committee make the recommendation?
Offer metformin	Clinical evidence for metformin from the initial therapy (E) review for the population at high risk of developing cardiovascular disease. When comparing metformin (modified release) to metformin (type unspecified): • Metformin type unspecified showed strong evidence of a clinically important benefit in reducing HbA1c. Modified release metformin showed weak evidence of a clinically important benefit. • Neither showed an effect on weight loss in the analysis. Pairwise analysis for additional outcomes. When comparing metformin (modified release) to metformin (type unspecified): • A harm in all-cause mortality. The committee agreed this was not important because the evidence was very low quality, including a single study with a single death in the people taking modified-release metformin and no deaths in people taking metformin (type unspecified). • No clinically important difference in hypoglycaemia episodes Cost information about modified release and standard release metformin.	HbA1c change = Low Weight loss = Very low For more information	Clinical evidence of low quality indicating reductions in HbA1c. Other evidence showing no difference. The committee highlighted they did not have access to evidence showing the effect on gastrointestinal adverse events. They agreed that in clinical experience people have less adverse effects with modified-release metformin. They acknowledged that wider literature was uncertain about the effect of this. At the time of making the recommendation, modified-release metformin was more expensive than standard-release metformin. Given the two were equivalent in efficacy and safety, the committee agreed to offer metformin, using the version with the lowest acquisition cost as the default.
Consider modified-release metformin for	Committee consensus based on clinical experience and living experience.	Not applicable	The committee agreed that there were circumstances where adherence

adults with type 2 diabetes when they or their healthcare professional have concerns about adherence to standard-release metformin therapy			may be a concern that may influence the choice of metformin therapy, for example: • People who would benefit from taking medication all at once during a day rather than spread out throughout a day • People who work shifts (and so reduces the risks from inconsistent dose timings) • People who may find it difficult to take their medication consistently (for example: people with dementia) The committee noted that modified-release metformin would not be suitable for people with swallowing difficulties who need medication to be crushed. Standard-release metformin is a better option in this scenario.
For people with type 2 diabetes who are taking standard-release metformin: if it is effective and tolerated, continue; if it is not tolerated, offer modified-release metformin.	Committee consensus based on clinical experience and living experience.	Not applicable.	Committee members with living experience acknowledged that metformin adverse events can be a barrier to initiating medicine treatment as the side effects can have a significant impact on quality of life, people may not want to talk to their healthcare professionals about them and be able to access appointments to do so in a timely manner and so may reduce motivation to continue treatment. The committee agreed that modified-release metformin should be offered if

			people have adverse effects from standard-release metformin. Recommendations also discuss options for people who do not tolerate metformin.

1.2.2 Initial therapy: Metformin, SGLT-2 inhibitors

What is being recommended?	What is the evidence?	What is the quality of the evidence?	Why did the committee make the recommendation?

For adults with type 2 diabetes (and no significant comorbidity), offer dual therapy with metformin and an SGLT-2 inhibitor	Clinical evidence from the network meta-analysis (NMA) for the subsequent therapy (F) review for the population at high risk of developing cardiovascular disease.
	
	• SGLT-2 inhibitors were more effective at reducing cardiovascular events than placebo
	  ○ Canagliflozin, dapagliflozin and ertugliflozin showed strong evidence of clinically important reductions in hospitalisations for heart failure over 3 years
	  ○ Canagliflozin showed strong evidence of reductions in 3-item MACE while dapagliflozin showed mild evidence of reductions in 3-item MACE
	  ○ Canagliflozin, dapagliflozin and empagliflozin showed a mixture of benefits or no difference for individual events that make up MACE. The committee acknowledged the lower power in these trials for measuring these events making them less reliable measures.
	• Dapagliflozin showed strong evidence of clinically important reductions in end-stage renal failure over 3 years, this was milder but still clinically important for canagliflozin
		Cardiovascular and renal outcomes = Moderate
		
		HbA1c change = Low
		
		Weight change = Very low
		
		For more information
			Strong clinical evidence of moderate quality indicating reductions in cardiovascular and renal events and low quality indicating reductions in HbA1c.
			
			Limited evidence for metformin. However, clinical experience indicating benefits for HbA1c and weight loss.
			
			While there is no evidence for specific subgroups in the analysis, the committee agreed that the evidence for the population at high risk of developing heart disease could be applied to the general population with type 2 diabetes (and so applies to people living with obesity and people living with overweight).

	• All SGLT-2 inhibitors showed strong evidence of clinically important reductions in HbA1c change and weight change. Clinical evidence for metformin from the initial therapy (E) review for the population at high risk of developing cardiovascular disease. This showed that metformin reduced HbA1c. Pairwise analysis for additional outcomes. This indicated no specific efficacy or safety factors that influenced the decision making. No evidence for specific subgroups in the clinical review (for example: people living with obesity, people living with overweight, people with frailty, people with early onset type 2 diabetes). Health economic modelling evidence from the groups of people living with obesity and people living with overweight that showed that SGLT-2 inhibitors were cost effective for people living with obesity and were above the cost effectiveness threshold with an ICER of £23,039.		It is cost effective for people living with obesity. While it is not cost effective at a threshold of £20,000 per QALY for people living with overweight. The benefits that can be achieved for the population are important in primary prevention of cardiovascular disease. Providing early treatment reduces lifelong effects of disease and impacts on the healthcare system. Given this, and the uncertainties in the evidence, they agreed to lower the threshold and consider this as cost-effective for this case. Agreement that if metformin is contraindicated that an SGLT-2 inhibitor alone should be the next choice.
For adults with type 2 diabetes and heart failure, offer metformin and an SGLT-2 inhibitor	Clinical evidence from the network-meta analysis (NMA) for the subsequent therapy (F) review for the population with heart failure. The committee noted that the evidence came from subgroup analyses of larger trials containing people with and without heart failure. • Canagliflozin showed mild evidence for a reduction in 3-point MACE. Dapagliflozin and ertugliflozin showed an uncertain effect. • Canagliflozin, dapagliflozin and ertugliflozin showed strong evidence of clinically important reductions in hospitalisation for heart failure. • Canagliflozin and dapagliflozin showed a mixture of benefits or no difference for individual events that make up MACE. The	For heart failure NMA: 3-point MACE: Moderate Hospitalisation for heart failure: Low Other outcomes: Low-Very low	Direct clinical evidence supported by indirect clinical evidence indicating moderate to low quality benefits of SGLT-2 inhibitors in reducing cardiovascular adverse events and HbA1c. Limited evidence for metformin. However, clinical experience indicating benefits for HbA1c and weight loss. The committee acknowledged that SGLT-2 inhibitors are regularly

	committee acknowledged the lower power in these trials for measuring these events making them less reliable measures. Clinical evidence from the network meta-analysis (NMA) for the subsequent therapy (F) review for the population at high risk of developing cardiovascular disease. This was applied as studies where up to 85% of the population could have heart failure were included in this analysis. Therefore, it was agreed that it could be indirectly applied. For the results see: For adults with type 2 diabetes (and no significant comorbidity), offer dual therapy with an SGLT-2 inhibitor and metformin Clinical evidence for metformin from the initial therapy (E) review for the population at high risk of developing heart disease. This showed that metformin reduced HbA1c. Pairwise analysis for additional outcomes. This indicated no specific efficacy or safety factors that influenced the decision making. Health economic modelling evidence for people with heart failure that showed that SGLT-2 inhibitors were above the cost effectiveness threshold with an ICER of £26,919. Sensitivity analysis showing an ICER of £21,181 when background care costs for heart failure were set to zero.	For more information For high risk NMA: For adults with type 2 diabetes (and no significant comorbidity), offer dual therapy with an SGLT-2 inhibitor and metformin	prescribed for people with heart failure. They have significant benefits in improving heart failure as well as being a treatment for type 2 diabetes. Providing them in this scenario is likely to be beneficial for supporting both treatment needs. SGLT-2 inhibitors were provided under an offer recommendation in the previous version of the guideline and the committee did not feel that there was a reason to change this based on the clinical evidence. Given this, they agreed to lower the cost effectiveness threshold in this case and make this recommendation. Agreement that if metformin is contraindicated that an SGLT-2 inhibitor alone should be the next choice.

For adults with type 2 diabetes and an eGFR above 30 ml/min/1.73 m^2 offer metformin and either dapagliflozin or empagliflozin For adults with type 2 diabetes and an eGFR of 20 ml/min/1.73 m^2 and up to 30 ml/min/1.73 m^2 offer either dapagliflozin or empagliflozin alone For adults with type 2 diabetes and an eGFR below 20 ml/min/1.73 m^2, consider a DPP-4 inhibitor	Limited clinical evidence from the network-meta analysis for the subsequent therapy (F) review for the population with chronic kidney disease (CKD). For SGLT-2 inhibitors: • Canagliflozin had strong evidence of a benefit in reducing 3-point MACE events while dapagliflozin had weak evidence of benefit • All SGLT-2 inhibitors had strong evidence of benefit in reducing hospitalisation for heart failure events (with the exception of ertugliflozin that had very uncertain results) • Canagliflozin had strong evidence of a clinically important benefit in reducing end-stage renal failure while dapagliflozin had weak evidence of a clinically important benefit • Strong evidence of benefits in reducing HbA1c for canagliflozin, dapagliflozin and empagliflozin (this was clinically important for empagliflozin). Weak evidence of benefit for ertugliflozin. • Strong evidence of benefits for all SGLT-2 inhibitors in reducing weight. • A mixture of beneficial events across the different SGLT-2 inhibitors for the events that make up MACE. For DPP-4 inhibitors: • Linagliptin and saxagliptin showed strong evidence of clinically important reductions in HbA1c. Sitagliptin and vildagliptin showed weak evidence of reductions in HbA1c. • DPP-4 inhibitors did not show convincing benefits or harms for cardiovascular or renal adverse events. Existing technology appraisals for dapagliflozin and empagliflozin for people with chronic kidney disease. Clinical evidence from the network meta-analysis for the subsequent therapy (F) review for the population at high risk of developing heart disease. This was applied as studies where up to 85% of the population could have chronic kidney disease were included in this analysis. Therefore, it was	For CKD population: 3-point MACE and hospitalisation for heart failure: Low Other outcomes: Very low For more information For high risk NMA: For adults with type 2 diabetes (and no significant comorbidity), offer dual therapy with an SGLT-2 inhibitor and metformin	Direct clinical evidence supported by indirect clinical evidence indicating low to very low quality benefits of SGLT-2 inhibitors in reducing cardiovascular and renal adverse events. The committee acknowledged that for people with more significant CKD, HbA1c reduction was not the aim of SGLT-2 inhibitors (as renal excretion of sugar reduces). Limited evidence for metformin. However, clinical experience indicating benefits for HbA1c and weight loss. Though acknowledgement of need for dose reduction and contraindication as CKD becomes more severe. Health economic evidence supporting the cost effectiveness of these medicines. The committee acknowledged that dapagliflozin and empagliflozin were the only SGLT-2 inhibitors to have licenses for use in people with chronic kidney disease and therefore agreed to only recommend these medicines. Consensus agreement that DPP-4 inhibitors would be safe treatments to initially prescribe for people with a

	agreed that it could be indirectly applied. For the results see: For adults with type 2 diabetes (and no significant comorbidity), offer dual therapy with an SGLT-2 inhibitor and metformin Clinical evidence for metformin from the initial therapy (E) review for the population at high risk of developing cardiovascular disease. This showed that metformin reduced HbA1c. Pairwise analysis for additional outcomes. This indicated no specific efficacy or safety factors that influenced the decision making. Health economic analysis that showed that SGLT-2 inhibitors were cost effective for people with CKD stage 1-3 and stage 4. No analysis was conducted for people with CKD stage 5.		very low eGFR to manage hyperglycaemia. Agreement that if metformin is contraindicated that an SGLT-2 inhibitor alone should be the next choice for people with an eGFR above 30 ml/min/1.73 m^2.

1.2.3 Initial therapy: Metformin, SGLT-2 inhibitors, GLP-1 receptor agonists

What is being recommended?	What is the evidence?	What is the quality of the evidence?	Why did the committee make the recommendation?

For adults with type 2 diabetes and atherosclerotic cardiovascular disease, offer metformin, an SGLT-2 inhibitor and subcutaneous semaglutide	Clinical evidence from the network-meta analysis (NMA) for the subsequent therapy (F) review for the population with atherosclerotic cardiovascular disease. • Canagliflozin and empagliflozin showed strong evidence of beneficial effects in reducing 3-point MACE events, while the other SGLT-2 inhibitors showed weak evidence of beneficial effects. • All SGLT-2 inhibitors showed strong evidence in reducing hospitalisations for heart failure • The evidence for HbA1c change was uncertain. Dapagliflozin showed strong evidence of a clinically important reduction in HbA1c, while the others showed weak evidence of a reduction in HbA1c. The committee agreed the aim of the trials was not to reduce HbA1c so the interpretation of these results is difficult. • Dapagliflozin showed strong evidence of weight reduction. • All the SGLT-2 inhibitors showed benefits in reducing individual cardiovascular events (with the exception of empagliflozin in reducing the number of strokes based on one study). • The evidence for GLP-1 receptor agonists was limited – this was due to the majority of studies including a mixture of people with atherosclerotic cardiovascular disease and without atherosclerotic cardiovascular disease. Due to this indirect evidence from the population of people at high risk of developing cardiovascular disease had to be used to supplement the analysis. • The evidence for people with cardiovascular disease showed that dulaglutide and exenatide had beneficial effects at reducing 3-point MACE. Clinical evidence from the network-meta analysis for the subsequent therapy (F) review for the population at high risk of developing heart disease. This was applied as studies where up to 85% of the population could have atherosclerotic cardiovascular disease were included in this analysis. Therefore, it was agreed that it could be indirectly applied. For the results for SGLT-2 inhibitors see: For adults with type	Atherosclerotic cardiovascular disease NMA: 3-point MACE: Moderate Hospitalisation for heart failure and weight change: Low HbA1c change: Very low Other outcomes: Low or very low For more information For high risk NMA: see For adults with type 2 diabetes (and no significant comorbidity), offer dual therapy with an SGLT-2	Direct clinical evidence supplemented by indirect clinical evidence indicating moderate to low quality benefits of SGLT-2 inhibitors and GLP-1 receptor agonists in reducing cardiovascular adverse events, weight and HbA1c. Limited evidence for metformin. However, clinical experience indicating benefits for HbA1c and weight loss. The greatest clinical benefits from GLP-1 receptor agonists were seen with subcutaneous semaglutide in terms of cardiovascular risk reduction and weight reduction. Subcutaneous semaglutide was the only GLP-1 receptor agonist that was cost effective. Agreement that if metformin is contraindicated that an SGLT-2 inhibitor with a GLP-1 receptor agonist should be the next choice.

	2 diabetes (and no significant comorbidity), offer dual therapy with an SGLT-2 inhibitor and metformin For GLP-1 receptor agonists: • Subcutaneous semaglutide, liraglutide and dulaglutide had strong evidence of benefits in reducing 3-item MACE. This was clinically important for subcutaneous semaglutide. Oral semaglutide and exenatide had weak evidence of benefits. • Liraglutide, exenatide, dulaglutide and oral semaglutide had weak evidence of benefits in reducing hospitalisation for heart failure. Subcutaneous semaglutide had weak evidence of increasing hospitalisations for heart failure. • Dulaglutide, exenatide and liraglutide had weak evidence indicating clinically important benefits in reducing end-stage renal failure. • All GLP-1 receptor agonists had strong evidence (apart from lixisenatide that showed weak evidence) of clinically important reductions in HbA1c. • Subcutaneous semaglutide, oral semaglutide and liraglutide had evidence of clinically important reductions in weight. This was strong evidence for subcutaneous semaglutide. Other GLP-1 receptor agonists showed reductions in weight that were not clinically important. Clinical evidence for metformin from the initial therapy (E) review for the population at high risk of developing heart disease. This showed that metformin reduced HbA1c. Pairwise analysis for additional outcomes. This indicated no specific efficacy or safety factors that influenced the decision making. Health economic analysis that showed that SGLT-2 inhibitors were cost effective and subcutaneous semaglutide is the only GLP-1 receptor agonist that is cost effective.	inhibitor and metformin	

For adults with early onset type 2 diabetes: offer metformin and a n SGLT-2 inhibitor and consider adding a GLP-1 receptor agonist	No clinical evidence for people with early onset type 2 diabetes. Indirect clinical evidence from the network meta-analysis for the subsequent therapy (F) review for the population at high risk of developing heart disease. For the results for SGLT-2 inhibitors see: For adults with type 2 diabetes (and no significant comorbidity), offer dual therapy with an SGLT-2 inhibitor and metformin For the results for GLP-1 receptor agonists see: For adults with type 2 diabetes and atherosclerotic cardiovascular disease, offer metformin, an SGLT-2 inhibitor and subcutaneous semaglutide Pairwise analysis for additional outcomes. This indicated no specific efficacy or safety factors that influenced the decision making. Health economic modelling evidence for people with early onset type 2 diabetes that showed that SGLT-2 inhibitors were above the cost effectiveness threshold with an ICER of £28,056. Modelling for GLP-1 receptor agonists showed that they were above the threshold with ICERs ranging between £39,537 and £102,108. Health inequalities analysis showing that SGLT-2 inhibitors have a positive net benefit when delivered to the quintile with the most deprivation when measured on the index with multiple deprivation.	For SGLT-2 inhibitors see: For adults with type 2 diabetes (and no significant comorbidity), offer dual therapy with an SGLT-2 inhibitor and metformin For GLP-1 receptor agonists see: For adults with type 2 diabetes and atherosclerotic cardiovascular disease, offer metformin, an SGLT-2 inhibitor and subcutaneous semaglutide	No direct clinical evidence to base the economic findings on. The research is likely challenging to conduct as a randomised controlled trial due to the very long follow-up required to capture adverse events. Therefore, it may be difficult for further clarification using this approach in a timely period for updating this recommendation (while acknowledging the benefit of more research in this area). The committee agreed that observational evidence shows this group is at very high risk of developing cardiovascular events and developing them sooner than people who develop type 2 diabetes at a later age. Given the raised risk, taking strategies earlier to reduce their lifetime cardiovascular risk is important for reducing future adverse health events and impact on quality of life. Given the impact on people in the most deprived group, providing this recommendation allows for an opportunity to reduce health inequalities by ensuring easier access to treatments that can then be targeted through local initiatives to people who need them.

