Appendix A2: Summary of evidence from surveillance

2019 surveillance of [Type 2 diabetes in adults: management](#) (2015) NICE guideline NG28

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Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to specific parts of the guideline:

- Dietary advice

- Blood glucose management:

  - Self-monitoring of blood glucose

  - Drug treatment

New evidence and intelligence indicated that these areas were more likely than other areas to need updating. Intelligence was nevertheless gathered across all areas of the guideline and where relevant and eligible studies were identified, these were included in the evidence summary.

We found 184 studies in a search for RCTs and systematic reviews published between 1 June 2014 and 12 February 2019.

See [summary of evidence from surveillance](#) below for details of all evidence considered, and references.

Selecting relevant studies

Due to the large number of studies identified in the initial search, the following criteria were adopted to ensure only relevant studies were selected:

- Studies with a sample size lower than 100 were excluded.

- Studies that included both type 1 and type 2 diabetes were excluded if they did not distinguish between the populations in the results.

- Post-hoc, pilot and secondary analysis studies were excluded unless prespecified in study protocols

- Single studies already included in a Cochrane review were excluded.

- Non-Cochrane systematic reviews were only included for priority areas and if they had a publication date of 2018 or later.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 18 were assessed as having the potential to change recommendations; therefore we plan to check the publication status regularly, and evaluate the impact of the results on current recommendations as quickly as possible. These studies are:

- [Preventing cardiovascular and renal complications in patients with type 2 diabetes and microalbuminuria: the GP-Prompt study](#)

- [Can a new method of monitoring improve the control of blood glucose levels in patient with Type II diabetes who have had a heart attack?](#)

- [Glucose Lowering through Weight Management (GLoW)](#)

- [Effectiveness of multimodal imaging for the evaluation of retinal odema and new vessels in diabetic retinopathy](#)

- [TriMaster - a research study to help improve treatment of type 2 diabetes, by learning how individuals respond to different blood sugar-lowering drugs](#)

- [Embedding Diabetes Education (RCT)](#)

- [Circulating biomarkers to detect sight-threatening diabetic retinopathy](#)

- [Impact of a community based social prescribing intervention on people with type 2 diabetes in an ethnically diverse area of high socio-economic deprivation. Exploiting a natural experiment to evaluate effects on health and health care utilisation with economic assessment and ethnographic observation](#)

- [A comparison of standard laser with micropulse laser for the treatment of diabetic macular oedema](#)

- [Optimising cardiac surgery outcomes in people with diabetes](#)

- [Lowering Events in Non-proliferative retinopathy in Scotland](#)

- [Performance Check of the Abbott FreeStyle Libre Flash Glucose Monitoring System](#)

- [Education programme (DESMOND-ID) for the self-management of type 2 diabetes for adults with intellectual disabilities (ID)](#)

- [Implementation intentions for creating and breaking habits in care provided to patients with type 2 diabetes: a dual process approach](#)

- [Masked performance check of the Abbott FreeStyle Libre Flash Glucose Monitoring System](#)

- [A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Event-driven Phase 3 Study to Investigate the Safety and Efficacy of Finerenone, in Addition to Standard of Care, on the Progression of Kidney Disease in Subjects with Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease](#)

- [A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Event-driven Phase 3 Study to Investigate Efficacy and Safety of Finerenone on the Reduction of Cardiovascular Morbidity and Mortality in Subjects with Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease in Addition to Standard of Care](#)

- [EMPA-KIDNEY: the study of heart and kidney protection with empagliflozin](#)

- [A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (Dapa-CKD)](#)

- [A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects with Type 2 Diabetes (PIONEER 6)](#)

- [Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease, The VERTIS CV Study (MK-8835-004)](#)

Intelligence gathered during surveillance

Views of topic experts

For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to NICE guideline NG28.

We sent questionnaires to 20 topic experts and received 7 responses. The topic experts were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty.

All of the 7 responding experts felt that the guideline is in need of updating. The dominant area identified for update was drug treatment for blood glucose management.

Topic experts indicated that the management of T2D has changed considerably since publication of the guideline, and it now needs to be updated as a priority with new cardiovascular and renal evidence for the SGLT-2 inhibitor and GLP-1 analogue classes of drugs. The lack of explicit consideration of cardiovascular (CV) outcomes within the guideline was considered by experts to be a weakness. Practice was stated to be moving away from using DPP4 inhibitors as the first intensification option with new evidence pointing towards SGLT2 inhibitors and GLP1 receptor agonists. It should be noted that several drugs in these classes, with the exception of liraglutide for CV disease prevention, are covered by NICE technology appraisals (TAs) that are either undergoing review, have recently been reviewed, or are in development. Relevant evidence identified in the surveillance review has been passed to the NICE TA team for consideration in these topics.

In addition experts noted that the joint American Diabetes Association (ADA) and European Association for the study of Diabetes (EASD) guideline Management of Hyperglycemia in Type 2 Diabetes (2018) has moved to a risk stratification model of treating type 2 diabetes taking into account CV risk. This is considered to promote a much more patient-centred approach to drug therapy. The ADA/EASD guideline was also stated to include more expensive treatment combinations which are not recommended by NICE. These include metformin in combination with SGLT2 inhibitors and DPP4i drugs and metformin in combination with SGLT-2 inhibitors and GLP-1 analogues.

Furthermore, experts considered there to be a barrier to using the newer medications earlier in the treatment pathway because these are not currently recommended by NICE.

Newer insulins were also highlighted for consideration by experts, including the long-acting insulin analogues Toujeo (glargine) and Tresiba (degludec).

Other sources of information

We considered all other correspondence received since the guideline was published. An enquiry was received by NICE advocating the revision of NICE NG28 to recommend a high fat, low carbohydrate diet in the treatment of T2D. NICE NG28 includes recommendations on dietary advice (section 1.3) that were carried over from the earlier version of the guideline but are considered to remain current. It was also stated that none of the stakeholders or guideline committee members involved in developing NG28 raised the issue of high fat, low carbohydrate diets. However, in the light of emerging evidence on low calorie diets for T2D, this section was included in the priority areas for the surveillance literature search and eligible new evidence was included in the review. The Diabetes Remission Clinical Trial (DIRECT) trial was also suggested by a stakeholder, and the 2-year results of this were included in the evidence summary.