			The population is more likely to also include people living with obesity, and so may benefit from the weight loss effects of GLP-1 receptor agonists. While the health economic analysis shows large ICERs, the inputs are very uncertain. The model was not made using many people with early onset type 2 diabetes and so may have limitations when considering the group. Given the uncertainty in this area and the committee's strong view that there is a need to reduce the risk of this group developing cardiovascular events in the future, they made this recommendation. Agreement that if metformin is contraindicated that an SGLT-2 inhibitor with or without a GLP-1 receptor agonist should be the next choice.

1.2.4 Initial therapy: Metformin alone

What is being recommended?	What is the evidence?	What is the quality of the evidence?	Why did the committee make the recommendation?

For adults with type 2 diabetes who have a level of frailty that places them at risk of adverse events from SGLT-2 inhibitors, consider metformin alone	Indirect clinical evidence for metformin from the initial therapy (E) review for the population at high risk of developing heart disease. This showed that metformin reduced HbA1c. No evidence for specific subgroups in the clinical review (for example: people living with obesity, people living with overweight, people with frailty, people with early onset type 2 diabetes). Health economic modelling was not conducted for this group but they were considered alongside the results for the model.	HbA1c change = Low For more information	No direct clinical evidence. Limited evidence for metformin. However, clinical experience indicating benefits for reducing HbA1c. Committee consensus in the absence of evidence that SGLT-2 inhibitors are not appropriate for people with significant frailty (for example: people at high risk of falls or dehydration). Therefore, a different management strategy is needed for people in this scenario. The committee agreed for initial therapy with metformin and if that is contraindicated a DPP-4 inhibitor, as these were seen as safe options to manage hyperglycaemia.

1.2.5 Subsequent therapy: DPP-4 inhibitor, then sulfonylurea, pioglitazone or insulin

What is being recommended?	What is the evidence?	What is the quality of the evidence?	Why did the committee make the recommendation?
For adults with type 2 diabetes who need further medicines to reach their glycaemic targets: add a DPP-4 inhibitor to their current treatment, if	Clinical evidence from the network-meta analysis (NMA) for the subsequent therapy (B) review for the population at high risk of developing heart disease. For DPP-4 inhibitors: • All DPP-4 inhibitors showed strong evidence of clinically important benefits in reducing HbA1c	For high risk NMA: HbA1c change = Low Weight change = Very low	DPP-4 inhibitors, sulfonylureas, pioglitazone and insulin are medicines to manage hyperglycaemia rather than to support holistic management of type 2 diabetes. They did not show benefits for

this is contraindicated, not tolerated or is not effective, offer: a sulfonylurea or pioglitazone or an insulin-based treatment.	• DPP-4 inhibitors did not show convincing benefits or harms for cardiovascular or renal adverse events. For sulfonylureas: • Gliclazide and glimepiride showed strong clinically important evidence of reducing HbA1c, while glipizide showed strong evidence but not clinically important evidence of reducing HbA1c • Glimepiride and glipizide showed strong evidence of weight gain, while gliclazide showed weak evidence of weight gain • Sulfonylureas did not show convincing benefits or harms for cardiovascular or renal adverse events. For pioglitazone: • Pioglitazone showed strong clinically important evidence of reducing HbA1c • Pioglitazone showed strong clinically important evidence of weight gain For insulins (insulin was a comparator arm in the analysis): • Insulins showed strong clinically important evidence of reducing HbA1c • Insulins showed strong evidence of weight gain No evidence for specific subgroups in the clinical review (for example: people living with obesity, people living with overweight, people with frailty, people with early onset type 2 diabetes). Clinical evidence from the network meta-analysis for the subsequent therapy (F) review for the population with atherosclerotic cardiovascular disease. For pioglitazone: • Pioglitazone showed strong evidence of increasing the number of heart failure hospitalisations	For more information For atherosclerotic cardiovascular disease NMA: Hospitalisation for heart failure = Low For more information	cardiovascular and renal protection or weight loss. The medicines (except for insulin) are not expensive and when given for glycaemia management, will successfully achieve that goal. Insulin is required to manage glycaemia for some people with diabetes. DPP-4 inhibitors are relatively safe medications. The other medications have reasons why you may not give them in certain circumstances (for example: sulfonylureas may not be appropriate for people with more significant chronic kidney disease or people likely to have falls, pioglitazone is contraindicated for people with heart failure). Given this, the committee recommended that DPP-4 inhibitors should be considered first (for people who are not already taking GLP-1 receptor agonists as the two medicines work on the same pathway and do not add clinical benefit when given together). After that the person taking the medication and the healthcare professional should choose the medicine that is going to best suit their needs out of a sulfonylurea, pioglitazone and insulin noting the specific characteristics of the medicine.

	Pairwise analysis for additional outcomes. This indicated that sulfonylureas increased the risk of hypoglycaemia and severe hypoglycaemia episodes compared to other medications. There was limited evidence about insulin. Otherwise, no specific efficacy or safety factors that influenced the decision making. Costing information that showed that DPP-4 inhibitors, sulfonylureas and pioglitazone are relatively inexpensive medications.		For more information refer to the section discussing DPP-4 inhibitors, sulfonylureas, pioglitazone and insulin.

1.2.6 Subsequent therapy: Adding a GLP-1 receptor agonist

What is being recommended?	What is the evidence?	What is the quality of the evidence?	Why did the committee make the recommendation?
Consider adding subcutaneous semaglutide for adults with type 2 diabetes with heart failure, if: they are living with obesity; there are no concerns about frailty that may increase the risk of adverse events with the medicine; they have a preserved ejection fraction.	Indirect clinical evidence from the network meta-analysis for the subsequent therapy (F) review for the population at high risk of developing heart disease. This was applied as studies where up to 85% of the population could have atherosclerotic cardiovascular disease were included in this analysis. Therefore, it was agreed that it could be indirectly applied. For the results for GLP-1 receptor agonists see: For adults with type 2 diabetes and atherosclerotic cardiovascular disease, offer metformin, an SGLT-2 inhibitor and subcutaneous semaglutide Pairwise analysis for additional outcomes. This indicated no specific efficacy or safety factors that influenced the decision making. Committee knowledge of a trial (STEP-HFpEF DM) that was released after the cut-off date for the final rerun search that is relevant to this comparison that potentially shows benefits in	For GLP-1 receptor agonists see: For adults with type 2 diabetes and atherosclerotic cardiovascular disease, offer metformin, an SGLT-2 inhibitor and subcutaneous semaglutide For more information	Health economic evidence supporting that subcutaneous semaglutide was cost effective for people with heart failure. Clinical trials have shown that subcutaneous semaglutide could be effective for people living with obesity with preserved ejection fraction heart failure. The committee agreed that the medicine should not be given to people with heart failure with frailty that meant that they would be more prone to adverse events from weight loss because of the medicine.

	this area. It was agreed this would be extracted during the consultation period. Health economic analysis that showed that subcutaneous semaglutide was cost effective.		Given this, they agreed a weak recommendation for subcutaneous semaglutide under specific conditions for people with heart failure.
Consider adding a GLP-1 receptor agonist for adults with type 2 diabetes who are living with obesity, if: they have been taking initial therapy for at least 3 months; further medicines are needed to reach their glycaemic targets; they are not already taking a GLP-1 receptor agonist.	Indirect clinical evidence from the network meta-analysis for the subsequent therapy (F) review for the population at high risk of developing heart disease. This was applied as studies where up to 85% of the population could have atherosclerotic cardiovascular disease were included in this analysis. Therefore, it was agreed that it could be indirectly applied. For the results for GLP-1 receptor agonists see: For adults with type 2 diabetes and atherosclerotic cardiovascular disease, offer metformin, an SGLT-2 inhibitor and subcutaneous semaglutide Pairwise analysis for additional outcomes. This indicated no specific efficacy or safety factors that influenced the decision making. No evidence for specific subgroups in the clinical review (for example: people living with obesity, people living with overweight, people with frailty, people with early onset type 2 diabetes). Health economic analysis that showed that the ICER for GLP-1 receptor agonists varied from £27,693 to £61,348. Health inequality analysis that showed that people in the two most deprived quintiles according to the index of multiple deprivation achieve a positive net benefit from treatment with SGLT-2 inhibitors.	For GLP-1 receptor agonists see: For adults with type 2 diabetes and atherosclerotic cardiovascular disease, offer metformin, an SGLT-2 inhibitor and subcutaneous semaglutide For more information	The committee agreed that there were important clinical benefits from GLP-1 receptor agonists in reducing HbA1c and weight, as well as providing cardiovascular and renal protection. They considered that people living with obesity could be an important group to receive these benefits where there are cost-effective options that will support them in achieving their glycaemic targets. They agreed that this should be a consideration, and it will not be the most suitable treatment for everyone. Therefore, they made a weak recommendation.

1.2.7 Subsequent therapy: Tirzepatide

What is being recommended?	What is the evidence?	What is the quality of the evidence?	Why did the committee make the recommendation?
Tirzepatide is recommended as an option in NICE technology appraisal guidance for some adults with type 2 diabetes when it is insufficiently controlled. For full details, see the guidance on tirzepatide (TA924, 2023).	Evidence included in the technology appraisal for tirzepatide. Clinical evidence from the network meta-analysis for the subsequent therapy (F) review for the population at high risk of developing cardiovascular disease. • Strong evidence of clinically important benefits in reducing HbA1c • Strong evidence of clinically important benefits in reducing weight • Very uncertain evidence on the effects on cardiovascular outcomes	Cardiovascular and renal outcomes = Moderate HbA1c change = Low Weight change = Very low For more information	The technology appraisal is pre-existing in the NICE programme and includes people with type 2 diabetes. Given the specific indication and instructions from the technology appraisal, this was not changed in this update of guideline.

1.3 The outcomes that matter most

1.3.1 Pairwise meta-analysis outcomes

The committee agreed that they should focus on the following critical outcomes when evaluating the clinical evidence: health-related quality of life, cardiovascular mortality, composite MACE, hospitalisation due to heart failure, development of end-stage kidney disease, HbA1c and weight change. The committee members, particularly those with living experience, highlighted the need to consider the biopsychosocial experiences of people with type 2 diabetes. This includes the importance of assessing health-related quality of life, including generic scores and diabetes-specific scores. However, they acknowledged that there may be limited evidence for this in these trials that mostly focus on physiological aspects of the condition. The committee considered mortality to be a critical outcome, and they chose to focus on cardiovascular mortality, as this is more disease-specific and would provide greater information around the cardio-protective benefits of treatment.

The committee highlighted an important consensus that has grown in the management of type 2 diabetes, that care should be less glucose-centric and more focused on the holistic benefits and needs of the person: particularly the cardiovascular and renal protective effects. In terms of cardiovascular benefits, the committee agreed that using a composite MACE outcome was more useful than evaluating the individual events that make up MACE, as it would be better powered to detect an effect. As hospitalisation due to heart failure is not included in all the MACE outcomes (only 5-item MACE, which is less frequently reported), the committee decided it was critical to also consider this separately in decision making. Regarding renal benefits, the committee chose to focus on development of end-stage kidney disease, as this outcome was most directly important to people with the condition. The committee continued to consider change in HbA1c to be an outcome of critical importance, as it is a surrogate marker for retinopathy and neuropathy, but not as the main outcome of review giving it an equal weighting to others. The committee also agreed that it was critical to consider weight change as one of the management goals, due to the relationship between obesity, its related comorbidities and their wider effects on health and wellbeing.

In order to assess the holistic benefits of diabetes treatment, the committee agreed that it was also important to consider other cardiovascular outcomes such as the individual events that make up MACE (cardiovascular mortality as previously mentioned, non-fatal stroke, non-fatal myocardial infarction and unstable angina), and other renal outcomes (including acute kidney injury, signs of worsening kidney function, and death from renal causes), as well as all-cause mortality, progression to liver disease, hypoglycaemia events (including hypoglycaemia episodes, at night hypoglycaemia and severe hypoglycaemia), and serious adverse events (including cardiac arrhythmia, diabetic ketoacidosis and falls requiring hospitalisation) to consider the safety of treatment. Remission was included to assess whether any treatment could be given for a period to reverse the disease process so that people would not require treatment after that time, as this is currently an important area of research. The committee acknowledged that this is a newer area of research and is more commonly seen as an outcome in studies investigating other interventions (such as exercise and diet programmes).

1.3.2 Network meta-analysis (NMA) outcomes

For the NMAs, the committee agreed on a subset of the above outcomes that were most important to people with T2DM, to capture a broad view of the effectiveness of interventions, including the cardiovascular and renal benefits, the glycaemic effects and weight. The choice of outcomes considered for NMA was also based on outcomes that would provide high quality evidence for the economic modelling. MACE and its individual components were included in the NMAs. While the MACE outcome was better powered for detecting an effect

within the clinical evidence, it was necessary to consider the costs associated with the separate contributing events within the economic model. The subset of outcomes agreed for NMA were cardiovascular mortality, 3, 4 and 5-item MACE, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalisation for heart failure, development of end-stage renal failure, HbA1c change and weight change.

1.3.3 Outcomes identified

The committee sought to include evidence for people with T2DM stratified into different groups: people with T2DM and heart failure (model 1), people with T2DM and atherosclerotic cardiovascular disease (model 2), people with T2DM and chronic kidney disease (model 3), people with T2DM and low cardiovascular risk (model 4) and people with T2DM and high cardiovascular risk (model 5). However, no evidence was identified for model 1, 2, 3 and 4 for initial therapy and model 4 for subsequent therapy.

1.3.3.1 Initial therapy - Model 5: People with type 2 diabetes and high cardiovascular risk

No evidence was identified for: 3-item MACE, 4-item MACE, 5-item MACE, development of end-stage kidney disease and falls requiring hospitalisation. Evidence for remission was identified. However, this was in a very small study (20 participants) where the definition for the outcome measured was not provided.

1.3.3.2 Subsequent therapy - Model 1: People with type 2 diabetes and heart failure

No evidence was identified for the following outcomes: health-related quality of life, 5-item MACE, development of end-stage kidney disease, death from renal cause, diabetic ketoacidosis, falls requiring hospitalisation, progression of liver disease, remission, at night hypoglycaemic episodes, severe hypoglycaemic episodes, and weight change.

1.3.3.3 Subsequent therapy - Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease

No evidence was identified for the following outcomes: health-related quality of life, falls requiring hospitalisation, remission, and at night hypoglycaemic episodes.

1.3.3.4 Subsequent therapy - Model 3: People with type 2 diabetes and chronic kidney disease

No evidence was identified for the following outcomes:4-item MACE, unstable angina, falls requiring hospitalisation, progression of liver disease, remission, and at night hypoglycaemia episodes.

1.3.3.5 Subsequent therapy - Model 5: People with type 2 diabetes and high cardiovascular risk

No evidence was identified for remission. Otherwise, evidence was identified for all other outcomes.

1.4 The quality of the evidence

1.4.1 Initial therapy - Model 5: People with type 2 diabetes and high cardiovascular risk

One-hundred and eighteen studies were included in the review of initial therapy. The quality of the outcomes ranged from high to very low.

This review question was looking at therapies for initial treatment of type 2 diabetes. Evidence was identified both from studies where people were treatment naïve, and studies where people were previously treated but had a washout period prior to randomisation, and were therefore not on treatment at the start of the trial. Evidence from both populations were combined for the analysis. However, a sensitivity analysis was conducted to investigate the effect of including only the studies in which the population was treatment-naïve. This had no effect on the results when it could be conducted, but it should be noted that it could not often be conducted in scenarios where the validity of the sensitivity analysis could be investigated due to: a small number of studies being included in each analysis; the relative rareness of trials where truly treatment naïve populations were solely invited to participate and the significant number of trials that did not report methods clearly.

The majority of the evidence was low or very low quality and there was minimal high quality or moderate quality evidence. Outcomes were commonly downgraded for inconsistency, risk of bias, and imprecision. Inconsistency was not explained by subgroup analysis or resolved by sensitivity analyses, as there were generally too few studies contributing to each outcome and comparison in order to perform subgroup analysis or sensitivity analysis. Risk of bias concerns were common, with the most common problems being concerns with allocation concealment, blinding and attrition.

Where possible for both reviews and all population groups, NMAs were conducted for the outcomes of cardiovascular mortality, 3, 4 and 5-item MACE, development of end-stage kidney disease, non-fatal myocardial infarction, non-fatal stroke, unstable angina, HbA1c and weight change. Otherwise, pairwise analyses were conducted. The network meta-analysis for the initial treatment review only reported results for HbA1c change and weight change while all other outcomes were reported in pairwise comparisons. The evidence was rated as very low quality for both outcomes due to risk of bias and imprecision.

Pairwise comparisons reported outcomes for health-related quality of life, all-cause mortality, cardiovascular mortality, 4-item MACE, 5-item MACE, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalisation due to heart failure, acute kidney injury, persistent signs of worsening kidney disease, death from renal causes, cardiac arrythmia, diabetic ketoacidosis, progression of liver disease, hypoglycaemia episodes, at night hypoglycaemic episodes, severe hypoglycaemic episodes and BMI change. The quality of the evidence ranged from high to very low quality with the main reasons for downgrading being for risk of bias, imprecision and inconsistency.

There were 95 comparisons in total, with interventions being mostly compared to metformin, with 26 interventions (with a mixture of individual drugs and combinations) and placebo, with 19 interventions (including mostly individual drugs except for three combinations of different DPP-4 inhibitors and metformin). Also included were comparisons to DPP-4 inhibitors (20 interventions across 5 drugs in the class), GLP-1 receptor agonists (6 interventions across 3 drugs in the class), SGLT-2 inhibitors (4 interventions across 3 drugs in the class), sulfonylureas (5 interventions across 2 drugs in the class), pioglitazone (8 interventions), insulin (4 interventions) and combinations (including gliclazide + saxagliptin compared to saxagliptin + metformin, glimepiride + metformin compared to canagliflozin + metformin, pioglitazone + metformin compared to glimepiride + metformin).

The committee noted the relatively high between-study standard deviation in the base-case NMA for change in HbA1c, which highlights between-study heterogeneity in terms of the study populations, treatment doses, and baseline HbA1c values. However, the committee considered that this heterogeneity reflects real-world variation in populations and current practice, and that it would not substantially affect the ability of the committee to make recommendations based on the evidence.

1.4.2 Subsequent therapy - Model 1: people with type 2 diabetes and heart failure

Network meta-analysis was performed for the outcomes of cardiovascular mortality, 3-item MACE, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure and HbA1c change. All other outcomes were reported in the pairwise comparison. The quality of network meta-analysis outcomes ranged from moderate to very low with most outcomes being assessed as low quality. The reason for this was mainly due to imprecision.

Evidence was only identified for studies that used a strategy of adding a therapy to an existing therapy. No evidence was identified for saxagliptin, dulaglutide, any sulfonylureas listed in the protocol or tirzepatide.

Twelve comparisons compared a single drug to placebo, and with the exception of canagliflozin compared to placebo, all results were from single-study analyses. The quality of the evidence ranged from very low to high. Risk of bias was mainly judged to be low, except for outcomes from the EXAMINE (high risk of bias due to lack of information about randomisation and due to significant attrition) and DECLARE-TIMI trials (moderate risk of bias due to lack of information about allocation concealment). Almost all outcomes were judged as directly applicable. Consequently, except for those with concerns about risk of bias, the lowered GRADE ratings were driven by imprecision.

All evidence from analyses comparing addition of one therapy to either insulin, or another single therapy were assessed as very low quality. Evidence for these comparisons was from Chen 2017 and Arturi 2017 where outcomes were assessed as having high risk of bias (due to concerns around allocation concealment, blinding, method of analysis, and attrition). The studies both had small sample sizes and consequently imprecision was generally high with outcomes with wide confidence intervals.

1.4.3 Subsequent therapy - Model 2: people with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD)

Network meta-analysis was performed for the outcomes of cardiovascular mortality, 3-item MACE, non-fatal myocardial infarction, non-fatal stroke, unstable angina, hospitalisation for heart failure, HbA1c change and weight change. All other outcomes were reported as pairwise comparisons. The quality of network meta-analysis outcomes ranged from moderate to very low with the majority being of low quality. This was mainly due to imprecision and risk of bias. Evidence was identified for studies that used a strategy of adding treatment to an existing therapy. No evidence was identified for semaglutide, or for the sulfonylureas gliclazide, glipizide or tolbutamide.

There were 11 comparisons where there was addition of either a single therapy or placebo to existing treatment, 8 of which were from single-study analyses. The quality of the evidence ranged from very low to high. Risk of bias ranged from low to high risk, with the majority being of low risk. Concerns for these studies included high attrition rates, methods of analysis, and reporting and adherence to protocols.

There were 5 comparisons where there was an addition of either a single therapy or insulin to existing treatment, all of which were from single study analyses, with the quality of evidence rated from very low to high. Evidence for 4 of the comparisons was assessed as

having a high risk of bias due to concerns about randomisation and allocation concealment, blinding, method of analysis, attrition and sample size.

There were 4 comparisions between a single therapy and another single therapy, with the quality of evidence rated as moderate to very low. Risk of bias at the outcome level was assessed as low for one comparison (linagliptin compared to glimepiride) and moderate risk for the remaining 3 comparisions. Concerns included attrition, allocation concealment, method of analysis and sample size.

1.4.4 Subsequent therapy - Model 3: people with type 2 diabetes and chronic kidney disease (CKD)

Network meta-analysis was performed for the outcomes of cardiovascular mortality, 3-item MACE, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure, development of end-stage kidney disease, HbA1c change and weight change. All other outcomes were reported in the pairwise comparison. The quality of network meta-analysis outcomes ranged from low to very low quality. This was mainly due to imprecision and risk of bias.

Evidence was identified for studies that used strategies of either adding treatment to an existing therapy or switching to a different therapy. No evidence was identified for alogliptin, lixisenatide, tirzepatide and the sulfonylureas, gliclizide, glipizide and tolbutamide.

There were 9 comparisons where there was addition of either one therapy or placebo. The quality of evidence ranged from high to very low. There were 6 comparisions where there was addition of either a single therapy to insulin or another single therapy, with the quality of outcomes rated from moderate to very low quality.

Evidence from a single three arm trial comparing dapaliflozin + saxagliptin with either placebo or dapagliflozin was assessed as low to very low quality due largely to concerns with risk of bias with some concerns with imprecision where very low quality was noted.

There were 2 comparisons of switching therapies compared to another single therapy with the quality of the evidence rated from moderate to very low quality, both of which had low sample sizes (Hiramatsu 2018, n = 90, Takahashi 2023, n = 90), which contributed to imprecision in the final quality ratings.

1.4.5 Subsequent therapy - Model 5: people with type 2 diabetes and high cardiovascular risk

Evidence was identified for studies that used a strategy of either adding treatment to an existing therapy or switching to a different therapy. No evidence was identified for stopping a treatment. No evidence was identified for the sulfonylurea tolbutamide.

There was sufficient evidence to perform all planned NMAs in the high cardiovascular risk population.

The quality of the NMAs ranged from moderate to very low as judged by a modified GRADE approach. Most analyses were assessed as moderate quality and were primarily downgraded due to imprecision. This was a particular problem for the network meta-analysis estimates of some binary outcomes due to the presence of zero events in one arm of some comparisons, which made the calculation of estimates difficult. In other cases, this related to small sample sizes in comparisons for different outcomes making estimates uncertain (for example: 4-item MACE). Analyses that were judged as low or very low quality also tended to be downgraded due to risk of bias.

Pairwise comparisons included results for the following outcomes: all-cause mortality, acute kidney injury, persistent signs of worsening kidney disease, death from renal causes, cardiac

arrythmia, diabetic ketoacidosis, falls requiring hospitalisation, progression of liver disease, hypoglycaemia episodes, at night hypoglycaemic episodes, severe hypoglycaemic episodes and BMI change. The quality of the evidence ranged from high to very low quality. The main reasons for downgrading this evidence were risk of bias and imprecision.

One-hundred and nine comparisons were identified where one or more drugs were added to an existing therapy, of which nineteen were compared to placebo, 12 were compared to insulin and the remainder compared the addition of one or more to therapies to other therapies.

Ten comparisons investigated switching from one drug to another. Six of these compared people who switched to alternative therapies, whilst four of these compared where some people remained on the same therapy while the other arm switched to alternative therapies. The majority of the evidence was low or very low quality, due mainly to concerns around risk of bias and imprecision, with only one exceptional comparison of moderate quality.

1.5 Benefits and harms

1.5.1 Key uncertainties

The committee acknowledged several areas of uncertainty in the analysis

1. Classification of trials into initial or subsequent therapy based on whether people were receiving any concomitant therapy
2. Classification of trials into the different population stratifications prespecified in the protocol, given the details and population characteristics reported in the trials (in particular, for determining presence of chronic kidney disease)
3. Limited evidence for the population stratifications of type 2 diabetes and heart failure (HF), atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), and no evidence for people with type 2 diabetes and low risk of cardiovascular disease
4. Exclusion of trials from the analysis where less than 80% of the trial population had type two diabetes, some of which were considered by the committee as significant trials in the fields of HF and CKD (for example: DAPA-HF, EMPEROR-Reduced, DAPA-CKD, EMPA-KIDNEY)
5. Imprecision in the NMA findings due to the large number of comparisons where only zero event data is available in one arm.

1.5.1.1 Classification as initial or subsequent therapy

Trials were first assessed as to whether they considered initial or subsequent therapy with an antidiabetic agent for type 2 diabetes based on whether people were receiving any concomitant therapy during the trial. We also considered that anyone receiving concomitant therapy with other antidiabetic medication was receiving a subsequent antidiabetic therapy. This could miss the nuance that people may be receiving antidiabetic medication for different reasons (for example: someone may have started taking metformin to reach their glycaemic targets, but then later have a myocardial infarction and start taking an SGLT-2 inhibitor for the potential cardioprotective effects even though their HbA1c is well controlled). In this case it would not necessarily be a treatment escalation. This nuance is not easily captured in this review design and so may have led to some heterogeneity in the treatment effects.

1.5.1.2 Population stratification

Trials were then assessed as to whether they included: people with HF, ASCVD, CKD and people at low risk of cardiovascular disease. Trials were only included in a group if at least 80% of the population had the characteristic. If trials included people in multiple groups (over 80% of people in the trial had both HF and ASCVD), then the trial was included in multiple analyses. If trials could not be assigned to these groups, then they were included in the people at high risk of cardiovascular disease group. This meant that the group where people were at high risk of cardiovascular disease, which was also the largest group, was more heterogeneous as it could include studies where some of the population could have HF, ASCVD or CKD. The heterogeneity of the group with people at high risk of cardiovascular disease was further exacerbated by the difficulties defining these groups.

- HF was often defined in trials by the New York Heart Association (NYHA) functional classification, which is based on clinical interpretation, while only specific trials used more objective measures such as echocardiography.
- ASCVD diagnosis varied on which diseases were included, with the majority including myocardial infarction and stroke in the definition, but some including transient ischaemic attacks, angina, peripheral arterial disease and previous revascularisation procedure.

- CKD was sometimes diagnosed in the trials but often was not stated with trials providing eGFR or albumin creatinine ratio (ACR) values. The decision was made to only define trials as including people with CKD if they were stated to have CKD explicitly. This means that there could be trials that include people who could be classified as having CKD who were included in the model at high cardiovascular risk. The committee agreed with this decision as in the majority of trials the number of people with an eGFR and ACR below a certain value was not provided, and where it was provided, it wasn't clear how many people had both an eGFR and ACR below a certain value so it was not possible to classify them using the KDIGO guidelines as recommended by the NICE guideline on chronic kidney disease: assessment and management.
- Risk of cardiovascular disease was dependent on either the reporting of the QRISK score or reporting the age of people in the trial and the number of cardiovascular risk factors that they had. This was either not reported or not reported at a participant level in the trial (for example, most trials reported the average age and average presence of risk factors), so it was not possible for the reviewer to classify for certain the proportion of participants at high cardiovascular risk. Given the lack of clarity in reporting, it was agreed that a lower risk label would only be given if it was stated explicitly. It was not stated explicitly in any trials.
    - Furthermore, the number of people with early onset type 2 diabetes (age less than or equal to 40 at diagnosis) was not reported in the studies, which did not support the stratification used by the committee.

After this stratification there was limited data for the HF, ASCVD and CKD populations. The committee also noted that some large trials fell into the ASCVD model analysis, and other large trials fell into the higher risk model analysis. This contrasts with previous analyses for this guideline and to other published NMAs within the literature, where all large CV trials have been analysed together. However, while the committee noted this contrast, this was agreed to be appropriate for the investigation of the effects for the different populations in this guideline update. They noted that some larger trials had subgroup analyses within the trials that were included in the analyses of different populations (for example: DECLARE-TIMI 58).

1.5.1.3 Large trial grouping or exclusion due to protocol criteria

The committee agreed that the evidence presented was broadly in line with their expectations. However, they had expected to see a number of large T2DM cardiovascular trials within this evidence for people with T2DM and established ASCVD (for example, the LEADER, REWIND and SUSTAIN trials). It was explained that the cohort of individuals in the REWIND trial fell below the 80% threshold for individuals with established ASCVD for inclusion of the overall trial in this evidence. However, a subgroup analysis from the REWIND trial for people with established ASCVD had been included for the outcome of 3-item MACE. The LEADER and SUSTAIN trials also included people with T2DM with and without established ASCVD, and although the proportion of people with established ASCVD disease as reported by the trial was above 80%, the trial definitions meant that this group also included people with CKD or heart failure but without ASCVD. Therefore, the subgroup analysis could not be used in this evidence as the subgroup was not purely people with established ASCVD. Due to these limitations in classifying the studies into population strata, there were a number of studies within the model 5 evidence (people with T2DM and a high risk for cardiovascular disease) in which a proportion of the people included in the studies may have established ASCVD and some conclusions about the most effective treatments in this population will be able to be extrapolated from this evidence. It was confirmed that all three trials with full datasets would be included in the analysis for people with T2DM and a high risk for cardiovascular disease.

The committee also noted that some trials were excluded from the analysis (for example: DAPA-HF, EMPEROR-Reduced, DAPA-CKD, EMPA-KIDNEY). These were trials where less than 80% of the population had type 2 diabetes and so they were excluded, as per the

protocol. However, they are significant trials for people with HF and CKD respectively. These trials included subgroups for people with type 2 diabetes. It was agreed and prespecified by the committee not to include these as they could not be confident that the search will have identified all trials where all people with HF or CKD where a subgroup analysis may have been conducted that may have included people with type 2 diabetes. Trials such as these, which were highlighted as important trials in the field of HF and CKD, were looked at by the technical team and it was noted that the outputs from the subgroup analyses (in a subgroup of people with type 2 diabetes) were often conducted only on the primary outcome of the studies which, in most instances, was an outcome that was not relevant for inclusion for the review. Given the above reasons, the committee agreed on the exclusion of these trials from the clinical evidence review. However, they were considered in the cost-effectiveness analysis.

1.5.1.4 Network meta-analysis imprecision due to inclusion of zero events data

There was a significant amount of imprecision in treatment effects. This was primarily due to the events being rare occurrences in studies with sample sizes and follow-ups that were typically not statistically powered to detect these outcomes. The committee noted that the reduction in cardiovascular events seen for the majority of drugs included in the review would be seen after 2-3 years, while a large number of trials were included in the analysis with a follow up between 6 months and 1 year. They noted that these trials were likely investigating the effect of these drugs on HbA1c rather than their effect on cardiovascular or renal events, and so they were likely to be underpowered for these outcomes.

The rarity of the outcomes meant that the committee agreed that using MACE as an important outcome for the NMAs and for decision making was a way of managing this limitation. Aggregating the different cardiovascular events together could manage the rarity of the individual events allowing them to identify effects within the trials with greater certainty. A limitation of this approach is that it implies that a treatment is likely to work simultaneously on all MACE components. There was limited reporting of 5-item MACE, which included hospitalisation for heart failure. The committee noted the importance of hospitalisation for heart failure and how reducing the incidence of this is a major aim of type 2 diabetes treatment. Therefore, evidence for the outcomes of 3-item MACE and hospitalisation for heart failure was considered particularly important for decision making. There was limited data to assess end-stage kidney disease.

1.5.1.5 Continuous outcome baseline differences

A greater volume of data was available for HbA1c change and weight change. The committee acknowledged the effect that the baseline value could have on each outcome respectively. Therefore, the NMA took this into account in a sensitivity analysis by fitting a linear regression within the analysis. This found that the model fit was similar, with the model with the meta regression fitting better. However, this had very little impact on the overall treatment effect estimates. To assess weight change, the committee agreed that the baseline weight would also have an effect. There appeared to be a distribution of two peaks of average weights, one at around 60 kg and one at around 90 kg. Therefore, the proportional change on weight was assessed and modelled for people who had a baseline weight of 60 kg and 90 kg to provide data to support their decision making.

1.5.1.6 Intervention-specific concerns

There were also limitations in the evidence for specific interventions. There was no evidence identified for the intervention tolbutamide. The committee did not identify this as a significant problem for making their recommendations as tolbutamide is not used as commonly as other drugs in current clinical practice.

1.5.1.7 Clinical importance and statistical significance

More generally, the committee discussed the advantages of using clinical importance for decision making and that this is generally a more appropriate approach than using the relative hazard ratios or risk ratios and statistical significance. However, it was highlighted by the committee that the scientific community and many international guidelines are familiar with using HRs and statistical significance. Therefore, the committee also assessed the HRs and considered whether these measures would lead to the same conclusions in the clinical benefits and harms of the intervention. It was noted that use of HRs alone may lead to the conclusion that there is clinical benefit, when in fact the absolute effect indicates no clinically important difference.

1.5.2 Committee's combined analysis of initial and subsequent review findings

The committee agreed to combine the evidence and findings from the initial and subsequent evidence reviews and apply this to discuss the benefits of treatment for people with type 2 diabetes receiving initial treatment. As an underlying principle, it was the opinion of the committee that the historical approach of first line monotherapy followed by multiple treatment intensification steps based purely on HbA1c is no longer appropriate. They agreed that a holistic approach taking into account all of the person's needs, including cardiovascular and renal risk reduction, weight management and HbA1c reduction was important for managing their overall health and leading to better outcomes. Therefore, it was necessary to start more therapies initially to achieve this. Furthermore, people started on monotherapy often experience significant waiting times until review and initiation of subsequent therapies due in part to uncertainties of whether treatment should be started based on HbA1c values. The committee strongly agreed that the recommendations for initial therapy should be based on not only glycaemic control, but also on the effect on cardiovascular and renal outcomes.

1.5.2.1 Initial drug treatment: Dual therapy for most

The committee highlighted that SGLT-2 inhibitors were used in practice due to their cardiovascular protective properties. There was a strong consensus that SGLT-2 inhibitors were found to be clinically effective in practice. NMA findings from the subsequent treatment review showed evidence of cardiovascular and renal protective properties with NMA findings from the initial and subsequent treatment review showed strong evidence that SGLT-2 inhibitors in combination with metformin were effective at reducing HbA1c and in some cases, body weight relative to metformin alone as initial therapy. Economic modelling showed the SGLT-2 inhibitors were commonly cost-effective for people with type 2 diabetes (for more information see the section on health economics). After considering these findings, the committee agreed that it was sufficient to support the use of SGLT-2 inhibitors as dual therapy with metformin.

The committee considered real-world evidence based on prescribing data which showed the uptake of SGLT-2 inhibitors to be low for those people with T2DM recommended for use. Those people ranked in the most deprived group were most affected, particularly when stratified by age and sex. Based on this evidence the committee made a research recommendation to address the low prescribing rates by identifying barriers to individuals receiving SGLT-2 inhibitors and determine the most effective way to increase their uptake.