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts, who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a view on the need to update each section of the guideline.

1.1 Individualised care

Surveillance proposal

This section of the guideline should not be updated.

Editorial amendments

The guideline will be amended with the following standard text placed at the beginning of the recommendations section:

'People have the right to be involved in discussions and make informed decisions about their care, as described in your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations and has information about prescribing medicines (including off label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.'

2019 surveillance summary

Integrated personalised management

An RCT(1) (101 practices n=907) (Table 1) found that integrated personalised diabetes management led to a greater reduction in HbA1c after 12 months than usual care for people with type 2 diabetes (T2D). Patient adherence and satisfaction were also significantly higher than in the usual care group.

Intelligence gathering

An expert noted that there are multiple studies on individualised care and education, but the principles already laid out in NG28 are evidence based. It was further noted that there is variation in the extent to which individual interventions are effective and recent trials do not provide evidence that helps explain the role of context and differing groups of individuals.

Impact statement

The new evidence on personalised diabetes management for T2D in adults is consistent with recommendation 1.1.1, which recommends an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account

their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy.

New evidence is unlikely to change guideline recommendations.

1.2 Patient education

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

We identified 9 studies on patient education (Table 2).

Web-based self-management

An RCT and accompanying cost effectiveness study(2) (21 general practices, n=374) aimed to develop, evaluate and implement a web-based self-management programme for people with T2DM at any stage of their condition, with the goal of improving self-management support in a cost-effective manner. The intervention was the HeLP-Diabetes programme; an evidence based theoretically informed web-based self-management programme. The main outcome measures of the trial were glycated haemoglobin (HbA1c) level and diabetes mellitus-related distress, as measured with the Problem Areas in Diabetes (PAID) scale. The within-trial health economic analysis found that incremental costs were lower in the intervention group than in the control group and the quality-adjusted life-years (QALYs) were higher, meaning that the HeLP-Diabetes programme group was more cost-effective than the control group. At 12 month follow-up, participants in the intervention group had lower HbA1c than those in the control group. There was no significant overall difference between groups in the mean PAID score, but prespecified subgroup analysis of participants who had been more recently diagnosed with diabetes showed a beneficial impact of the intervention in this group.

A further RCT(3) (n=139) found that an insulin glargine titration web tool was not superior to an enhanced usual therapy diabetes education programme.

Structured education

A Cochrane review(4) (33 studies n=7453) assessed the effectiveness of culturally appropriate health education for people in ethnic minority groups with T2D.

The review found that culturally appropriate health education has short- to medium-term effects, up to 12 months, on HbA1c reduction, triglycerides and on knowledge of diabetes and healthy lifestyles.

A National Institute for Health Research (NIHR) commentary was identified on a systematic review comparing the effectiveness of diabetes self-management education to either usual care or a minimal educational intervention, in people with T2D. The commentary concluded that, based on a large number of high and low quality studies, the systematic review suggests that self-management education interventions are broadly more effective at reducing blood sugar levels in people with T2D than usual care or minimal education interventions.

We identified 4 RCTs covering differing aspects of structured education for T2D. The results indicated that:

- Structured education with a module on self-monitoring for either blood or urine glucose were both effective for change in HbA1c at 18 months(5) (n=292).

- an education programme (MEDIAS 2 BSC) of non-intensive insulin treatment regimens was more effective in reducing HbA1c than an established education programme over 6 months(6) (n=182).

- Structured diabetes education plus insulin therapy compared to usual care improved HbA1c in insulin treated patients with T2D(7) (n=1289).

- Certified diabetes educator-delivered diabetes self-management and support with carbohydrate gram counting or a modified plate method improved glycaemic control in patients with an initial HbA1c between 7% and 10% compared to general health education (8) (n=150).

- A 6-week patient-centred, empowerment-based intervention programme was not superior to health education classes and post-discharge follow-up in reducing HbA1c, at 20 week follow-up (9).

Intelligence gathering

An expert noted that there are multiple studies on individualised care and education, but the principles already laid out in NG28 are evidence based. It was further noted that there is variation in the extent to which individual interventions are effective and recent trials do not provide evidence that helps explain the role of context and differing groups of individuals.

Impact statement

The guideline recommends offering structured education to adults with T2D and their family members or carers, that is evidence based and suits the needs of the person. As alluded to by topic expert feedback, the new studies identified on web-based self-management and structured education reflect a growing body of evidence that is consistent with these evidence based principles. The interventions are very diverse so the optimal intervention duration, provider, or contact hours are not clear. The specific interventions proposed for

various contexts are broadly encompassed under the general recommendations and therefore no impact on the guideline is anticipated.

The new evidence on culturally appropriate health education is consistent with recommendation 1.2.5 which advises ensuring that patient education programmes available meet the cultural, linguistic, cognitive and literacy needs within the local area.

> New evidence is unlikely to change guideline recommendations.

1.3 Dietary advice and bariatric surgery

Surveillance proposal

This section of the guideline should not be updated.

Editorial amendments

- Recommendation 1.3.10 should be updated to cross refer to NICE Stop smoking interventions and services to replace the obsolete links to smoking: brief interventions and referrals and stop smoking services. This should be done following the forthcoming review of the smoking suite of guidelines to ensure the cross referral is current.

2019 surveillance summary

Dietary advice

We identified 3 systematic reviews and 4 RCTs covering dietary advice for T2D (Table 3).

Low carbohydrate diet (LCD) and low calorie diets

We identified 3 systematic reviews(10–12) (9 studies, n=734;18 studies, n=2204; 23 studies, n=2178) comparing LCD with either normal or high carbohydrate diets (HCD) for T2D in adults. The findings indicated that:

- LCD significantly reduced HbA1c, triglyceride concentration and HDL cholesterol concentration relative to normal or HCDs, but that the difference in HbA1c was evident only in studies with a duration of 6 months or less and with a high risk of bias.