For more information about the clinical evidence for this, see the sections about SGLT-2 inhibitors for subsequent therapy and metformin for initial therapy for people at high risk of developing cardiovascular disease.

1.5.2.2 Initial drug treatment: Triple therapy for some

The committee discussed the evidence for GLP-1 receptor agonists. The committee acknowledged that it is currently more common to give SGLT-2 inhibitors alongside metformin as initial therapy but discussed whether GLP-1 receptor agonists should be introduced earlier in the pathway. After acknowledging the importance of reducing cardiovascular and renal risk in addition to glycaemic control in the management of T2DM, the committee agreed on the need to consider GLP-1 receptor agonists earlier in the pathway for some people with early onset T2DM and heart failure and to offer them for those with atherosclerotic cardiovascular disease. People with early onset T2DM are generally more likely to have developed obesity and their lifetime risk of cardiovascular and renal complications will be very high. The committee noted the psychosocial impact of early onset T2DM, particularly the stigma associated with it and potential feelings of shame around weight and eating habits. The committee agreed that people with atherosclerotic cardiovascular disease and heart failure should be prescribed subcutaneous semaglutide as it was the most clinically effective and the only cost-effective GLP-1 receptor agonist. If this is not available then there is no clinical reason why another GLP-1 receptor agonist should not be tried. However, at the time of writing the guideline no others were cost-effective.

The committee highlighted that SGLT-2 inhibitors and GLP-1 receptor agonists both have cardiorenal protective benefits, but that they work through different mechanisms. The committee discussed that SGLT-2 inhibitors lower glucose levels by increasing loss of glucose by urine, whereas GLP-1 receptor agonists function through slowing gastric emptying and inhibiting glucagon production. Therefore, it is plausible that using both treatments concurrently would further improve cardiovascular outcomes. Given the findings and the relative strength of the evidence, the committee supported the use of SGLT-2 inhibitors and metformin while considering adding GLP-1 receptor agonists for people with heart failure and early-onset type 2 diabetes and offering GLP-1 receptor agonists for people with atherosclerotic cardiovascular disease.

The committee noted that there was clinical evidence to recommend all GLP-1 receptor agonists, as the evidence showed each drug to have similar cardiovascular and renal protection, the exceptions being exenatide and lixisenatide which were shown to be less effective. This was also supported by the NMA evidence from the subsequent therapy review showing strong evidence of benefit in reducing the number of 3-item MACE events and in contributing to weight loss. The committee acknowledged the supply issue surrounding semaglutide in 2024 but agreed that the treatment is beneficial and should be provided. The committee also noted evidence of clinically important benefits with tirzepatide (recommendations for tirzepatide can be found in Technology Appraisal 924: Tirzepatide for treating type 2 diabetes). Additionally, the committee were concerned that there are likely to be new medicines coming through which may offer greater clinical and cost-effectiveness in the near future. They agreed this should be reviewed as new medication becomes available. Given all of these factors put together, the committee agreed to consider GLP-1 receptor agonists as a class in this population.

For more information on the clinical evidence for this, see the section on GLP-1 receptor agonists from subsequent therapy for people at high risk of developing cardiovascular disease. For information about the cost-effectiveness and resource use see the section on GLP-1 receptor agonists. For information on SGLT-2 inhibitors and metformin, see the sections about SGLT-2 inhibitors for subsequent therapy and metformin for initial therapy for people at high risk of developing cardiovascular disease.

1.5.2.3 At any phase of treatment: Factors to consider

There was concern around the use of dual and triple therapy with regards to sick day rules for when a person is unwell or undergoing surgery. Additionally, concerns were highlighted regarding people stopping medication but not starting again. The committee discussed the

importance of stopping medication where there is a risk of dehydration, vomiting and diarrhoea; this is especially important for metformin, SGLT-2 inhibitors and GLP-1 receptor agonists. The committee also highlighted the importance of continuing with insulin treatment during a period of illness to avoid hyperglycaemia but noted that the dose may need to be adjusted.

The committee discussed that initial triple therapy could result in a greater number of adverse effects, and the importance of the order in which people start dual or triple therapy to minimise the risk. Metformin treatment that has not been initiated optimally can lead to gastrointestinal side effects. It is therefore important to start an SGLT-2 inhibitor after optimising metformin treatment so as not to increase the risk of diabetic ketoacidosis. The committee also discussed the impact of initial triple therapy on primary care, where additional injection training would need to be provided. They highlighted that currently many GPs do not initiate treatment with GLP-1 receptor agonists. A committee member with living experience also raised concerns that some people may find it overwhelming to receive initial triple therapy, however, confirmed that injection training is available online. Given this, healthcare professionals are advised to take this into account when initiating treatment.

This was agreed as consensus recommendations and does not have another section in the committee discussion focussing on it.

1.5.2.4 People with moderate or severe frailty: Working together

Whilst the committee used SGLT-2 inhibitors for most people in practice for their effectiveness and general tolerability, they acknowledged that they can be problematic for people with frailty, as they are associated with adverse effects such as dehydration (and sometimes diabetic ketoacidosis due to dehydration) or urinary tract infections. People with frailty may be taking multiple medications for multiple comorbidities. Therefore, adding multiple medications can increase the risk of adverse effects. Due to this it is recommended to start with monotherapy with either metformin, or a DPP-4 inhibitor. DPP-4 inhibitors are associated with fewer side effects and therefore, tend to be more appropriate and better tolerated. The committee agreed that DPP-4 inhibitors which showed clinical and cost-effectiveness have a role in treating people who have clinically significant frailty if metformin and SGLT-2 inhibitors are not viable treatment options. The committee agreed that individual choice is paramount, combined with an informed discussion of the risks and benefits of the available treatments, so that people can make an informed choice about what is best for them. Subsequently, the committee agreed that if people with frailty require additional treatment to be added then either a DPP-4 inhibitor (if they are not already receiving it), a sulfonylurea, pioglitazone or insulin can be effective treatment dependent on their needs. The committee agreed that a care approach looking at symptom management is likely the most suitable approach, considering current medication burden and trying to minimise additional adverse effects while achieving a good quality of life.

The committee acknowledged that the recommendations for people with clinically significant frailty were based on expert consensus as no clinical evidence was identified to determine the optimal management of type 2 diabetes. Based on this the committee made a research recommendation to determine the optimal clinical and cost-effective treatment strategy to address the lack of evidence in this ever-increasing group of people.

For more information about the committee's thoughts on this, see the section on people with frailty. For information about the cost and resource impact see the section about people with moderate or severe frailty.

1.5.2.5 People with chronic kidney disease: distinction between stages

The committee acknowledged the lower amount of evidence identified for people with CKD and discussed reservations in some prescribers to start metformin where the eGFR is below

45 ml/min/1.73 m^2 but agreed that there is no difference for people with an eGFR above 45 ml/min/1.73 m^2 compared to the general type 2 diabetes population to warrant a different treatment to be used. The committee acknowledged that people with an eGFR between 30 and 45 ml/min/1.73 m^2 can be prescribed metformin but this will require a dose modification. Information about this can be found in the BNF and SmPC. Given this, the committee recommended that anyone with an eGFR above 30 ml/min/1.73 m^2 could be offered dapagliflozin or empagliflozin (the SGLT-2 inhibitors licensed for use for people with chronic kidney disease) and metformin. For people with an eGFR above 20 ml/min/1.73 m^2, the committee agreed that dapagliflozin and empagliflozin can be offered as it is an effective treatment to reduce the risk of developing cardiovascular adverse events. For people with an eGFR at and below 20 ml/min/1.73 m^2, a recommendation was made for people to consider a DPP-4 inhibitor, or if that is not appropriate, pioglitazone or an insulin-based treatment.

For more information about the evidence and the committee's thoughts about this, see the sections about the network meta-analysis findings for people with chronic kidney disease and about initial therapy for people with chronic kidney disease.

1.5.2.6 Treatment options if further interventions are needed: a place for DPP-4 inhibitors, sulfonylureas, pioglitazone and insulin in the management of glycaemia

The committee discussed that the evidence does not show sulfonylureas to be more clinically effective than other treatments, and in some cases, there was evidence of clinically important harms from sulfonylureas when compared to other treatments. The same was true for pioglitazone, where there was generally no evidence where it was more beneficial, with some evidence showing that it was less effective than GLP-1 receptor agonists. The committee agreed that sulfonylureas and insulin have an acute benefit on glycaemic control, but do not have renal and cardioprotective benefits. They are both inexpensive options. Sulfonylureas may be widely used, but it was agreed that they are not always the most clinically appropriate option for initial therapy. It was the opinion of the committee that there is currently a lot of inappropriate overprescribing of sulfonylureas that, while they may manage hyperglycaemia, they do not provide the cardiorenal protection that many people with type 2 diabetes require. The committee also agreed that whilst pioglitazone does have a place as a subsequent treatment option, there are other more clinically effective and cardiorenal protective treatments that would come before pioglitazone as initial therapy options. Given this, the three were not recommended as a part of initial treatment and instead as a part of the subsequent therapy of type 2 diabetes after DPP-4 inhibitors have been trialled. There are cases where specific medicines may not be appropriate for specific groups (for example: pioglitazone is contraindicated for people with heart failure; sulfonylureas are contraindicated for people with an eGFR below 30 ml/min/1.73 m^2). Healthcare professionals should discuss and work with the person to account for each their individual circumstances when choosing a medicine to suit them.

The committee discussed co-prescription of GLP-1 receptor agonists and DPP-4 inhibitors. No evidence was identified where these medications were combined. However, they agreed that this was unlikely to be studied as these medications act on the same metabolic pathway, as both are involved in the metabolism of GLP-1 (acting on the GLP-1 receptor to mimic GLP-1s effect or inhibiting the DPP-4 enzyme which stops the breakdown of endogenous GLP-1) which prevents a number of hyperglycaemic, pro-inflammatory, lipid raising and blood pressure raising conditions. Due to this, there is unlikely to be any additional benefits from prescribing both together, as this will only provide an excess of GLP-1 or mimetics which will not be able to be used by the GLP-1 receptor. Therefore, they recommended that these medications are not prescribed together. Instead, in most cases, if a GLP-1 receptor agonist has been prescribed then a DPP-4 inhibitor should not be added, and if a GLP-1 receptor agonist needs to be added then the DPP-4 inhibitor should be discontinued before the GLP-1 receptor agonist is started. This ensures that the most cost-effective treatments are being provided, as the GLP-1 receptor agonist will provide additional cardiovascular and

renal protection, and weight reducing benefits that are more useful than the benefits of the DPP-4 inhibitor for most people. This may not be the case in some scenarios (for example: some people with clinically significant frailty where weight loss may not be beneficial).

For more information about the evidence behind this, see the sections about subsequent therapy for DPP-4 inhibitors and sulfonylureas, pioglitazone and insulin for people at high risk of developing cardiovascular disease. For information about the cost and resource impact see the section about insulin compared to GLP-1 receptor agonists.

1.5.2.7 Type 2 diabetes and pregnancy - SGLT-2 inhibitors and GLP-1 receptor agonists

The committee considered the potential risks of taking SGLT-2 inhibitors and GLP-1 receptor agonists during pregnancy. The committee acknowledged that there is some evidence to indicate that GLP-1 receptor agonists and SGLT-2 inhibitors may be associated with effects on embryonic development and that both have cautions in the BNF. Given this, the committee discussed the potential implications of wider prescribing for people of childbearing potential. The committee highlighted that weight reduction can result in increased fertility, meaning that people who previously thought that they were unable to get pregnant, can become pregnant after starting treatment. The committee stressed the importance of clinicians discussing the need for robust contraception with women, trans men and non-binary people who can become pregnant while receiving these treatments.

For more information, see the section about GLP-1 receptor agonists, fertility and pregnancy.

1.5.3 Initial therapy - Model 5: People with type 2 diabetes and a high risk of cardiovascular disease

1.5.3.1 Evidence review findings (network and pairwise meta-analysis)

The NMA showed that all treatments were effective in reducing HbA1c compared to placebo. Combination therapies of SGLT-2 and DPP-4 inhibitors with metformin (such as dapagliflozin and metformin, empagliflozin and metformin, linagliptin and metformin, sitagliptin and metformin) and pioglitazone in combination with DPP-4 inhibitors (such as pioglitazone and sitagliptin) were more effective than individual therapies. When compared to other active treatments, metformin was effective at reducing HbA1c relative to linagliptin, saxagliptin and vildagliptin.

The NMA showed that there was strong evidence for tirzepatide and SGLT-2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) both alone and in combination with metformin in reducing body weight compared to placebo. There was also strong evidence for weight reduction with subcutaneous semaglutide when compared to placebo, but not for other GLP-1 receptor agonists. Although the majority of the evidence was judged to be of low or very low quality according to modified GRADE, the committee agreed that the findings broadly matched their clinical experience, and therefore they were confident in using the evidence to inform recommendations.

In the pairwise comparison, clinically important benefits were identified for HbA1c and weight change (as also noted from the NMA). However, no clinically important differences were seen for most other outcomes, with only a few instances where clinically important effects were noted by the committee. Where these clinically important effects were present, they were most often low or very low quality outcomes with small sample sizes. The committee did not have confidence in these effects and whether they represented a true effect.

Evidence was identified comparing standard-release metformin with modified-release metformin looking at 4 outcomes: all-cause mortality, hypoglycaemia episodes, HbA1c change and weight change. There was no clinical difference for the outcomes of HbA1c,

weight and hypoglycaemia. A clinically important harm was observed in one study, in which modified-release metformin was deemed to lead to more all-cause mortality events. However, the committee agreed this was not relevant because the evidence was very low quality – it included a single study with a single death in people taking modified-release metformin compared with no deaths in people taking standard-release metformin.

1.5.3.2 Modified-release metformin - more expensive but reduced adverse events

Based on experience and evidence, the committee agreed that modified-release metformin is equivalent in efficacy, has reduced adverse effects and is generally better tolerated when compared with standard-release metformin. Currently modified-release metformin is marginally more expensive than standard-release metformin but given the wide use of metformin this represents a significant resource impact. Based on these factors, the committee agreed that standard-release metformin should be offered as first-line therapy for type 2 diabetes.

Standard-release metformin is likely tolerated by the majority of people with type 2 diabetes. Committee members with living experience acknowledged that adverse reactions to metformin, in particular standard-release metformin, can be a barrier to continuing this medication and that this can have a significant impact on quality of life. People may not want to talk to their healthcare professionals about the side effects they experience and may not be able to access health care appointments in a timely manner. This may affect their motivation to continue treatment with this medication and lead to worse long-term outcomes. Therefore, even though only a smaller proportion of people report adverse events, there was concern that a larger proportion of people may experience these effects while on the medication than is seen in primary care. The committee members with living experience expressed the challenges in accessing appointments as a contributing factor for this, making it difficult to change medication during the early stages of treatment. This is a critical time for ensuring adherence and so may have a meaningful impact for all further treatment. However, the committee did note that taking modified-release metformin did not mean that these adverse events will not happen, and that some people will not be able to tolerate either medication formulation. Given all of this, the committee recommended that if there is concern about adherence with standard-release metformin, that modified-release metformin is an alternative to consider. This should involve a conversation between the person taking the medication and the healthcare professional before starting the treatment. Alternatively, if metformin is not tolerated, then other treatments could be tried instead. The committee made recommendations throughout the guideline to recommend treatments if metformin is not tolerated.

For people with type 2 diabetes who are already taking the standard-release formulation, the committee agreed this should be continued. However, if it is not tolerated, they agreed that this should be changed to modified-release metformin. The committee acknowledged that modified-release formulation may not be suitable for people who have swallowing difficulties or learning disabilities as modified release formulations cannot be crushed. The committee noted that changing to modified release could be an option for some people as part of a medicine optimisation strategy if, for example, other pharmacological treatments are already being taken once daily.

1.5.3.3 Initial drug treatment - limitations and need to consider wider evidence base

The committee acknowledged the limitations of the evidence. Most of the studies included in this review were smaller studies and did not include the larger, long-term cardiovascular outcome studies that would assess the effect on the efficacy outcomes that the committee were interested in. While these were useful for studying the effect on HbA1c and weight change (and had shown the drug efficacy for these), they were likely not appropriate for considering these outcomes as the follow up time was too short, and the sample sizes were too small to adequately power the studies for these outcomes. This meant that the committee

agreed that the results for these outcomes may not be a true reflection of the effects of the drugs in real life clinical practice and that this may be difficult to achieve in a trial setting for the numbers required and follow up duration to truly study the outcomes of interest. The committee discussed that cardiovascular and renal disease are the biggest drivers of morbidity and mortality in people with T2DM and agreed that they would need to incorporate findings from the subsequent therapy review, alongside their expert knowledge applied to the findings for the initial therapy review to help guide their recommendations so they could truly incorporate the cardiorenal protective effects of these drugs. For more information about this, see the sections about dual therapy and triple therapy from the committee's combined analysis of initial and subsequent treatment review findings.

1.5.4 Subsequent therapy - Model 1: people with type 2 diabetes and heart failure

1.5.4.1 Evidence review findings (network and pairwise meta-analysis)

Evidence for the subsequent therapy review was from trials in which people were already on background therapy at the start of the trial. Therefore, the intervention was added to background therapy and compared to either another therapy or placebo added to background therapy.

Important effects were shown in the network meta-analysis for hospitalisation for heart failure, non-fatal myocardial infarction, non-fatal stroke and HbA1c change. The 3 SGLT-2 inhibitors included in the NMA analyses (canagliflozin, dapagliflozin and ertugliflozin) all reduced the risk of hospitalisation for heart failure. There was limited data for non-fatal myocardial infarction and non-fatal stroke with none of the three and four interventions respectively appearing to be effective in reducing the event rate when compared to placebo. The NMA for the continuous outcome of HbA1c compared three therapies (exenatide, liraglutide and sitagliptin) with insulin instead of placebo as it was not in the network. Liraglutide and exenatide showed no difference while sitagliptin indicated in an increase in HbA1c relative to insulin.

Considering the pairwise comparison, clinically important benefits were seen for SGLT-2 inhibitors. Canagliflozin showed clinically important benefits over placebo, with moderate quality evidence of reduced all-cause mortality and acute kidney injury. Limited outcomes of interest were reported for empagliflozin, however, there was moderate quality evidence indicating reduced persistent signs of worsening kidney disease. Based on the absolute values, low and very low quality evidence indicated that dapagliflozin reduced all-cause mortality and cardiac arrhythmia. There was moderate quality evidence that vildagliptin increased all-cause mortality (54 more per 1,000 [4 fewer to 231 more]).

Few outcomes were reported for exenatide, lixisenatide, and semaglutide, however where outcomes were reported, no clinically important difference was found (evidence of high quality for exenatide and low quality for lixisenatide and semaglutide). However, moderate quality evidence indicated that liraglutide has a clinically important benefit on all-cause mortality).

1.5.4.2 People with type 2 diabetes and heart failure: Committee conclusions

The evidence from the review indicates that people with type 2 diabetes and heart failure who take SGLT-2 inhibitors are more likely to experience cardiorenal protective clinically important benefits, particularly in reducing hospitalisation for heart failure. Other data was inconsistent and may reflect the limited evidence available for this population. The committee highlighted that the clinical benefits were not as strong as they had expected to see in the evidence. There were gaps from what they expected to be in this evidence in terms of some of the interventions and some of the outcomes reported. The reason for this was explored

and agreed to be due to the more specific population of people with T2DM and heart failure (and only including studies where at least 80% of the people had heart failure, as per the protocol), and that more of the familiar cardiovascular trials from the literature are included in the other population models in the evidence (such as model 2, people with T2DM and ASCVD, and model 5, people with T2DM and high CV risk). It was discussed that trials such as DAPA-HF, EMPEROR-preserved, EMPEROR-reduced and DELIVER are not included in this evidence as these trials are in heart failure populations, but not exclusively people with type 2 diabetes. It was highlighted that these studies could not be included for this reason, as they do not match the protocol population, and even if the trials provide subgroup analysis in people with T2DM, this would only be for a single outcome (usually the primary outcome of the trial) and where reported these outcomes are not relevant to the protocol for this review (for example: an aggregate of cardiovascular mortality and hospitalisation for heart failure, instead of a standardised MACE score). Additionally, as this would only be data from a subgroup with T2DM within each trial, details about the background therapies or baseline characteristics may not be sufficient.

It was highlighted by the committee that the evidence available for people with type 2 diabetes and heart failure in the current review was largely from subgroup analysis from larger trials (subgroup data for people with heart failure). A disadvantage with this is that the robustness of the diagnosis of heart failure in these trials may not be at the same standard as in other wider heart failure trials (such as DAPA-HF). This is because diagnosis may have been taken from past medical history, and not through trial recording of heart failure parameters and a thorough definition. Unlike the wider heart failure trials, these subgroups also do not differentiate between preserved and reduced ejection fraction. Therefore, these factors may introduce some heterogeneity in this subgroup with heart failure. It was discussed that this may have contributed to the less pronounced clinical benefit seen than what the committee expected.

Despite the limitations in the evidence, the committee agreed that these trials held valuable information about the use of interventions for people with T2DM and heart failure and so would be relevant towards their recommendation making in this instance. Given this, they drew on their clinical experience and knowledge of these trials in people with heart failure (irrespective of diabetes status) in which SGLT-2 inhibitors have a strong clinical benefit in people with heart failure and are recommended in the following NICE TAs: TA679, TA902, TA929, and TA773. The committee also agreed that in their clinical experience there was a strong clinical benefit for SGLT-2 inhibitors in people with both T2DM and heart failure. The committee concluded that the wider evidence from other population strata in the subsequent treatment review, along with their experience, was sufficient for a strong recommendation for initial treatment of dual therapy with an SGLT-2 inhibitor and metformin in most people with T2DM, and that this approach is appropriate for people with T2DM and heart failure. Furthermore, it was highlighted that the evidence from the subsequent treatment review is addition of therapy to existing therapy, which in most cases was or included metformin. The effectiveness of these treatments in combination will be greater due to the disparate reasons; with metformin predominantly targeting the HbA1c levels and the SGLT-2 inhibitors reducing the CV risk.

There was health economic evidence to show that subcutaneous semaglutide was cost-effective for people with heart failure and T2DM. There was one study that reported 3-item MACE in this population which showed no clinically important difference in the outcome. The data supporting this was derived from the high risk population data findings from the network meta-analysis. However, towards the end of guideline development the developers became aware of the STEP-HFpEF DM study, which included people living with obesity and heart failure with preserved ejection fraction with T2DM. This was published after the cutoff date for the final rerun search. The results aligned with the findings from the high risk population. The committee was aware of data from published trials for people in the same population without T2DM that showed the same results. Given these factors, it was agreed that

subcutaneous semaglutide should be considered for people with T2DM and preserved ejection fraction heart failure living with obesity. The committee agreed that this should take into account the weight and frailty of the person given that it is unlikely to be suitable for people living with underweight or significant frailty or both. It was agreed that the STEP-HFpEF DM study would be added to the review during the stakeholder consultation period.

The committee highlighted that they would not use pioglitazone ahead of other treatments for treatment intensification, echoing recommendations in the BNF that state that pioglitazone should not be used by people with heart failure or a history of heart failure.

1.5.5 Subsequent therapy - Model 2: people with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD)

1.5.5.1 Network meta-analysis findings

Evidence from the network meta-analysis for all four SGLT-2 inhibitors showed a reduction in hospitalisation for heart failure, whilst only canagliflozin, dapagliflozin and empagliflozin showed a reduction for 3-item MACE and non-fatal myocardial infarction. Furthermore, empagliflozin reduced the number of deaths from cardiovascular causes. Although the evidence was judged mainly to be of low and very low quality using the modified GRADE approach, the committee discussed that the evidence agreed with their clinical experience in that SGLT-2 inhibitors have a beneficial effect on cardiovascular outcomes in this population. Therefore, the committee were confident in using this evidence to inform recommendations.

Of the GLP-1 receptor agonists, exenatide and dulaglutide reduced the number of 3-item MACE events compared to placebo. No evidence of change was seen for people taking lixisenatide for cardiovascular mortality or hospitalisation for heart failure. None of the evidence for the DPP-4 inhibitors indicated reduced rates of any cardiorenal events included in the NMA. This was also true for glimepiride, though there was greater uncertainty in the effect shown by wide credible intervals. Evidence for pioglitazone showed a reduction in 3-item MACE. However, there was no difference in cardiovascular mortality and an increased rate of hospitalisations for heart failure.

There was limited data for both non-fatal stroke and unstable angina, with no evidence of a difference in effectiveness seen for any intervention included in either analysis. Evidence for all interventions indicated that they reduced HbA1c in comparison to placebo. Stronger effects were seen with tirzepatide, pioglitazone, glimepiride and dapagliflozin compared to other treatments.

Evidence of a strong effect on weight loss was only present for dapagliflozin when compared to placebo. The central esimates for empagliflozin, sitagliptin and vildaglitpin indicated a weight gain. The committee noted that the results of the NMA are not reflective of what is seen in clinical practice. They noted that the data for this NMA came from trials with small sample size and so may not be adequately powered to see the true effect of these interventions on weight in a type 2 diabetes population.

1.5.5.2 Pairwise meta-analysis findings

For the pairwise comparisons, evidence for all SGLT-2 inhibitors showed clinically important reductions in deaths from any cause when compared to placebo. Canagliflozin was also associated with a clinically important reduction in persistent signs of worsening kidney disease. When empagliflozin was compared to placebo the evidence showed clinically important harms through increases in BMI. The evidence also showed clinically important harms when canagliflozin was compared to placebo through an increase in the rate of diabetic ketoacidosis. However, in both cases the evidence was of low quality. Dapaglliflozin use led to clinically important reductions in BMI when compared to vildagliptin (low quality).

Of the DPP-4 inhibitors, when compared to placebo, the only clinically important benefit was for alogliptin where there was a reduction in all-cause mortality (very low quality). However, there was also high quality evidence that sitagliptin marginally increased all-cause mortality with 1 more per 1,000 incidences.

When compared to placebo, evidence for lixisenatide showed clinically important reductions in all-cause mortality (moderate quality). No other clinically important benefits were seen with GLP-1 receptor agonists. Pioglitazone also led to clinically important reductions in all-cause mortality compared to placebo (very low quality). A clinically important harm was also identified with an increase in hypoglycaemia episodes (low quality).

Tirzepatide showed clinically important benefits when compared to insulin of reduced all-cause mortality (moderate quality) and hypoglycaemia episodes (high quality). Glimepiride showed a clinically important benefit in reducing the number of hypoglycaemia episodes when compared to insulin (high quality). Exenatide showed a clinically important benefit in reduction in BMI when compared to insulin (very low quality evidence).

1.5.5.3 Initial therapy for people with atherosclerotic cardiovascular disease: SGLT-2 inhibitors and GLP-1 receptor agonists

The committee discussed that the evidence showed a clear cardiovascular benefit for the SGLT-2 inhibitors in people with ASCVD, highlighting improvements in hospitalisation for heart failure, 3-item MACE, non-fatal myocardial infarction, and CV mortality. Therefore, the committee agreed that metformin and an SGLT-2 inhibitor should be recommended as initial therapy in people with type 2 diabetes and ASCVD in line with recommendations for treatment of most people with T2DM. More information about the committee's decision can be found in the section about dual therapy from the committee's combined analysis of initial and subsequent treatment review findings. The committee agreed the effects seen in the data presented for the SGLT-2 inhibitors showed a class effect and that the choice of SGLT-2 inhibitor used will depend on other factors, such as eGFR levels and presence of CKD.

The committee also considered the beneficial effects of the GLP-1 receptor agonists for 3-item MACE. The evidence for the GLP-1 receptor agonists in the NMA analysis was limited as the larger cardiovascular outcome trials were conducted in mixed populations where less than 80% of the population had ASCVD. Therefore, these trials were included in the evidence for the higher CV risk population. Given this, the committee also assessed the data for the higher CV risk population, as they agreed that this was applicable as the studies included sufficiently sized proportions of people with ASCVD and T2DM that they could indirectly apply the evidence. The committee noted that all GLP-1 receptor agonists showed evidence of a positive effect for 3-item MACE, but that subcutaneous semaglutide was the most effective. GLP-1 receptor agonists were also associated with weight loss, with semaglutide (both oral and subcutaneous forms) showing a clinically important weight loss. This was greatest for subcutaneous semaglutide. All GLP-1 receptor agonists, except for lixisenatide, showed a clinically important reduction HbA1c. The health economic analysis showed that subcutaneous semaglutide was the only cost-effective GLP-1 receptor agonist for people with T2DM and ASCVD. Based on this evidence, in addition to their clinical experience, the committee agreed that there was sufficient evidence to make a strong recommendation for initial triple therapy for people with ASCVD and T2DM with metformin, an SGLT-2 inhibitor and subcutaneous semaglutide. The committee discussed the mode of action for each of these medicines, highlighting the differences between the mode of action of each which are complementary to one another, and therefore each of these therapies is likely to have an additive beneficial effect.

There was a general concern from the committee about whether side effects of the different therapies were captured within the evidence. It was explained that it was not possible to identify evidence for all the side effects for all the different therapies within this review protocol. A safety review would be necessary to identify more information about side effects.

Information about side effects of different medications can be found in the BNF. When considering this for recommendations, the committee used their clinical and personal experience with regards to the possible side effects and how these can affect compliance. The committee discussed that adherence can be affected by adding multiple therapies on at the same time. They highlighted that feeling of 'medicines fatigue' can be experienced and that it can feel like a conveyer belt with no destination. Therefore, it was highlighted that it was important to communicate clearly to the person with type 2 diabetes why they are receiving each medication, to start each medication sequentially and give support to them during the process to help them achieve their goals.

For more information about this, see the section about triple therapy from the committee's combined analysis of initial and subsequent treatment review findings.

1.5.5.4 Treatment options if further interventions are needed for people with atherosclerotic cardiovascular disease – DPP-4 inhibitors and tirzepatide

The committee discussed that the cardiovascular benefits of DPP-4 inhibitors do not appear to be as pronounced as the SGLT-2 inhibitors and GLP-1 receptor agonists. However, the committee discussed that DPP-4 inhibitors tend to have fewer side effects and may be more appropriate in some patient populations such as those with frailty (see discussion in section discussing people with moderate or severe frailty: working together).

The committee discussed the possibility of recommending tirzepatide as there was some moderate and high-quality evidence of a clinically important benefit when compared to insulin. The committee discussed evidence around tirzepatide and highlighted that tirzepatide studies in this population compared against insulin. The committee discussed that these studies might represent a slightly different population, as if insulin is being considered as a treatment option, then this is usually at a later stage of management when pancreatic function has declined considerably and other antihyperglycemic therapies alone are no longer sufficient. Tirzepatide may also have side effects and not be as easily tolerated, and as this is a more recent therapy, less is known about how side effects will impact management with tirzepatide. The committee acknowledged the role of tirzepatide in glycaemic and weight management if triple therapy has failed to give adequate weight loss, and therefore have cross-referenced to NICE TA924 Tirzepatide for treating type 2 diabetes. For more information see the section discussing the evidence for tirzepatide for people at high risk of developing cardiovascular disease and the discussion about referring to technology appraisal 924 for tirzepatide in that section

1.5.6 Subsequent therapy - Model 3: people with type 2 diabetes and chronic kidney disease (CKD)

1.5.6.1 Network meta-analysis findings

The evidence included in the networks for the CKD populations came from trials with small numbers of events which led to uncertainty in the effect intervals.

The majority of evidence focussed on SGLT-2 inhibitors. In the network meta-analysis, evidence showed canagliflozin had the greatest number of outcomes showing benefits when compared to placebo with reductions in event rate for 3-item MACE, hospitalisation for heart failure and end-stage kidney failure. Evidence for empagliflozin showed a reduction in event rate for cardiovascular mortality and hospitalisation for heart failure. Evidence for dapagliflozin showed a reduction in the rate of hospitalisation for heart failure, no evidence for a reduction in 3-item MACE or end-stage kidney failure, with zero events in one arm of the single trial included in the analysis for the latter outcome. Lastly, evidence for ertugliflozin also showed no evidence for a difference in hospitalisation for heart failure owing to zero events in one arm of the single trial included in the analysis.

The evidence for GLP-1 receptor agonists showed a clinically important benefit of semaglutide for all-cause mortality, CV mortality, persistent signs of worsening kidney disease, development of end-stage kidney disease, HbA1c change and weight change. There was no clinically important difference for all other reported outcomes and a potential clinically important harm for hypoglycaemia for oral semaglutide, but this was from a smaller study. The clinically important benefits of semaglutide in terms of cardiovascular and renal protection, HbA1c reduction and weight loss were driven by a large study comparing subcutaneous semaglutide with placebo. For cardiovascular protection and weight loss, these benefits were larger than those provided by all other antidiabetic medication studied in this population. Liraglutide showed no evidence for reducing event rates when included in the analysis for any outcome.

Of the DPP-4 inhibitors included in the NMA, saxagliptin was effective in reducing end stage kidney failure although there was uncertainty owing to zero events in one arm of the single trial included in the analysis. Linagliptin and sitagliptin showed no evidence for reducing event rates when included in the analysis for any outcome. There was also limited data for non-fatal myocardial infarction and non-fatal stroke which resulted in extremely uncertain estimates for both interventions included in both networks.

All of the treatments included in the network showed effectiveness for reducing HbA1c, with uncertainty for exenatide, ertugliflozin, sitagliptin and vildagliptin. The network for proportional weight change in the CKD population showed the 4 SGLT-2 inhibitors, semaglutide and linagliptin to be effective in reducing body weight but linagliptin was associated with very wide credible intervals highlighting the uncertainty in the estimate. These results were mirrored in a sensitivity analysis using an additive model for weight change which assumed that everyone lost the same amout of weight. In this analysis, insulin, exenatide and glimepiride increased weight, whilst all 4 SGLT-2 inhibitors, oral and subcutaneous semaglutide, liraglutide and dulaglutide caused a reduction.

1.5.6.2 Pairwise meta-analysis findings

In the pairwise analysis, SGLT-2 inhibitors had additional benefits for other outcomes when compared to placebo. Evidence for canagliflozin and empagliflozin showed clinically important benefits in reducing all-cause mortality. Evidence for dapagliflozin showed clinically important benefit in reducing the risk of acute kidney injury. Evidence for canagliflozin showed reduced death from renal causes and and a clinically important reduction in persistent signs of worsening kidney disease. However, clinically important harms were identifed for increases in incidence of diabetic ketoacidosis (canagliflozin) and all-cause mortality (ertugliflozin). The former of these was based on high quality evidence while the latter was based on very low quality evidence due to risk of bias and imprecision. The committee acknowledged that diabetic ketoacidosis could be a risk due to dehydration and so the treatment needs to be managed carefully. The committee agreed that the recommendations in the guideline should be widened based on the health economic findings (that showed that SGLT-2 inhibitors were cost-effective for people with CKD stage 1-4) and that people in the studies appeared to benefit from SGLT-2 inhibitors without safety concerns when these were used within license. Therefore, they recommended that dapagliflozin and empagliflozin can be recommended for all people with an eGFR above 20 ml/min/1.73 m^2 to help reduce the risk of cardiovascular disease developing in the future, as these are licensed for use by people with chronic kidney disease. Other treatments may be required to manage chronic kidney disease itself dependent on the severity of the condition, for these people healthcare professionals should refer to the chronic kidney disease guideline.

Benefits were identified for semaglutide when compared to placebo in reducing all-cause mortality, CV mortality, persistent signs of worsening kidney disease, development of end-stage kidney disease, HbA1c change and weight change, but an increase in hypoglycaemia episodes. When compared to insulin, dulaglutide and exenatide showed clinically important benefits in reducing the number of hypoglycaemia and severe hypoglycaemia episodes, and

dulaglutide showed benefits in reducing persistent signs of worsening kidney disease and at night hypoglycaemic episodes. The evidence showed clinically important benefit for liraglutide for reducing severe hypoglycaemic episodes but also clinically important harms identified for all-cause mortality, diabetic ketoacidosis, and hypoglycaemia episodes. The committee noted the limited evidence in this area and the high amount of uncertainty in the findings.