- LCD was not associated with a decreased level of total or LDL cholesterol or diastolic blood pressure.

- LCD led to short term weight loss, but this was not maintained over longer term periods of more than 6 months.

- Dietary adherence was considered to be a barrier in most studies, and definitions of LCD varied between studies.

A further 3 RCTs were identified on LCD and intermittent energy restriction for T2D in adults, the findings of which indicated that:

- A low carbohydrate high protein diet combined with omega-3 polyunsaturated fatty acid supplementation diet provided greater effects on HbA1c and fasting glucose and faster effects on fasting glucose than either dietary component alone(13) (n=122).

- A very-low-carbohydrate, high-unsaturated fat, low-saturated fat (LC) diet and a high carbohydrate, low-fat (HC) diet achieved similar outcomes in weight loss, reduced HbA1c and fasting glucose. However the LC diet provided significantly better lipid profile, blood glucose stability, and reductions in diabetes medication requirements over 12 months(14) (n=115). Although these benefits remained at 24 months, only 61 participants completed the second year of the study(15)

- Intermittent energy restriction (2 days per week) was non-inferior to continuous energy restriction for the reduction of HbA1c and weight loss over 12 months (16) (n=137).

Primary care-led weight management

The DiRECT trial (17,18) (n=298) assessed remission of T2D during a primary care-led low calorie diet weight-management programme. The intervention consisted of withdrawal of anti-diabetes and anti-hypertensive drugs, total diet replacement (825-853 kcal per day formula diet for 12-20 weeks), stepped food reintroduction (2-8 weeks), and then structured support for weight loss maintenance. The primary outcomes, analysed hierarchically in the intention-to-treat population at 24 months, were weight loss of at least 15 kg, and remission of diabetes, defined as HbA1c less than 6·5% (48 mmol/mol) after withdrawal of anti-diabetes drugs at baseline.

At both 1 year and 2-year follow-up, significantly more intervention participants were in remission and had achieved at least 15 kg weight loss. Serious adverse events were similar to those reported at 12 months but were fewer in the intervention group than in the control group in the second year of the study.

Vitamin D supplementation

Two RCTs(19,20) (n=275 and n=127) found that neither intermittent high dose (50,000 iu per month) nor daily (4000 units) supplementation of vitamin D were superior to placebo in reducing HbA1c over 26 to 48 weeks for T2D.

Exercise training compared to medication and diet

An additional RCT found that supervised structured aerobic exercise training compared to a routine medication and dietary plan improved fasting blood glucose, plasma insulin level, glycaemic control and insulin resistance(21) (n=102).

Intelligence gathering

The Diabetes Remission Clinical Trial

The DiRECT trial was highlighted by a stakeholder and the 2-year results are included in the evidence summary. The longer-term results will be monitored for publication.

Some participants will be followed for 4 years, and so the cost effectiveness of the programme can be evaluated. This will help to understand the longer-term benefits and provide the NHS with more information to inform future action.

Another stakeholder also highlighted the importance of the DiRECT trial, and also the risk that prescribed insulin can cause more harm than benefit, due to the strong positive correlation between the amount of insulin prescribed and blood sugar levels. The 'twin cycle' hypothesis was cited; the accumulation of fat in liver and secondarily in the pancreas will lead to self-reinforcing cycles that interact to bring about type 2 diabetes.

The DiRECT study has also been the subject of an NIHR commentary which concluded that the challenge will be to see if the results can be maintained over the planned 4 year follow-up period. If successful, the programme could be easily replicated by other GP surgeries with minimal training requirements. NHS England has committed to a pilot programme in 2019 involving low-calorie diets.

Motivational interviewing

An NIHR commentary was identified on a systematic review covering motivational interviewing for adults with T2D. The review of 14 trials (7 covering diet and healthy eating) looked at a range of outcomes and showed a consistent impact of motivational interviewing on healthy eating. The commentary concluded that the evidence doesn't support the wide adoption of motivational interviewing, as described in this review because it is not known yet why many studies showed no effect. Next steps could be to identify which components of the interventions worked, how intensive they need to be and what the impact of prior skill and training in delivery of the intervention was.

Impact statement

The guideline recommends the same dietary advice that is given to the general population (1.3.3). This includes eating a high-fibre, low glycaemic index, low-fat diet with plenty of fruit and vegetables. It encourages weight loss and exercise but does not specify low or very low-calorie diets to go into remission. It also recommends (1.3.6) individualising recommendations for carbohydrate and alcohol intake, and meal patterns.

New systematic review evidence indicates that benefits of LCDs are evident only in the short term and are not maintained beyond 6 months. In terms of calorie restriction, the DiRECT trial suggests that it is possible to achieve remission from type 2 diabetes through a low calorie diet, as evaluated over 2 years. It represents a promising relatively low resource intervention which is likely to be cost-saving in the long run if the results can be maintained.

The longer-term results of the DiRECT study beyond 2 years, and other longer-term LCD studies, are likely to be needed to establish any definite impact on the guideline.

A joint working group of The Scientific Advisory Committee on Nutrition, NHS England and Diabetes UK, with input from the British Dental Association and Royal Colleges, is reviewing the evidence on low carbohydrate diets with publication expected in 2020. This will be tracked by the surveillance team and the results will be considered when available.

The collective evidence and intelligence in this area will also be considered in the update of the NICE guideline on obesity (CG189) as the main study identified in this area (DiRECT) fed into the decision to update NICE guideline CG189.

Motivational interviewing

The new evidence on motivational interviewing for adults with T2D was inconclusive, with variation in trial design and the interventions themselves making it difficult to identify best practice strategies. There is unlikely to be any impact on the guideline, which does not include any recommendations on motivational interviewing.

> New evidence is unlikely to change guideline recommendations.

1.4 Blood pressure management

Surveillance proposal

No new information was identified at any surveillance review.

This section of the guideline should not be updated.

Editorial amendments

Anti-hypertensive drug treatment

NG28 recommends

- (1.4.8) The first-line anti-hypertensive drug treatment for a person of African or Caribbean family origin should be an ACE inhibitor plus either a diuretic or a generic calcium channel blocker

- (1.4.10) For a person with continuing intolerance to an ACE inhibitor (other than renal deterioration or hyperkalaemia), substitute an angiotensin II-receptor antagonist for the ACE inhibitor.

However NICE's guideline on hypertension in adults, published 2011, recommends (1.6.15) considering an angiotensin II-receptor blocker, in combination with a calcium channel blocker,

in preference to an ACE inhibitor in all African or Caribbean people because of the low risk of angioedema.

It is proposed that the NICE NG28 recommendations in question be reviewed by the committee and aligned appropriately with NICE's guideline on hypertension in adults. A cross referral from NICE NG28 section 1.4 to NICE CG127 section 1.6 should be considered following the update of NICE CG127.

1.5 Antiplatelet therapy

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

Aspirin

An NIHR commentary was identified on the ASCEND study, which examined the use of aspirin in people with diabetes without evidence of CVD. The type of diabetes was not reported in the abstract. The primary efficacy outcome of a first serious vascular event (myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial haemorrhage) was significantly lower in those receiving aspirin. However, this was offset by a significant increase in major bleeding events in the aspirin group. The NIHR commentary concluded that, on balance, aspirin should be reserved for secondary prevention of CVD in people with T2D.

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

The new evidence on the use of aspirin in people with T2D without CVD supports NICE NG28 recommendation 1.5.1 that aspirin should not be prescribed to people with diabetes who do not have existing CVD.

New evidence is unlikely to change guideline recommendations.

1.6 Blood glucose management

Surveillance proposal

This section of the guideline should be updated, specifically in the area of drug treatment for blood glucose management.

Editorial amendments

- Recommendations 1.6.24 and 1.6.26, 1.6.31 and 1.6.37: the following text will be added in the paragraph at the end to replace existing text cross referring to technology appraisals: "Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. Following the development of this guideline, new technology appraisals are available that are relevant to this section. Please see the Type 2 diabetes in adults' pathway for further information."

- An additional footnote will be added to the first sentence of the above paragraph as follows:

  Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2019) warned that Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) has been reported rarely in people taking an SGLT-2 inhibitor. The MHRA advised that if Fournier's gangrene is suspected, stop the SGLT2 inhibitor and urgently start treatment (including antibiotics and surgical debridement as required).

HbA1c measurement and targets

Intelligence gathering

A topic expert highlighted a follow up study of an RCT(22) (n=1655). The original RCT (n=1791) found that a median of 5.6 years of intensive as compared with standard glucose lowering in military veterans (average age 60 years) with type 2 diabetes resulted in a risk of major cardiovascular events that was significantly lower after a total of 10 years of combined intervention and observational follow-up. The follow up study found after 15 years of follow-up, the risks of major cardiovascular events or death were not lower in the intensive-therapy group than in the standard-therapy group. The risk of major CVD outcomes was reduced, however, during an extended interval of separation of the glycated hemoglobin curves, but this benefit did not continue after equalisation of the glycated haemoglobin levels.

Impact statement

NICE NG28 recommends that for adults with type 2 diabetes managed either by lifestyle and diet, or by lifestyle and diet combined with a single drug not associated with hypoglycaemia, the person should be supported to aim for an HbA1c level of 48 mmol/mol (6.5%). For adults

on a drug associated with hypoglycaemia, the person should be supported to aim for an HbA1c level of 53 mmol/mol (7.0%). It provides further advice to consider relaxing the target HbA1c level on a case-by-case basis, with particular consideration for people who are older or frail, for adults with T2D in specific circumstances (recommendation 1.6.9)

The new evidence, based on a 15 year follow up of an RCT in older people, reinforces the recommendations to individualise targets according to a person's needs, and to involve adults with type 2 diabetes in decisions about their individual HbA1c target. No impact on the guideline is anticipated.

Self-monitoring of blood glucose

We identified 12 studies covering self-monitoring of blood glucose (SMBG) (Table 4)

SMBG specific studies

An RCT(23) (n=120) found that SMBG was not effective in reducing HbA1c compared to no SMBG over 8 months.

An NIHR commentary on a systematic review observed that self-monitoring gave a small, short term reduction in HbA1c at 6 months. People who had poorer blood glucose control at the start saw a greater benefit. This is unlikely to be clinically meaningful because there was no difference between the self-monitoring and control groups by 12 months. Furthermore, the meta-analysis included studies with highly variable results, giving less confidence in the pooled estimate.

Continuous glucose monitoring

An RCT(24) (n=158) found that continuous glucose monitoring in T2D patients taking multiple daily insulin injections was more effective than usual care in reducing HbA1c over a 6 month period.

Flash glucose monitoring

An RCT(25) (n=224) assessed the impact of flash glucose-sensing technology (FreeStyle Libre™ Flash Glucose Monitoring System) as a replacement for SMBG over a 12-month period in people with T2D who were on intensive insulin therapy. Flash glucose-sensing system significantly reduced hypoglycaemia without resulting in any serious adverse events.

An RCT(26) (n=101) assessed flash glucose monitoring compared to usual care for people with T2D on multiple daily insulin injections for at least 1 year. Improvements were seen in HbA1C levels and patient satisfaction.

Remote monitoring

The findings from 8 RCTs identified on remote monitoring of SMBG for T2D, including the use of new technologies, indicated that:

● SMBG with enhanced patient feedback including automatic tailored messages did not confer any advantage over once daily SMBG or no SMBG for change in HbA1c or health related quality of life over 52 weeks(27) (n=450).