Evidence for DPP-4 inhibitors was limited but showed that in general DPP-4 inhibitors were less effective than placebo, with evidence for linagliptin showing clinically important harms in all-cause mortality and acute kidney injury and both linagliptin and saxagliptin showing clinically important harms leading to increases in hypoglycaemia episodes. The committee agreed that DPP-4 inhibitors would not be used for their cardiorenal protective effects, but are effective at reducing HbA1c and would therefore be used for glycaemic control. They also acknowledged the limited evidence included in this review and uncertainty for some outcomes, such as all-cause mortality and acute kidney injury. Very limited evidence was found for pioglitazone and glimepiride. Glimepiride was compared to insulin only and showed that glimepiride caused fewer hypoglycaemia episodes than insulin, while pioglitazone when compared to placebo showed no difference in the number of hypoglycaemia episodes. The committee acknowledged that sulfonylureas may be associated with more hypoglycaemia episodes for people with more severe renal impairment (eGFR below 30 ml/min/1.73 m^2) and so recommended caution when prescribing them in this population. Given this they did not recommend them to be a part of the treatment options in this group.

1.5.6.3 People with chronic kidney disease and initial therapy: when can metformin and SGLT-2 therapy be given?

The committee highlighted that the clinical benefit in patients with type 2 diabetes and CKD was not as strong as they had expected, and that there are gaps in the evidence in terms of some of the interventions and outcomes reported. It was agreed that the paucity of evidence is likely to be due to the challenges in defining a population with chronic kidney disease. This population group included people with a range of different risk categories of CKD and so required eGFR and ACR parameters to provide a diagnosis. As this was not reported in all studies in a way that could be extrapolated to define whether people had CKD, this required studies to report whether people had CKD or not. This narrowed the number of studies that could be included in this stratum. It was noted that, due to these limitations, there will be a number of studies within the model 5 evidence (people with type 2 diabetes and high cardiovascular risk) in which a proportion of the people included in the studies may have CKD, and that it will be possible to extrapolate some conclusions about the most effective treatments in this population from this evidence.

The evidence from the review confirmed the committee's existing view that the SGLT-2 inhibitors are of particular benefit for people with type 2 diabetes and chronic kidney disease in providing cardiorenal protection. The committee questioned whether the evidence would be reflective of all stages of CKD, or whether people enrolled in the trials would have less severe disease. Many of the trials included people with eGFR levels as low as 15 ml/min/1.73 m^2, and therefore captured all stages of CKD except for end-stage kidney disease. This is important because more people are presenting with severe CKD in all healthcare settings. It was also highlighted that the glucose lowering effect of SGLT-2 inhibitors is reduced in people with lower eGFR levels (around 45ml/min/1.73m^2). However, the committee agreed that the renal benefits persist. The committee discussed that in their experience, they wouldn't treat most people with T2DM and CKD stage 1 to 3a differently to the wider T2DM population. The committee discussed how the dose of metformin would be reduced for people with an eGFR below 45 ml/min/1.73 m^2 and that metformin is contraindicated for people with an eGFR below 30 ml/min/1.73 m^2. The committee agreed that SGLT-2 inhibitors are important in enabling people with CKD to manage type 2 diabetes as long as eGFR is above 20 ml/min/1.73 m^2. Only two SGLT-2 inhibitors are licensed for people with CKD, dapagliflozin and empagliflozin. The committee agreed that either of these

two SGLT-2 inhibitors should be used for people with CKD in order to ensure that their kidney health is maintained during care. Otherwise the committee agreed that other treatments are also required for people with CKD (such as finerenone) and so healthcare professionals should also refer to the guidance for Chronic kidney disease: assessment and management (NG203) for more information.

1.5.6.4 Subsequent therapy for people with chronic kidney disease

The committee discussed the use of DPP-4 inhibitors in people with T2DM and CKD stages 4 to 5 and decided that although they do not appear to have the same cardiorenal protective benefits as the SGLT-2 inhibitors, they can play an important role in glycaemic control. Therefore, they recommended a DPP-4 inhibitor if initial treatment failed to provide adequate glycaemic control or if an SGLT-2 inhibitor is not suitable initial therapy (for example: for people with an eGFR less than 20 ml/min/1.73 m^2). The committee noted the importance of considering the needs of each person individually and how some treatments may be more suitable than others based on a person's comorbidities and their specific clinical situation. For example, the adverse effect of fluid retention with pioglitazone, may render it unsuitable for people with oedema and suspected heart failure. The committee also discussed that in practice it is not uncommon to use insulin in people with T2DM and CKD if glucose targets have not been achieved with sulfonylureas or pioglitazone or before trying these medications if they are contraindicated. The committee acknowledged that sulfonylureas may be associated with more hypoglycaemia episodes for people with more severe renal impairment (eGFR below 30 ml/min/1.73 m^2). Given this they did not recommend them in this group but still considered them an option for people with an eGFR above this value.

1.5.7 Subsequent therapy - Model 5: people with type 2 diabetes and high cardiovascular risk

This review did not identify any evidence for people with type 2 diabetes and a low cardiovascular risk. Cardiovascular risk is assessed using a QRISK score which is largely dependent on age. Using the QRISK3 score cut-off of 10% for 10 year risk, a male aged 52 and a female aged 60 with type 2 diabetes are classed at high risk for cardiovascular disease (without taking into account other risk factors). Therefore, people with type 2 diabetes who are younger than the high risk age but are older than the cut-off for early-onset type 2 diabetes may not be currently classed as being high risk for cardiovascular disease. However, the committee agreed that people with T2DM diagnosed within this age range will have an increased lifetime risk of cardiovascular disease acknowledging that the QRISK score was originally applied to modelling for statin use rather than antidiabetic medication. Therefore, they agreed that it was appropriate to treat all people with T2DM as if they had a high risk of cardiovascular disease if they did not already have cardiovascular disease or another relevant comorbidity. For this reason, the committee agreed that dual therapy with an SGLT-2 inhibitor and metformin would be appropriate for most people as initial therapy, in order to reduce the risk of future adverse cardiovascular events.

1.5.7.1 Pairwise meta-analysis specific consideration

The majority of evidence for the pairwise comparisons was for monotherapy compared to placebo, with most trials reporting all-cause mortality and at least one hypoglycaemia outcome. Sensitivity and subgroup analysis, as specified in the protocol, failed to resolve the heterogeneity where identified. In the case of the hypoglycaemia episodes outcome, various definitions were used in the included trials, which may also explain the presence of heterogeneity in some of the comparisons for this outcome.

1.5.7.2 SGLT-2 inhibitors

The NMA evidence showed dapagliflozin to be more effective compared to placebo for a reduction in hospitalisation for heart failure, non-fatal myocardial infarction and end-stage renal failure and a positive effect for 3-item MACE and non-fatal myocardial infarction but with weaker evidence. No evidence of a difference in effectiveness was identified when compared to placebo for cardiovascular mortality, unstable angina and non-fatal stroke. Similarly, canagliflozin was shown to be more effective than placebo in reducing the number of events of 3-item MACE and hospitalisation for heart failure, and there was weaker evidence of a small effect in reducing the number of non-fatal myocardial infarction and cardiovascular mortality events. Canagliflozin was not included in the network for unstable angina, and there was no evidence of a difference in effectiveness when compared to placebo for non-fatal stroke or end-stage renal failure. No evidence was identified showing a difference in effectiveness when empagliflozin was compared to placebo in reducing cardiovascular mortality, non-fatal stroke, unstable angina and hospitalisation for heart failure, and data was not available for 3-item MACE, non-fatal myocardial infarction and end-stage renal failure. The evidence showed that all SGLT-2 inhibitors were effective at reducing HbA1c and weight compared to placebo.

Similar to the NMA evidence, the pairwise analyses appeared to show evidence of renal protective benefits for the SGLT-2 inhibitors, with dapagliflozin reducing acute kidney injury and the hazard of renal death, and both canagliflozin and dapagliflozin reducing the hazard for persistent signs of worsening kidney disease. Evidence for empagliflozin showed a clinically important benefit in improving health-related quality of life. There was conflicting data for all-cause mortality, with dapagliflozin showing a clinically important benefit and canagliflozin and empagliflozin showing a clinically important harm when compared to placebo. However, the evidence of benefit was low quality and evidence of harm was very low quality. There was no evidence of clinically important change in BMI for the SGLT-2 inhibitors.

1.5.7.3 GLP-1 receptor agonists

In the NMA, liraglutide and dulaglutide were more effective than placebo for 3-item MACE, but there was no evidence of a difference when compared to placebo for unstable angina, non-fatal myocardial infarction and end-stage renal failure. The evidence revealed liraglutide to be more effective than placebo for cardiovascular mortality, weak evidence for a small positive effect for hospitalisation for heart failure, but no evidence of a difference for non-fatal stroke. Dulaglutide was shown to be more effective than placebo in reducing the number of non-fatal strokes but showed no evidence of an effect on cardiovascular mortality. Exenatide showed weak evidence for a positive effect for cardiovascular mortality and non-fatal stroke but no evidence of a difference for non-fatal myocardial infarction, unstable angina, hospitalisation for heart failure or end-stage renal failure. Lixisenatide showed no evidence for a difference in effectiveness when compared to placebo for any of the outcomes analysed, with no data for 3-item MACE and end-stage renal failure.

Subcutaneous semaglutide was more effective than placebo for 3-item and 5-item MACE and non-fatal stroke, and there was very weak evidence for a positive effect for non-fatal myocardial infarction. There was no evidence of a difference in effectiveness for cardiovascular mortality, unstable angina or hospitalisation for heart failure. No data was available for end-stage renal failure. Oral semaglutide was more effective than placebo for cardiovascular mortality, but there was no difference to placebo for 3-item MACE, hospitalisation for heart failure, non-fatal stroke and non-fatal myocardial infarction. There was some evidence of increased rates of unstable angina with oral semaglutide, although there was a high degree of uncertainty. The committee considered that the result may be due to chance, given the relatively rare event and that oral semaglutide was shown to be protective of overall cardiovascular mortality. No data was available for end-stage renal failure. The NMA evidence showed that all the GLP-1 receptor agonists were effective at

reducing HbA1c compared to placebo, and that dulaglutide, exenatide, liraglutide, semaglutide (both oral and subcutaneous) were associated with reduction in weight and there was weaker, more uncertain evidence for a reduction in weight compared to placebo for lixisenatide.

For the pairwise meta-analyses, there was some evidence that the GLP-1 receptor agonists improved mortality outcomes compared to placebo, with dulaglutide, exenatide, liraglutide, semaglutide and lixisenatide all showing a clinically important benefit for all-cause mortality. However, there was also very low quality evidence that liraglutide lead to a clinically important harm compared to placebo in terms of death from renal causes (1 more event per 1,000). There was mixed evidence for the hypoglycaemia outcomes for the GLP-1 receptor agonists. Some evidence showed that liraglutide and exenatide had a clinically important harm for hypoglycaemia episodes compared to placebo. However, there was also low-quality evidence that exenatide had a clinically important benefit for at night hypoglycaemia episodes. There was also evidence that exenatide had a clinically important harm on diabetic ketoacidosis compared to placebo. Similarly to the NMA evidence for weight change, the pairwise evidence showed that exenatide, liraglutide and semaglutide had a clinically important benefit on BMI change compared to placebo.

1.5.7.4 Tirzepatide

Limited data available for tirzepatide showed no evidence of a difference in effect for any of the adverse event outcomes analysed in the NMAs, with no data available for 5-item MACE, unstable angina and end-stage renal failure. However, the NMA evidence showed that tirzepatide was effective at reducing HbA1c and weight compared to placebo. Similarly, the pairwise evidence showed that tirzepatide had a clinically important benefit on BMI change. However, there was also evidence that tirzepatide may have had a clinically important harm compared to placebo for progression of liver disease and hypoglycaemia episodes.

1.5.7.5 DPP-4 inhibitors

The NMA analysis showed that all the DPP-4 inhibitors had a clinically important benefit on change in HbA1c compared to placebo. However, there was no evidence that any were more effective than placebo for change in weight or any of the cardiorenal outcomes. Additionally, saxagliptin and sitagliptin were shown to be less effective when compared to placebo for hospitalisation for heart failure. Evidence for sitagliptin showed no difference in any other outcomes when compared to placebo. Alogliptin was included in the analysis for cardiovascular mortality, non-fatal myocardial infarction and hospitalisation for heart failure. Linagliptin was included in the analyses for all outcomes, saxagliptin was analysed for all outcomes except 4-item and 5-item MACE, sitagliptin was included for all outcomes except end-stage renal failure, 3-item and 5-item MACE and vildagliptin was included in the analyses for cardiovascular mortality, 4-item and 5-item MACE and non-fatal stroke.

The pairwise evidence showed mixed results for the impact of DPP-4 inhibitors compared to placebo for mortality outcomes, with linagliptin, sitagliptin and vildagliptin showing a clinically important benefit for all-cause mortality, and alogliptin and saxagliptin showing a clinically important harm. Additionally, very low quality evidence showed that there was evidence of clinically important harm for saxagliptin for the outcome of death from renal causes compared to placebo. There was no evidence of a clinically important impact of the DPP-4 inhibitors on hypoglycaemia outcomes. However, there was some evidence that sitagliptin had a clinically important benefit on BMI change despite the NMA evidence showing no clinically important change in weight. This was due to the BMI and weight results coming from different trials which may represent different populations, given the heterogeneity seen in this population (discussed in Key uncertainties).

1.5.7.6 Sulfonylureas, pioglitazone and insulin

The NMA analysis revealed no evidence for the sulfonylureas to be more effective than placebo for any of the cardiorenal outcomes included in the analyses. Glipizide was less effective than placebo for cardiovascular mortality, and there was no difference for non-fatal myocardial infarction. The evidence showed that gliclazide, glimepiride and glipizide were all more effective than placebo at reducing HbA1c. The evidence also showed a smaller reduction in weight change compared to placebo for glipizide and glimepiride. No further data for glipizide was available for any of the other outcomes. All other results for sulfonylurea treatments showed no evidence of a difference when compared to placebo. Data for glimepiride was available for all outcomes except for 5-item MACE and end-stage renal failure, whilst data for gliclazide was only available for cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke. The pairwise evidence showed that glimepiride and glipizide had a clinically important harm for hypoglycaemia compared to placebo, and glimepiride had a clinically important harm for BMI change compared to placebo. There was also low quality evidence from one study that showed a clinically important harm for glimepiride compared to gliclazide for hypoglycaemia episodes.

The NMA evidence for pioglitazone failed to show a difference in effectiveness for any outcomes included in the analyses, including 3-item MACE, hospitalisation for heart failure, cardiovascular mortality and unstable angina. However, pairwise evidence for pioglitazone showed clinically important harm for hypoglycaemia episodes and change in BMI compared to placebo.

Compared to sitagliptin, there was pairwise evidence that glimepiride and gliclazide had a clinically important harm for all-cause mortality, hypoglycaemia episodes, and severe hypoglycaemia episodes, and that glipizide had a clinically important harm for cardiovascular mortality. Compared to sitagliptin there was also evidence that pioglitazone had a clinically important harm for health-related quality of life, all-cause mortality and change in BMI. The evidence also showed that pioglitazone had a clinically important benefit compared to gliclazide, and a clinically important harm compared to glimepiride. Pioglitazone also had a clinically important benefit when compared to gliclazide on hypoglycaemia episodes but also a clinically important harm compared to glimepiride and glipizide on falls requiring hospitalisation and HbA1c change respectively. In the NMA analysis, no evidence of a difference in effectiveness was identified for IGlarLixi or IDegLira when compared to placebo for those outcomes where data was available except for change in HbA1c where IGlarLixi and IDegLira were more effective than placebo. IDegLira was included in all analyses except end-stage renal failure, 4-item and 5-item MACE, whilst IGlarLixi was not included in the analyses for 3-item, 4-item and 5-item MACE, non-fatal myocardial infarction and end-stage renal failure. Insulin was shown to be more effective when compared to placebo for non-fatal stroke and change in HbA1c, however it was found to be associated with smaller weight loss than placebo. There was no evidence of a difference for any of the other available outcomes.

The pairwise evidence for the addition of one therapy compared to insulin generally showed a clinically important benefit for the intervention or no clinically important differences between the two groups. Exceptions included exenatide and semaglutide, where very low quality evidence showed a clinically important harm compared to insulin for the outcome of all-cause mortality, and glimepiride, where moderate and very low quality evidence showed a clinically important harm compared to insulin for all-cause mortality and hypoglycaemia episodes.

1.5.7.7 Metformin

The NMA showed that metformin was more effective at reducing HbA1c than placebo, and there was weaker, more uncertain evidence that metformin was more effective at reducing weight than placebo. Metformin did not show any evidence of difference in effectiveness compared to placebo when included in the NMA analyses for cardiovascular mortality, unstable angina and hospitalisation for heart failure. No data was available for the remainder

of the outcomes for metformin. It was highlighted by the committee that there was limited evidence available for metformin in this review, since this is subsequent treatment for diabetes and metformin is often used as a first line treatment. Therefore, most of the people included in the studies for this review were already taking metformin as their background medication. The committee did not consider evidence around metformin to be relevant to the subsequent treatment recommendations, as everyone with diabetes would be taking metformin as part of initial therapy unless contraindicated or not tolerated.

1.5.7.8 Weighing up the effects of each medicine on the most important outcomes in the network meta-analysis

The limited number of studies reporting data on 4-item MACE and 5-item MACE resulted in these outcomes having smallest networks for the analyses, consisting of 5 and 3 treatments respectively (excluding placebo). Of the five treatments included in the analyses for 4-item MACE, none were shown to be more effective than placebo, whilst subcutaneous semaglutide was shown to be more effective than placebo for the outcome of 5-item MACE. Additionally, the data identified for non-fatal stroke and unstable angina included multiple studies with zero events in one arm resulting greater uncertainty in the findings for these outcomes.