- Use of a wireless glucose meter (OneTouch Verio Flex glucose meter) alone or in combination with a diabetes app (OneTouch Reveal) resulted in significant improvements in HbA1c after 12 and 24 weeks(28) (n=137).

- Video conferences preceded by uploads of measurements as add-on to clinic-based care led to a significant reduction of HbA1c compared to that in standard care, but this effect was not maintained at 6 month follow-up(29) (n=165).

- A supported telemonitoring intervention, involving self-measurement and transmission of glucose data to a secure website for clinician review, was effective in reducing HbA1c and systolic and diastolic blood pressure at 9 month follow-up(30) (n=285).

- Remote lifestyle coaching plus a connected glucose meter with certified diabetes educator support improved HbA1c levels and weight loss compared with either no glucose meter or no lifestyle coaching over 12 weeks(31) (n=330).

- A telemedical lifestyle programme (TeLiPro) comprising coaching, medical-mental motivation, a formula diet, and SMBG improved HbA1c levels, 10 year CVD risk and quality of life when compared to standard care, with results maintained at 52 week follow-up(32) (n=202).

- Telemonitoring and health counselling did not improve HbA1c and quality of life relative to usual care only, over 19 months(33) (n=166).

- Structured SMBG improved HbA1c in T2D over 12 months. No additional benefit was observed with the addition of once-monthly TeleCare support(34) (n=446).

Intelligence gathering

Experts indicated that for blood glucose self-monitoring for T2D, the guidance remains valid. There remains considerable pressure for using new technology on the basis of personalising care using structured SMBG testing, but experts considered there too few trials, with either small or no effect sizes.

Flash glucose monitoring

In November 2018, NHS England announced that FreeStyle Libre (a Flash glucose monitoring system in the form of a wearable sensor) will be available on prescription for patients with type 1 diabetes who meet certain criteria, but not for T2D.

One of the trials(25) identified in this surveillance review has already been considered in the NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110). It is important to note that whilst NICE MIB110 emphasises the great potential of this innovative device, they also warn of the lack of available clinical data and economic analysis.

This was also noted by topic experts, who did not consider the studies currently available to be conclusive enough for use in assessing effectiveness of the technology.

In January 2019, the MHRA issued a medical device alert warning that some users of the FreeStyle Libre device were experiencing skin reactions to the adhesive provided. This led to

them applying barrier creams and sprays before attaching the sensor which may have affected the performance of the device. The manufacturer has confirmed that the formulation of the adhesive has been revised.

We identified 2 ongoing trials (ISRCTN87654534 and ISRCTN12543702) examining the performance of FreeStyle Libre in people with both type 1 and type 2 diabetes. These trials are being tracked and we will assess the impact of the results on the guideline when they are available.

Impact statement

Self-monitoring of blood glucose

NG28 recommends (1.6.5) that patients are involved in discussions around their individual HbA1c target, considering adverse effects such as hypoglycaemia. Self-monitoring of blood sugar is only recommended in specific circumstances and not routinely (1.6.13). It also recommends (1.6.32) continuing telephone support when starting insulin therapy but does not mention other forms of telemedicine.

The collective new evidence indicates that for people with T2D who are not using insulin, any benefit from self-monitoring is small and is unlikely to last beyond 6 months. This supports NG28 recommendation 1.6.13 that self-monitoring is not used routinely for people with type 2 diabetes unless there is a specific reason to do so. Doctors may consider offering self-monitoring of blood glucose in the short term for people starting treatment with steroids or to confirm suspected hypoglycaemia (recommendation 1.6.14).

Continuous glucose monitoring

The new RCT evidence supporting the use of CGM for T2D is limited by the 6-month duration and no impact on the guideline is anticipated until the findings are substantiated by further longer-term studies.

Remote monitoring and telemedicine

The current evidence on the effectiveness of remote monitoring using new technologies is conflicting and RCTs showing benefits for T2D are limited by varying durations and study sizes. While the new technologies have potential value in improving glucose control, there is a need to establish which telemedicine interface or format is best, and whether the interventions improve outcomes at a reasonable cost. Further evidence may therefore be needed to determine the best interface or format, before an impact on the guideline can be established.

Flash glucose monitoring

The NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110) emphasises that all evidence to date is limited to people with well-controlled diabetes and that the resource impact is unclear due to uncertainty around staff training and support requirements that may be needed. Long-term impact on patient outcomes is also uncertain, with the longest follow-up being 6 months. We are monitoring the progress of 2 ongoing trials in this area (ISRCTN87654534 and ISRCTN12543702) which may clarify the long-term

effectiveness of FreeStyle Libre in patients with T2D. We will review these results and assess impact on the guideline as soon as they are published.

New evidence is unlikely to change guideline recommendations.

Drug treatment

2019 surveillance summary

Class level comparisons

An NIHR commentary was identified covering systematic review evidence that compared 9 classes of blood glucose lowering drugs against each other, given alone or in combination to treat T2D, for risk of death from CVD and overall mortality. The commentary concluded that metformin remains the drug of first-choice when starting to treat T2D. Further recommended blood sugar lowering treatments can be tailored to the control of sugar levels and individual patients' priorities, such as avoiding weight gain or hypoglycaemia.

Initial therapy

We identified a total of 12 studies covering initial therapy for T2D in adults (table 5)

Initial therapy: Metformin

An RCT(35) (n=571) evaluated the glycaemic effects and safety of metformin delayed-release (DR) compared to metformin immediate release (IR) and placebo in adults with T2D and with either normal renal function or mild renal impairment (defined as eGFR ≥60 mL/min/1.73 m^2) who were not taking metformin for 2 or more months. Metformin DR 1200 and 1500 mg significantly reduced HbA1c and fasting plasma glucose compare to placebo. Metformin IR had a significantly greater reduction in HbA1c than metformin DR and placebo, but with a 3-fold greater plasma metformin exposure.

Initial therapy: SGLT-2 inhibitors

We identified a systematic review(36) and a health technology assessment(37) covering canagliflozin, dapagliflozin and empagliflozin monotherapies. However, these interventions are covered as monotherapies by the technology appraisal (TA guideline):

TA390 Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (May 2016)

This information will be passed onto the NICE TA team for consideration in reviewing this guidance.

We identified 7 RCTs covering ertugliflozin (38–44). However, this intervention is covered by the NICE TAs:

TA572 Ertugliflozin as monotherapy or with metformin for treating type 2 diabetes for treating type 2 diabetes

This information will be passed onto the NICE TA team for consideration in reviewing this guidance.

Initial therapy: DPP-4 inhibitors

RCT results showed that:

- Evogliptin monotherapy was superior to placebo in reducing HbA1c in T2D(45) (n=160).

- Initial combination therapy with gemigliptin and metformin was superior to monotherapy with either drug in reducing HbA1c, without severe side effects(46) (n=433).

- Initial combination therapy with linagliptin and metformin was superior to linagliptin monotherapy in reducing HbA1c(47) (n=316).

Initial therapy: Sulfonylureas

An NIHR commentary covered systematic review evidence of the safety of sulfonylureas for mortality and CV outcomes in adults with T2D. This review found that sulfonylurea drugs were not associated with an increased risk of death, heart attack or stroke when compared with placebo, diet control or other diabetes drugs. The commentary concluded that clinically, the benefits and low costs of sulfonylureas in treating T2D need to be weighed against their potential risks of hypoglycaemia or weight gain. The evidence needs to be considered alongside the benefits and safety of newer drugs now available for treatment.

First intensification

We identified a total of 56 studies covering first intensification of drug treatment for T2D in adults (table 6)

First intensification: Class level comparisons

A systematic review and network meta-analysis(48) (NMA) (9 studies, n=87,162) compared the CV outcomes of new classes of antidiabetic medications (DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors) in patients with T2DM. The primary outcomes were:

- the composite endpoint of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke

- death from CV causes

- nonfatal MI

- nonfatal stroke

- death from any cause.

Hospitalisation for heart failure and unstable angina were evaluated as secondary outcomes. The NMA results showed no significant differences among the individual DPP-4 inhibitors in any of the CV outcomes. Similarly, no significant changes were observed among the GLP-1 receptor agonists nor the SGLT-2 inhibitors. DPP-4 inhibitors had a CV safety profile non-inferior to, but not superior to, placebo. GLP-1 agonists showed significant reduction in the composite CV outcome, and death from CV or any cause, compared to placebo. SGLT-2

inhibitors showed a significant reduction in hospitalisation for heart failure events compared to placebo.

A systematic review(49) (3 studies, n=34,322) examined the effectiveness of SGLT-2 inhibitors, compared to placebo, on primary and secondary prevention of CV and renal outcomes in T2D. SGLT2 inhibitors reduced major adverse CV events with benefit only seen in patients with atherosclerotic CVD and not in those without. SGLT2 inhibitors reduced the risk of CV death or hospitalisation for heart failure, with a similar benefit in patients with and without atherosclerotic CVD, and with and without a history of heart failure. SGLT2 inhibitors reduced the risk of progression of renal disease in all patients, but with a lesser effect for those with more severe kidney disease at baseline.

A Cochrane review (50) (44 studies, n=13,036) examined the efficacy and safety of insulin and other pharmacological interventions for lowering glucose levels in people with diabetes and chronic kidney disease (CKD). Studies were identified examining SGLT2 inhibitors, DPP-4 inhibitors, GLP-1 agonists and glitazones. Results indicated that compared to placebo, SGLT-2 inhibitors may significantly reduce HbA1c, fasting blood glucose, systolic blood pressure, systolic blood pressure, and weight. However, there was no significant effect on risk of CV death, hypoglycaemia and acute kidney injury. Compared to placebo, DPP-4 inhibitors may significantly reduce HbA1c but there was little or no effect on fasting blood glucose, risk of CV death and weight. Compared to placebo, GLP-1 agonists may significantly reduce HbA1c. The evidence on glitazones was uncertain. Additionally, SGLT2 inhibitors were found to increase genital infections, and slightly increase creatinine. The safety profile for GLP-1 agonists was found to be uncertain.

First intensification: SGLT-2 inhibitors

We identified 19 studies covering individual SGLT-2 inhibitors canagliflozin(51–57), dapagliflozin(58–66) and empagliflozin(67–69) and one cost effectiveness study of different drugs in this class(70). However, these interventions are covered by the published technology appraisals:

TA315 Canagliflozin in combination therapy for treating type 2 diabetes (June 2014)

TA336 Empagliflozin in combination therapy for treating type 2 diabetes (March 2015)

TA288 Dapagliflozin in combination therapy for treating type 2 diabetes (June 2013)

TA418 Dapagliflozin in triple therapy for treating type 2 diabetes (November 2016)

This information has been passed onto the NICE TA team for consideration in the current and future review proposal processes for these topics.

We identified 2 RCTs covering ertugliflozin in a triple therapy regimen with other drug treatments(40,43). However, this intervention is covered by the published technology appraisal TA583 Ertugliflozin with metformin and a dipeptidyl peptidase-4 inhibitor for treating type 2 diabetes (June 2019)

This information will be passed onto the NICE TA team for consideration.

An RCT (71) (n=165) found that Ipragliflozin added to metformin significantly reduced HbA1c and body weight after 12 weeks and showed a safety profile comparable to placebo.

First intensification: GLP-1 analogues

Semaglutide

The findings from 12 RCTs identified on semaglutide indicated that:

- Once weekly 1.0 mg semaglutide improved HbA1c levels and body weight compared to exenatide extended release 2.0 mg over 56 weeks(72) (n=813).

- Subcutaneous once weekly 0.5 mg or 1.0 mg semaglutide improved HbA1c levels and body weight compared to daily oral sitagliptin over 56 weeks(73) (n=1225).

- Once weekly semaglutide 0.5 mg or 1.0 mg improved HbA1c levels and reduced body weight and hypoglycaemic episodes compared to daily titrated insulin glargine over a 30 week period(74) (n=1089).