For the hospitalisation for heart failure NMA, inconsistency was detected between the direct and indirect evidence. This inconsistency resulted from the GRADE study, where there was high residual deviance in the fixed effects consistency model. The GRADE study was a four-arm trial of glimepiride, liraglutide, sitagliptin and insulin, and the high residual deviance was primarily driven by the glimepiride arm, where the HR (95% CIs) when glimepiride was compared to sitagliptin was 0.71 (0.47 to 1.08) in the NMA, compared to 1.01 (0.61 to 1.67) in the trial. Although the doses of liraglutide, sitagliptin, and insulin in the GRADE study were consistent with those used in clinical practice, participants in the glimepiride arm were titrated up to 8 mg glimepiride, which is higher than the dose used in clinical practice. Previously, non-clinical doses were not excluded from analyses. However, as the glimepiride arm from the GRADE study was causing inconsistency in the model, this arm was excluded from the base-case analysis for the outcomes of hospitalisation for heart failure, 3-item MACE, 4-item MACE, cardiovascular mortality and unstable angina, so that it did not impact the health economic analysis. Additionally, sensitivity analyses that included the glimepiride arm of the GRADE study were performed to assess the impact of removing the arm on each outcome. Some small differences were apparent between the results of the base-case analysis and sensitivity analysis for the outcomes of hospitalisation for heart failure and 4-item MACE. However, there was no notable difference between the base-case and sensitivity analyses for the outcomes of cardiovascular mortality, 3-item MACE, and unstable angina.

1.5.7.9 Cardiovascular and renal protective effects of SGLT-2 inhibitors and GLP-1 receptor agonists

The committee discussed that the evidence highlighted the cardiorenal protective benefits of the SGLT-2 inhibitors and provided further justification for the strong recommendation around most people with type 2 diabetes using them initially to prevent future cardiovascular and renal complications. The committee discussed that this is especially true for people who have early onset type 2 diabetes as they have a high lifetime risk of cardiorenal events, and therefore would benefit greatest from early intervention with SGLT-2 inhibitors. Given these benefits, the committee also agreed that SGLT-2 inhibitors should be started as initial therapy where there is a contraindication to metformin. For more information about this see the sections about dual therapy and triple therapy from the committee's combined analysis of initial and subsequent treatment review findings.

The committee considered the evidence around the cardiovascular outcomes for GLP-1 receptor agonists, and in particular 3-item MACE. The committee reiterated that the GLP-1 receptor agonists have a clear cardiovascular benefit. They agreed that although it may not

be cost-effective to offer GLP-1 receptor agonists to most people as part of initial therapy, there are some groups who would benefit from initial triple therapy as previously discussed for people with ASCVD. The committee agreed that lixisenatide and exenatide were less effective than other GLP-1 receptor agonists. Dulaglutide, liraglutide and subcutaneous semaglutide were associated with strong evidence of effectiveness at reducing the number of 3-item MACE events, with subcutaneous semaglutide being associated with clinically important reductions in the outcome. Subcutaneous semaglutide was also associated with strong evidence of effectiveness and a clinically important effect at reducing the number of non-fatal strokes. All the GLP-1 receptor agonists apart from lixisenatide led to a strong effect at reducing HbA1c, with the strongest evidence of effect being seen with semaglutide, dulaglutide and liraglutide. Lastly, semaglutide and in particular the subcutaneous formulation, lead to clinically important reductions in weight with the subcutaneous formulation having strong evidence of an effect (3.84 kg loss). While liraglutide did not achieve strong evidence of an effect or a clinically important reduction, it did achieve the next largest reduction in weight (2.5 kg loss). Furthermore, the health economic analysis showed that only subcutaneous semaglutide was cost-effective in many scenarios. In the committee's clinical experience, all of the GLP-1 receptor agonists have been used historically, but lixisenatide and exenatide were now used less commonly (prescribing data from the CPRD database from August 2024 of 0.0% and 0.2% of medication prescribed in the diabetes population respectively, while oral semaglutide, subcutaneous semaglutide, liraglutide and dulaglutide representation 2.0%, 0.7%, 0.9% and 3.1% of medication prescribed in the diabetes population respectively). They also acknowledged that lixisenatide is no longer available in the United Kingdom and that only one form (the once weekly formulation) is available in the United Kingdom at this time and so agreed that it is unlikely that use of it would change after this recommendation.

The committee discussed recommendation 1.7.22 from the 2015 update of the guideline, which stated to only continue GLP-1 mimetic therapy if the adult with T2DM has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and or weight loss of at least 3% initial body weight in 6 months). This recommendation is similar to recommendations discussing semaglutide in NICE CG189 Obesity: identification, assessment and management, where the guideline recommends using semaglutide for a maximum or 2 years, and consider stopping semaglutide if less than 5% of initial weight has been lost after 6 months. The committee decided to remove recommendation 1.7.22, as GLP-1 receptor agonists play an important role in protecting against cardiovascular and renal adverse events, including people with atherosclerotic cardiovascular disease and early-onset T2DM, and the committee believe that this effect is independent of HbA1c and weight reduction. However, the committee did agree that GLP-1 receptor agonists should be stopped if they have no impact on glycaemic or weight targets in those people not included in these populations.

The committee discussed that when treatments are discontinued because HbA1c control has been achieved, this can lead to a rebound to poor HbA1c values. This should be considered before treatment is stopped. It was agreed that because of their cardiovascular and renal benefits, SGLT-2 inhibitors should be considered as standard care for most people with T2DM and should not be discontinued even if glycaemic targets have not been met. This is reflected in recommendations about reviewing drug treatment.

1.5.7.10 Weight and glycaemia management for people living with obesity

The committee noted that based on clinical experience, it is still possible for people to have marked improvement in weight with an SGLT-2 inhibitor and metformin. However, they noted that the mechanism for this may lead to a transient weight loss as part of this may be due to fluid loss due to the SGLT-2 inhibitor causing increased urination as a part of its mechanism of action. Due to this, the committee were keen to make a recommendation around subsequent treatment for people when initial therapy with metformin and an SGLT-2 inhibitor had regardless of the effect on weight. The committee also noted that weight loss is more

difficult to achieve for people with T2DM compared to people without T2DM. The committee noted that of all the GLP-1 receptor agonists, the NMA showed that only semaglutide (oral and subcutaneous) had a clinically important benefit on weight change compared to placebo, but liraglutide had strong evidence of a benefit even if it was not clinically important. The committee acknowledged that GLP-1 receptor agonists were not cost-effective for people living with obesity. However, they took into account the potential benefits for specific groups of people who are continuing to have difficulties maintaining their HbA1c after therapy with SGLT-2 inhibitors and metformin, where there may be greater benefits to be had. Considering these factors, they recommended that people with T2DM and obesity consider adding a GLP-1 receptor agonist to their therapy when treatment has not helped to achieve their glycaemic management goals.

The committee discussed the overlap with the NICE CG189 Obesity: identification, assessment and management, where people with at least a BMI of 30 kg/m^2 to 34.9 kg/m^2 and meeting criteria for referral to specialist weight management services (lower BMI threshold for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds) and at least one weight related comorbidity and use within a specialist weight management service. They agreed that people living with obesity and uncontrolled HbA1c should not have to wait for referral to a specialist overweight and obesity management service to initiate treatment with semaglutide. The committee also discussed that in their experience there are patients who experience weight rebound following cessation of treatment with GLP-1 receptor agonists. The committee also discussed the psychological impact of weight rebound, and whether this could trigger disordered eating and eating disorders. They agreed that based on these factors, healthcare practitioners should consider continuing medicines that have contributed to glycaemic and weight targets even after those goals have been met. The committee discussed the issue of polypharmacy and the psychological impact of triple therapy for T2DM in addition to other treatments they may be receiving. The committee acknowledged the significant burden on mental wellbeing already experienced by people with T2DM due to societal stigma; the assumptions and judgements made about lifestyle choices of people with T2DM. They noted a systematic review of randomised and non-randomised trials from De Giorgi, et al. 2025 that showed benefits from using GLP-1 receptor agonists to manage mental health conditions. They agreed that people being started on triple therapy should be effectively counselled on the treatment they are receiving and that the impact of starting a lot of treatment at once, particularly if they are at critical points in life (for example: early onset type 2 diabetes and receiving treatment when they would not expect to be, or older and receiving treatment when other life events are occurring) that may interact with their ability to successfully start a complicated treatment plan.

The committee discussed the complex interplay of mental health and weight loss when prescribing GLP-1 receptor agonists. They discussed that disordered eating and eating disorders are more common in people with type 2 diabetes and so extra consideration of this is important to ensure that holistic management of their health is achieved during a weight management approach. These elements may not be disclosed due to stigma and so approaching conversations with care and support is important due to the consequences that can occur from managing healthcare encounters inappropriately and providing treatments that can add health consequences (for example: increased risk from weight loss for people with anorexia). The committee referenced NICE guideline NG246 Overweight and obesity management and NG69 Eating disorders: recognition and treatment to highlight where additional guidance can be found about this.

1.5.7.11 Referring to NICE TA924 Tirzepatide for treating type 2 diabetes

The evidence showed that tirzepatide improves HbA1c and weight outcomes, and the committee discussed that this reflects what they experience in practice. The committee agreed that the evidence around the cardiorenal outcomes was limited because tirzepatide is a newer treatment, and therefore there are a lack of trials with sufficient follow-up times to

measure the longer-term cardiorenal outcomes. The committee agreed that the recommendations should only refer to NICE TA924 Tirzepatide for treating type 2 diabetes, which recommends tirzepatide for treating type 2 diabetes alongside diet and exercise in adults when it is insufficiently controlled if triple therapy with metformin and 2 other oral antidiabetic drugs is ineffective, not tolerated or contraindicated, and they have a body mass index (BMI) of 35 kg/m^2 or more, and specific psychological or other medical problems associated with obesity, or they have a BMI of less than 35 kg/m^2, and: insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity-related complications, and to use lower BMI thresholds (usually reduced by 2.5 kg/m^2) for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds. The committee discussed that the technology appraisal for tirzepatide applies if a person's T2DM is uncontrolled, and that this lack of control could relate to glycaemic, weight or cardiovascular management. Therefore, referring to the technology appraisal gives clinicians the option to prescribe tirzepatide if oral medication has been unable to control HbA1c and weight, or weight alone, after a treatment review.

1.5.7.12 DPP-4 inhibitors, sulfonylureas, pioglitazone and insulin for subsequent therapy

The evidence showed that the DPP-4 inhibitors, sulfonylureas, and pioglitazone are all effective at reducing HbA1c. Overall, the committee discussed that all are effective and appropriate at reducing HbA1c in people who have not met glycaemic control with dual therapy with metformin and an SGLT-2 inhibitor. The evidence for subsequent treatment was limited in people receiving triple therapy with metformin, an SGLT-2 inhibitor and a GLP-1 receptor agonist. As the effect may not be additive, the committee did not feel there was sufficient evidence to recommend subsequent treatment with DPP-4 inhibitors in people who are taking GLP-1 receptor agonists. The committee considered their experience and the clinical effectiveness evidence showing benefits of sitagliptin over sulfonylureas and pioglitazone and agreed that subsequent treatment to achieve glycaemic control should begin with a DPP-4 inhibitor, followed by a sulfonylurea, pioglitazone or insulin. The committee agreed that insulin is an effective treatment, especially when rapid glycaemic control is needed, or a person has very poor glycaemic control. Insulin should be considered at the same time as a sulfonylurea and pioglitazone, with the decision on which treatment should be selected based on the comorbidities and other personal factors for the individual. To find out more about the use of DPP-4 inhibitors for people with frailty see the section on People with moderate or severe frailty: Working together.

The committee also highlighted the need for healthcare professionals to discuss lifestyle modification with people with T2DM. This is a critical part of the management of type 2 diabetes and is highlighted in this guidance (sections 1.2 Education and 1.3 Dietary advice and bariatric surgery). Lifestyle modification, including dietary changes and exercise, need to be maintained as a part of treatment to ensure successful achievement of treatment goals. Healthcare professionals should continue to provide guidance and support to people with type 2 diabetes to help them to achieve this and take active control of their health in this manner.

1.5.8 Subgroup analyses: Early-onset type 2 diabetes, people with type 2 diabetes and frailty and people with type 2 diabetes living with obesity

There was insufficient evidence identified for subgroup analysis for the populations of:

- Early-onset type 2 diabetes (age below 40 years of age)
- People with frailty
- People living with obesity

The committee considered these groups highly important for the guideline and so chose to make specific recommendations for them in the absence of clinical evidence. When informing the economic model for people with early-onset type 2 diabetes and people living with obesity, values from the higher risk of cardiovascular disease population network meta-analysis results were used as an estimation for treatment effects.

1.5.8.1 Early-onset type 2 diabetes

The committee agreed that treatment should be escalated early for people with early-onset type 2 diabetes. This group often includes people who are living with obesity and are often in more deprived health groups, which can mean that they are more likely to develop worse outcomes long term if they are not treated early. The health economic modelling results were highly uncertain in this group. This is due to:

- the absence of evidence from clinical trials focusing solely on people with early-onset type 2 diabetes
- the trial that informed the model including some but not a substantial number of people with early onset type 2 diabetes and
- the short time horizon for evaluating the benefits of the treatment, which comparably disadvantages this group where the benefits are likely seen much further in the future.

Given this, the committee were not confident in the findings of the model for this population. Therefore, they agreed to make a weaker recommendation to consider a GLP-1 receptor agonist in addition to an SGLT-2 inhibitor and metformin. If it is not considered for initial treatment, it can be considered again for subsequent treatment, and dependent on whether a GLP-1 receptor agonist is used, a DPP-4 inhibitor can be offered or either a sulfonylurea, pioglitazone or insulin-based treatment can be offered.

Due to the uncertainty in this population, while also expecting that further research would add to understanding in the future and could change the recommendation, the committee made a research recommendation to understand more about the clinical and cost-effectiveness of GLP-1 receptor agonists, SGLT-2 inhibitors and metformin for people with early-onset type 2 diabetes.

1.5.8.2 People with frailty

For people with frailty, it was agreed that the aim of giving medication may be different, changing to symptom management with the general aim to manage the effects of hyperglycaemia. Given this, the recommendation changed to consider giving metformin alone. This reduced the possibility of causing more adverse effects from SGLT-2 inhibitors (caused by increased urinary frequency leading to more falls). Otherwise, they recommended a review of the diabetes treatment plan to ensure that the smallest effective number of medications are being taken at the lowest effective dose to optimise the person's treatment and reduce the impact on their quality of life. If more treatment is required, then a DPP-4 inhibitor can be considered, as this is likely to be the next most tolerated option. After this, options include pioglitazone, a sulfonylurea or an insulin-based treatment. The committee made a recommendation to highlight the risk that sulfonylureas and insulin-based treatments have in causing hypoglycaemia and falls. However, they also highlighted that insulin-based treatments can be an effective option in this group and that it is important to consider each person on a case-by-case basis.

1.5.8.3 People living with obesity

For people living with obesity, the committee agreed that the standard therapy available to most people with type 2 diabetes (an SGLT-2 inhibitor and metformin) was appropriate for this population. The health economic model highlighted that SGLT-2 inhibitors may not be cost-effective in this population. However, when looking at health inequality analyses, those

in the most deprived quintiles (1 and 2) in the Index of Multiple Deprivation showed the greatest net benefits from treatment being given. Providing population-wide intervention increases the access of treatments to everyone at a baseline, which then allows for community action to be taken to improve access to people from more deprived groups. Given these treatments will provide significant benefits to people who are currently not accessing the treatments, removing barriers to treatments while focussing on other moderators to treatment (considered in the research recommendation on this topic) will support better healthcare long term. Therefore, being able to provide treatment to the whole population in order to reduce health inequalities to the people from the most deprived groups was seen as worthwhile. After initial treatment, they agreed that a GLP-1 receptor agonist could be considered for people who had been taking initial therapy for at least 3 months, if further medicines are needed to reach their glycaemic targets and if they are not already taking a GLP-1 receptor agonist. After this they agreed that a sulfonylurea, pioglitazone or insulin-based product could be added to help reach glycaemic targets if they are not otherwise met.

1.6 Cost effectiveness and resource use

1.6.1 Consideration of previous economic evidence

The committee considered NICE bespoke economic evaluations from 2 previous updates of the guideline which covered the review questions. Whilst previously published economic evaluations were identified in the literature search, the evidence was either not directly applicable to the review question (i.e. using outdated background treatments or unit costs having significantly changed) or did not cover all the interventions of interest. The committee therefore did not use these to inform their recommendations. Whilst both studies presented were highly applicable, with both considering an NHS & Personal Social Services (PSS) perspective, they both had some limitations which reduced their usefulness for informing the current recommendations. These included the modelling of insulin treatments which are no longer widely used in the NHS, costs of treatments that have changed significantly and the exclusion of important cardiovascular events from the perspective of the analysis. The previous evidence also did not present subgroup analyses for populations of particular interest for which the committee wished to make tailored recommendations. They also assumed an intensification pathway based on HbA1c values which the committee did not think was reflective of current practice. As a bespoke economic evaluation was produced for informing this guideline, considering the outcomes and populations of interest to the committee, very limited weight was placed on the previous economic evidence in making recommendations.

1.6.2 Metformin standard-release versus metformin modified-release

Modified-release metformin was recommended when individuals or their healthcare professionals had concerns about either pill burden or adverse events with standard-release metformin. The committee considered including both standard-release metformin and modified-release metformin in the bespoke economic evaluation. Given that the economic model was looking at the addition of interventions to metformin monotherapy and therefore a potential increase in pill burden, it was decided that modified-release metformin was the most appropriate comparator.

Whilst the additional costs per individual were relatively small, the T2DM population who are prescribed metformin is very large. The committee considered additional costs of modified-release metformin and balanced them against the potential savings from reduced GP appointments for gastro-intestinal events and cardio-renal events prevented through improved adherence to treatment. They also considered the improvements in quality of life through decreased adverse events and reduction of cardio-renal events. The committee however noted the large resource impact around a universal recommendation of modified-release metformin and the paucity of evidence supporting the assumptions around GP appointments and reduction in adverse events. Modified-release metformin was therefore not recommended universally.