- Daily oral semaglutide (ranging from 2.5 mg to 40 mg) or weekly subcutaneous semaglutide 1.0 mg improved HbA1c levels when compared to placebo respectively over 26 weeks(75) (n=632).

- Daily semaglutide (range 0.05 mg to 0.3 mg) improved HbA1c levels when compared to daily liraglutide (range 0.3 mg to 1.8 mg) or a placebo over 26 weeks(76) (n=705).

- Changes in HbA1c level and body weight improved with semaglutide 0.5 mg and 1.0 mg once weekly compared to dulaglutide 0.75 mg and 1.5 mg once weekly, respectively, over 40 weeks(77) (n=1201).

- Weekly subcutaneous semaglutide 0.5 mg or 1.0 mg in addition to basal insulin improved HbA1c levels and body weight compared to a placebo but did not improve hypoglycaemia over 30 weeks(78) (397).

- Compared to sitagliptin 100 mg, daily oral semaglutide 3 mg had no effect on HbA1c levels, but oral semaglutide 7 mg and 14 mg improved HbA1c levels and body weight over 26 weeks(79) (1864).

- Weekly subcutaneous semaglutide 0.5 mg or 1.0 mg improved HbA1c levels and body weight when compared to a placebo over 30 weeks(80) (n=387).

- Subcutaneous semaglutide 1.0 mg improved HbA1c levels and body weight compared to a volume matched placebo over 30 weeks(81) (n=301).

- Once-weekly semaglutide 0.5 mg or 1.0 mg was non-inferior to placebo over 104 weeks in patients with T2D who were at high CV risk, for the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke(82) (n=3297).

A cost-effectiveness study found improvements in QALY and lifetime savings cost with both 0.5 mg and 1.0 mg weekly subcutaneous semaglutide when compared to weekly dulaglutide 1.5 mg over 40 weeks(83) (n=not stated).

Albiglutide

The Harmony Outcomes RCT(84) (n=9463) assessed the safety and efficacy of albiglutide in preventing death from CVD, MI, or stroke. It found that albiglutide was superior to placebo with respect to major adverse CVD events in patients with T2D and established CVD, with no significant differences in other serious adverse effects. Established CVD was defined as MI, at least 50% stenosis in 1 or more coronary arteries, previous coronary revascularisation, ischemic stroke, at least 50% carotid artery stenosis, a previous carotid vascular procedure, intermittent claudication and an ankle to brachial index below 0.9, non-traumatic amputation, or a previous peripheral vascular procedure. However, albiglutide was withdrawn from the market for commercial reasons and is no longer available in the UK.

Dulaglutide

The findings from 6 RCTs identified on dulaglutide indicated that:

- HbA1c levels were improved with dulaglutide 0.75 mg and 1.5 mg compared to insulin glargine over 26 weeks(85) (n=591).

- Weekly dulaglutide 0.75 mg or 1.5 mg, both with an SGLT2 inhibitor improved HbA1c levels but not adverse events compared to a placebo plus SGLT2 inhibitor over 24 weeks(86) (n=424).

- Weekly dulaglutide 0.75 mg or 1.5 mg improved HbA1c levels and body weight when compared to 100 mg sitagliptin for 52 weeks(87) (n=1098) and 104 weeks(88) (n=657).

- Subcutaneous weekly dulaglutide 1.5 mg with titrated daily glargine improved HbA1c levels, body weight and the need for increases in mean glargine dose when compared to a placebo with titrated daily glargine over 28 weeks(89) (n=300).

- Weekly dulaglutide 0.75 mg (n=384) or 1.5 mg (n=387), both in addition to insulin lispro, improved eGFR rates at 52 weeks and displayed non-inferiority for HbA1c levels at 26 weeks in people with T2D and CKD compared to insulin glargine and insulin lispro. No effect was seen for urine albumin–to–creatinine ratio reduction or adverse events at 52 weeks(90).

Exenatide

We identified 5 studies covering exenatide for T2D. The findings indicated that:

- Exenatide once-weekly autoinjection was associated with a significantly greater reduction in HbA1c, similar weight loss and a favourable gastrointestinal adverse effect (AE) profile compared with exenatide twice daily, sitagliptin once daily or oral placebo(91,92) (n=375, n=365).

- Exenetide once-weekly extended release injection was non-inferior to placebo but not superior with regard to CV safety(93) (n=14,752).

- Exenatide 2 mg once-weekly was cost-effective over a lifetime horizon compared to once daily liraglutide 1.2 mg, liraglutide 1.8 mg, and lixisenatide 20 mg(94).

- Exenetide was non-inferior to insulin and superior to pioglitazone in lowering HbA1c in the early stage of T2D(95) (n=416).

Liraglutide

We identified 3 studies covering liraglutide for T2D (see also insulin-based treatment for insulin combinations)(96–98). The findings indicated that for T2D:

- Liraglutide was cost-effective compared to exenatide and lixisenatide, based on improved quality-adjusted life expectancy, and reduced cost. Cost savings were gained from the avoidance of complications to offset increased acquisition costs(96).

- Liraglutide resulted in lower rates of the development and progression of diabetic kidney disease than placebo, over a median follow-up of 3.84 years(97) (n=9,340).

- Insulin glargine and liraglutide both reduced HbA1c to target levels of 7% but glargine had significantly greater reductions in HbA1c and fasting plasma glucose. Glargine was significantly worse for weight change over 24 weeks(98) (n=489).

First intensification: DPP-4 inhibitors

Sitagliptin

We identified 11 studies covering sitagliptin for T2D in adults. The findings indicated that:

- For reduction in HbA1c sitagliptin was superior to:

  - placebo when added to either metformin, metformin plus sulfonylurea, or acarbose monotherapy(99,100) (n=427, n=381).

  - glimepiride when added to metformin, with additional improvements in hypoglycaemia(101) (n=292).