Modified-release metformin was used as the comparator in the economic model for all but the CKD stage 4 population (where it is contraindicated and usual care was used as a comparator).

1.6.3 SGLT-2 inhibitors

The SGLT-2 inhibitor class was the preferred option for the CKD1-3, CKD 4 and living with obesity populations in the economic analysis. Further, the SGLT-2 inhibitor class was only just above the cost-effectiveness values at which NICE typically recommend interventions for the living with overweight and ASCVD populations.

For the ASCVD population the SGLT-2 inhibitor class became cost-effective when class effects were used in the economic model. The SGLT-2 inhibitor class was also marginally above the cost-effectiveness value at which NICE typically recommend interventions when the background treatment costs of cardiovascular events were set to zero. This is a population with a significant proportion of people with co-morbidities and high underlying treatment costs. Including such costs in the analysis subdues any improvement in cost-effectiveness from improved survival.

The HF population was not cost-effective in the base-case but was cost-effective when the underlying treatment costs were set to zero. As with the ASCVD population there are a significant proportion of individuals in this group with co-morbidities dampening any effect on cost-effectiveness from improving survival.

SGLT-2 inhibitors were not cost-effective in the early-onset population and this held under all sensitivity analyses performed. There was however a paucity of evidence for this population and the parameters of the model were largely taken from other populations. The committee also noted large health inequalities with this population compared to other people with T2DM. The type 2 diabetes health inequalities York tool report also noted benefits in the most socio-economically deprived quintile of the population with recommending the SGLT-2 inhibitor class.

Since the model was run, the UK court has declared the UK patent for dapagliflozin to be no longer valid with an expectation that this will lead to the entry of multiple generics and a large drop in price for dapagliflozin. It is therefore likely that for populations where the ICER is slightly above £20k per QALY that it would be under that value once these price drops take effect. Even where they are significantly over like for the early-onset population it is possible, given a significant drop in price, that they become cost-effective.

Based on the clinical evidence, cost-effectiveness evidence and the health inequalities report the committee made a recommendation for SGLT-2 inhibitors and metformin dual therapy for all populations in the model apart from for populations where they would not be clinically appropriate (i.e. some people with clinically significant frailty). Where recommendations for SGLT-2 inhibitors have not been made the reasons are presented above.

1.6.4 GLP-1 receptor agonists

In developing the economic model, the committee wanted to explore moving GLP-1 receptor agonists earlier in the treatment pathway if they were clinically and cost-effective. Oral semaglutide was the most effective treatment, in terms of QALYs, for all populations in the model but was also always amongst the treatments that bore the highest costs. This was because it was associated with the highest total treatment costs, a result of having both the highest list price and highest life expectancy. Oral semaglutide was not cost-effective compared to metformin in any of the populations considered in the analysis.

In the ASCVD and HF populations subcutaneous semaglutide was the preferred intervention. It was not cost-effective in any of the other populations for the base-case or any or the sensitivity analyses. No other GLP-1 receptor agonist was cost-effective in any of the populations considered. Liraglutide was cost-effective compared to metformin monotherapy in all populations with reduction in price of between 35-45%. Liraglutide has recently come off patent and has reduced in price by 36% since the economic model was run. Under this price liraglutide is cost-effective compared to metformin in the CKD1-3, CKD4 and HF populations and has an ICER just above £26k in the early-onset population. However, this is based on weak clinical evidence around liraglutide.

The committee also highlighted that, except for cardiovascular mortality, there was either no available evidence or the NMA could not generate estimates due to limited data for a number of GLP-1 agonists across all cardiovascular effectiveness inputs in the economic model.

Following the committee's decision rule, these were inputted with a hazard ratio of 1 (having no difference in effectiveness to metformin monotherapy). These estimates did not match the committee's clinical and living experience and agreed, if evidence was available, it would be a positive effect size in all these outcomes for people living with T2DM. The committee also highlighted the somewhat conservative estimates about maintaining weight loss in the economic model given the time horizons of the RCTs in the NMA used to inform that input into the model which would particularly impact the living with overweight and living with obesity populations. There are also likely to be other benefits with regards to weight loss, for which the GLP-1 receptor agonists were shown to be particularly effective for in the NMA, which were not included in the outcomes from the economic model such as the impact on undertaking everyday activities.

The committee also highlighted health inequalities within the under 40 population compared to other people with T2DM. Whilst the economic modelling did not show any GLP-1 receptor agonist to be cost-effective the committee noted the paucity of clinical evidence for the population. As with SGLT-2 inhibitors benefits from the recommendation of GLP-1 agonists are likely to be largest in socio-economically deprived individuals.

Based on the clinical and cost-effectiveness evidence, the committee made a recommendation to offer subcutaneous semaglutide alongside SGLT-2 inhibitors for people with ASCVD and to consider adding it alongside SGLT-2 inhibitors for people with HF and living with obesity if further treatment is needed, in the latter group as a means to reach glycaemic targets. For those with early-onset T2DM a broader recommendation for a GLP-1 receptor agonist was made reflecting the uncertainty around estimates of differences in effectiveness between individual GLP-1 receptor agonists. The committee also highlighted that GLP-1 receptor agonists were being more widely prescribed in people living with obesity and comorbidities (including T2DM) taking into account both their own knowledge and experience and the NICE technology appraisals in overlapping populations. The committee did not recommend GLP-1 receptor agonists for the people living with overweight population given the uncertainties around whether this would be an efficient use of NHS resources.

GLP-1 receptor agonists were not recommended earlier in the treatment pathway for the other populations considered as whilst they were often the most effective treatments the additional cost did not represent an efficient use of NHS resources.

1.6.5 Triple therapy with metformin, SGLT-2 inhibitors and GLP-1 receptor agonists

No clinical evidence was identified for triple therapy with metformin, SGLT-2 inhibitors and GLP-1 receptor agonists. The committee stated it is often done in practice in patients where benefits to cardiovascular and renal functions are likely to have a large health impact. They were also aware of a large trial currently being undertaken, comparing triple therapy to dual therapy with metformin and either a SGLT-2 inhibitor or GLP-1 receptor agonist which is yet to report. The committee recommended a triple therapy combination in people with ASCVD, HF and early-onset diabetes. For those with ASCVD, a recommendation to offer both a SGLT-2 inhibitor and subcutaneous semaglutide was made. In people with HF, this was a consider recommendation. In people with early-onset diabetes, a recommendation to offer a SGLT-2 inhibitor, and consider a GLP-1 receptor agonist class was made. The committee highlighted that both SGLT-2 inhibitors and GLP-1 receptor agonists work through different mechanisms and that any improvement to cardiovascular outcomes, renal outcomes and weight from the treatments would be additive if administered together. The analysis assumed that treatment effects from the individual components of triple-therapy were additive. Whilst this is not a conservative assumption, if it holds it is likely triple therapy would be an efficient use of NHS resources in some populations. These treatments will all likely be given at some point in the treatment pathway, to either improve control of diabetes or to modify cardio-

vascular risk factors such as weight. Any increase in treatment costs therefore would be less than the sum of treatment with SGLT-2 inhibitor or GLP-1 receptor agonist alone and plausibly at an acceptable cost for each additional QALY gained.

1.6.6 Insulin compared to GLP-1 receptor agonists

For all populations a sensitivity analysis was undertaken comparing GLP-1 receptor agonists to insulin. In all population groups insulin was both more expensive and led to less QALYs than GLP-1 receptor agonists. The committee agreed that insulin should be offered as an option alongside sulfonylureas or pioglitazone where other treatment options including DPP-4 inhibitors have been unable to manage glycaemia. This should take into account the person's comorbidities and personal situation.

1.6.7 People with moderate or severe frailty

Whilst the economic analysis did not explicitly consider people with clinically significant frailty, the committee did use the results from the economic model to make their recommendations. The committee used the comparison of DDP-4 inhibitors to metformin monotherapy as DPP-4 inhibitors have a lower adverse event profile than other drug classes and were more suited to groups who are likely to have multiple comorbidities and be taking a greater range of medications. The cost per additional QALY was below £20,000 for at least 1 DDP-4 inhibitor in the ASCVD and CKD stages 1 to 3 populations. They performed badly in the people living with overweight and obesity as well as the early onset T2DM population in some cases being more costly and less effective than metformin monotherapy. However, the committee thought these populations were likely to be less representative of the people with clinically significant frailty. This supported the committee's recommendation for DPP-4 inhibitors where metformin monotherapy or SGLT-2 inhibitors were not suitable treatment options.

1.6.8 Disutility associated with injections

Previous economic evaluations incorporated a disutility around injectables and hypothesised that injectables that needed to be administered less frequently or oral medications would have less of a detriment on quality of life. Estimates from the published literature were presented to the committee. There was scepticism, from the committee, about the size of the estimated detriments. They highlighted that the detriments from injectables often become inconsequential after the first few times and contextualised any disutility by comparing it to detriments from needing to take multiple oral medications as well as from frequent finger pricking. The committee decided not to include any utility detriments in the economic model or their considerations although emphasised the importance of highlighting these issues so that people can make informed and individualised choices about the treatment they receive.

1.6.9 Comparison with previous guideline update

There were several differences between the economic analysis in this guideline update and the previous update. This analysis moved away from the treatment intensification approach to an approach directly aiming for cardio-renal protection. This analysis considered a greater range of outcomes in the economic model and although there was significant overlap between subgroups considered between updates, they were divided to a greater extent in this analysis.

Despite this there was a large amount of concordance between the results. One or more SGLT-2 inhibitor was cost effective in all but 1 population in this analysis. The previous guideline update reported that only 1 SGLT-2 inhibitor was cost-effective for specific subgroups and lines of intensification. It also reported that GLP-1 agonists were not cost-effective in any subgroup, which also held for all lines of intensification and in all sensitivity

analyses. The most pronounced difference was in the ASCVD population for this group where SGLT-2 inhibitors and all GLP-1 agonists were cost-effective compared to metformin monotherapy whilst in the much wider previous cardio-vascular event group of the last update only one SGLT-2 inhibitor was cost-effective. For the most closely aligned subgroup between the 2 updates, people living with obesity and people with a BMI greater than or equal to 30kg/m^2 the results differed only slightly with the SGLT-2 inhibitors being cost-effective in this analysis whilst only 1 SGLT-2 inhibitor was cost-effective in the previous update. GLP-1 agonists were all above £20k per QALY gained in both analyses.

The main reasons for the differences in results was that this update included a greater range of outcomes in the economic model better capturing benefits from treatment. This update also had a greater range of subgroups. SGLT-2s and GLP-1s tended to perform better in subgroups with higher life expectancy, something that was brought out with the more fragmented populations.

1.6.10 Strengths and limitations of the economic model

The model assessed a large number of treatments directly against each other reflecting the wide range of treatment options available for T2DM. It moved away from a treatment intensification approach to one directly considering cardio-renal protection. The analysis split the T2DM cohort into sub-groups of particular clinical interest and across whom optimal treatment may vary. This better mirrors current practice than previous economic models in this area.

The model was underpinned by the UKPDS Outcomes Model 2.2, which was developed using data from a UK RCT, and large observational data from UK General Practice. Evidence informing the model was therefore highly applicable to the population under consideration.

The model used clinical estimates for ‘subsequent therapy’ in a prevalent cohort although the conclusions were used to support recommendations for both subsequent therapy and therapy in a newly treated population. Given the move away from a glucose-centric treatment intensification approach to tackling cardio-renal outcomes directly, the distinction between decision making in the 2 populations is much reduced. The committee therefore believed that making decisions based on the clinical estimates for subsequent therapy, where there was greater availability of evidence, was the correct approach. The evidence around GLP-1s in the initial therapy was particularly weak and often indirect. Comparisons between GLP-1s and other therapies would be associated with a great degree of uncertainty in any analysis using these values and its usefulness for decision making low. A newly treated cohort would be younger than a prevalent cohort and any benefits from treatment maybe realised for longer.

It was not possible to make the economic model probabilistic given the run-time and computational power required. Uncertainty around outcomes of the economic model could therefore not be quantitively assessed. There were several estimates in the supporting NMA that either had high levels of uncertainty or for which no direct evidence was identified. Some interventions in the economic model came out favourably but were not recommended by the committee given this uncertainty. It would have been ideal to have formally quantified this uncertainty using Monte Carlo simulation rather than relying on committee consensus about the strength of the estimates.

1.7 Other factors the committee took into account

1.7.1 Treatment access barriers

The committee also noted the importance of equity and equality in relation to having access treatment. They noted that there are significant barriers to people accessing healthcare services on a regular basis and being able to have appointments. The committee agreed there is regional variation in availability of GP services for appointments which may affect how easy it is to start individual therapy and combination therapy by the regimens suggested in the guideline, where therapy should be added in a stepwise manner. Having the time to organise this may be particularly difficult for people dependent on their accessibility requirements, where people who are currently working may find it hard to manage the different appointments they need to initiate multiple treatments when some of these are to prevent complications that they are not currently having, while people who find it difficult to use the technology that services are currently implementing more regularly (such as online booking systems) may put people who find it difficult to access technology at a disadvantage (dependent on their level of digital literacy). The committee noted how people from Black African, African Caribbean and South Asian family backgrounds are at a higher risk of developing T2DM from a younger age, and this may intersect with this with people finding it hard to manage work requirements around starting more rigorous therapy requirements. This is also important to consider when understanding mental wellbeing and considering the extra effects of societal stigma that can interact in this area. This is also likely to be a barrier for people with severe mental illness, people with learning disabilities and people with dementia who may find it difficult to manage their treatment regimen, schedule appointments and attend appointments. Further support is required to ensure that the correct care is provided to people from these groups to ensure that their holistic needs are considered.

Treatment access may also be impacted by inequalities in knowledge of healthcare. People from more privileged socioeconomic groups with more healthcare knowledge will know what to do when they have adverse events from treatments and may have access to greater social capital in accessing services to resolve this. However, people from less privileged socioeconomic groups with less healthcare education may not, which can impact decision making when trying to access treatments, leading to worse long term outcomes. The committee reflected the importance of explaining how to get in contact with healthcare professionals and when to follow up about different problems that can be experienced by people with type 2 diabetes.

1.7.2 Language use when working with people with type 2 diabetes

The committee discussed access to diabetes treatment and highlighted factors such as cultural values, societal stigma, certain beliefs and fear about side effects arising when discussing treatments with friends being contributing factors for deterring patients from treatment. Additionally, the committee acknowledged the burden of societal stigma associated with T2DM and potential assumptions made by the general population around the T2DM being solely a results of lifestyle choices resulting in feelings of shame, and therefore the importance of non-judgemental language used during appointments.

1.7.3 SGLT-2 inhibitor and initial drop in eGFR

The committee acknowledged that initiation of SGLT-2 inhibitors can result in a drop in eGFR function that recovers after 3 months. This can cause concern with healthcare professionals that can result in treatments being discontinued, leading to delays in initiation of treatment, which can be unnecessary in some cases. They noted that prescribers should monitor the person’s renal function, including the eGFR and ACR, and that monitoring requirements vary between SGLT-2 inhibitor treatments. For people with reduced renal function, dose adjustment or avoidance of SGLT-2 inhibitor treatment may be required depending on the

SGLT-2 inhibitor selected and the renal function test results obtained. The committee expected that as for other drugs, prescribers would consult the summary of product characteristics (SPCs) and any other relevant sources of information about dosing and safety for the SGLT-2 inhibitors. They noted that monitoring requirements are covered as one of the factors to consider when choosing a drug treatment in the first recommendation in the drug treatment section of the guideline.

1.7.4 GLP-1 receptor agonists, fertility and pregnancy

The committee discussed the effects of GLP-1 receptor agonists on fertility and the risks of use in pregnancy. Guidance from MHRA states that people should use effective contraception while taking GLP-1 receptor agonists and that they should continue using contraception during a wash-out period after stopping the drug (2 months for semaglutide, 0 month for liraglutide, 1 month for tirzepatide). They also explained that a non-oral, barrier contraception should be used with tirzepatide for four weeks after starting the medication and four weeks after increasing the dose if taking an oral contraceptive. This is due to the effect the drug can have in reducing the effectiveness of the contraceptive. The committee noted that the weight loss from the GLP-1 receptor agonists can lead to increased fertility in people, so stressed the importance of using contraceptives while taking the medication. They noted this as particularly relevant for people with early onset type 2 diabetes. Due to this, a recommendation was made to support the guidance provided by MHRA providing advice to women and trans people of childbearing potential.

1.7.5 Hormone replacement therapy and use of risk tools for group stratification for trans people

The committee discussed gender and the effects of gender reassignment on the management of type 2 diabetes. Studies included in the review did not report whether trans people were included. The committee were presented evidence by an expert witness from the Trans Gap project evidence group that provided information from small observational studies detailing how QRISK and eGFR can change when people take hormone replacement therapy. The evidence suggested that after 3 months of hormone replacement therapy, trans people may have similar values of eGFR to cisgender people. However, there was more evidence for trans men than for trans women, leading to more certainty in this group. Findings on QRISK highlighted disparities in the trans population in cardiovascular risk factors that note that both trans men and women would have heightened cardiovascular risk. There was no evidence for non-binary people. The committee agreed that there was very limited evidence in the population and that the evidence was not specific to a population with T2DM. Given this they concluded that they would not make a recommendation at this time and that more evidence was required that was specific to this population before they would consider this. In addition, although defining the population of people at high cardiovascular risk is of relevance to this guideline and may affect the treatment that would be available, the committee agreed that the assessment of risk using QRISK and how this should be adjusted in different populations was outside the scope of this guideline. They acknowledged that gender specialists can provide guidance about treatment if there are specific concerns about the overlap of hormone replacement therapy and medication for type 2 diabetes. They agreed that further inclusion of gender diverse people in research would be valuable to ensure that treatments are effective for everyone.

1.8 Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.6-1.8.32, 1.8.34,1.8.38-1.8.60 and the recommendation for research on treatment strategies for people with type 2 diabetes and frailty, access to SGLT-2 inhibitors and management of early onset type 2 diabetes. Evidence supporting these recommendations can be found in the evidence reviews on initial therapy (evidence review E) and subsequent therapy (evidence review F).