  - placebo during up-titration of metformin from 1000 mg/day to 2000 mg/day with similar safety and tolerability(102) (n=458).

- For reduction in HbA1c sitagliptin was non-inferior to:

  - glimepiride in all adults and specifically elderly patients, with a significantly lower risk of hypoglycaemia and lower increase in body weight and lower fasting plasma glucose (101,103) (n=388, n= 292).

  - pioglitazone in lowering HbA1c and superior in change in body weight when added to metformin over 12 weeks (104) (n=160).

- Over a 3 year follow-up in the TECOS study (n=14,671), sitagliptin was non-inferior to placebo for the risk of:

  - acute pancreatitis and pancreatic cancer(105)

  - fractures(106)

  - the composite of CV death, nonfatal myocardial infarction, nonfatal stroke(107)

- hospitalisation for heart failure or unstable angina(107).

- Sitagliptin was not superior to either evogliptin or anagliptin for glycaemic control, when added to metformin, with comparable adverse events (108,109) (n=222, n=180).

Saxagliptin

We identified 6 studies covering saxagliptin for T2D. The findings indicated that:

- saxagliptin was non-inferior to

    - glimepiride for reduction in HbA1c, change in body weight and hypoglycaemia in all adults (110) (n=388)

    - glimepiride for reducing HbA1c specifically in elderly and very elderly patients (111) (n=720).

    - placebo or acarbose for reduction in HbA1c across all age groups(112,113) (n=462, n=288)

    - placebo for composite of CV mortality, myocardial infarction, or ischemic stroke in older patients (114) (n=16,492).

- Across all age groups, saxagliptin treatment was associated with an increased risk or hospitalisation for heart failure (115) (n=16,492).

Other DPP-4 inhibitors

We found 8 Studies covering other DPP-4 inhibitors for T2D, the results of which indicated that:

- Linagliptin:

    - for T2D and early stages of diabetic kidney disease, improved HbA1c but did not lower albuminuria (116) (n=360). This study covered both first and second intensification, since patients were treatment-naive or receiving 2 or less oral glucose-lowering drugs (metformin, sulfonylureas, meglitinides or alpha-glucosidase inhibitors) or insulin.

    - with low dose metformin combination was non-inferior to high dose metformin for reducing HbA1c (117) (n=689)

    - among adults with type 2 diabetes and high CV and renal risk, linagliptin added to usual care compared with placebo added to usual care resulted in a non-inferior risk of a composite CV outcome, with similar renal outcomes (118) (n=6,979).

- Alogliptin:

    - was cost-effective as add-on therapy to metformin compared to sufonylurea, in terms of improved long-term patient outcomes, QALY gains, and ICERs (119) (n=2,639)

    - improved the mean change in carotid intima-media thickness (IMT) among patients without apparent CVD, in comparison with conventional treatment (120) (n=341)

- was non-inferior to placebo for CV mortality over a median follow-up of 18 months (121) (n=5,380).

- Vildagliptin as an add-on therapy to sulfonylurea:

  - significantly reduced HbA1c and fasting plasma glucose when combined with metformin, compared to metformin plus dose increasing sulfonylurea (122) (n=344)

  - was comparable to Neutral Protamine Hagedorn (NPH) insulin in achieving a composite endpoint of achieving HbA1c <7.0%, without any hypoglycaemic episodes or weight gain of 3% or more (123) (n=162).

Second intensification

We identified 18 studies on second intensification (table 7)

Second intensification: SGLT-2 inhibitors

A cost effectiveness study (124) found that an intensification strategy of SGLT-2 inhibitors compared with immediate NPH insulin intensification in patients with T2D who were not at goal on metformin and sitagliptin was cost-neutral (no interpretable incremental cost effectiveness ratio) or cost-effective, based on different scenario analyses. Additional drug costs were offset by diabetes-related complication decreases, leading to slightly lower direct medical costs.

Second intensification: GLP-1 analogues

We found 11 studies covering second intensification with GLP-1 analogues, the majority of which comprised insulin and oral diabetic drug combinations. The findings indicated that:

- Exenetide plus insulin glargine and metformin:

  - when compared to placebo, improved HbA1c, body weight and postprandial glucose, with similar rates of hypoglycaemia (125) (n=464).

  - when compared to insulin lispro plus insulin glargine and metformin, was non-inferior in improving HbA1c (126) (n=627).

- Lixisenatide in a titratable fixed-ratio combination with insulin glargine (100 units) was superior to its individual components alone for reducing HbA1c and change in body weight with similar rates of hypoglycaemia (127–129) (n=736, n=1,170, n=323).

- Liraglutide in combination with basal insulin, including degludec:

  - as a once daily injection with degludec was non-inferior to insulin degludec alone, and superior to liraglutide alone or insulin glargine alone in reducing HbA1c(130–133) (n=1663, n=557, n= 346, n=210). It also improved body weight, severe hypoglycaemia and total daily insulin dose required compared to insulin glargine alone(133).

  - improved glycaemic control, compared to placebo, reduced body weight, blood pressure and enabled patients to lower their insulin doses (134,135) (n=451, n=124).

This was also observed as add-on treatment to sulfonylurea with or without metformin (136) (n=435).

- – as a once-weekly dose based on 2 plasma glucose (PG) readings was non-inferior to a twice weekly dose titration based on 3 PG readings, in terms of HbA1c reduction (137) (n=420).

- – caused more incidences of hypoglycaemia, particularly when added to sulfonylurea treatment (n=435, n=451).

Second intensification: DPP-4 inhibitors

We identified 4 studies covering second intensification with DPP-4 inhibitors, all covering sitagliptin in combination with insulin. The results indicated that:

- In combination with sitagliptin, twice daily biphasic insulin aspart 30 had superior glycaemic control over a once daily dose, but the once daily dose had a lower rate of hypoglycaemia and resulted in lower weight gain (138) (n=582).

- When initiating insulin glargine therapy, continuation of sitagliptin, compared with discontinuation, resulted in a significantly greater reduction in HbA1c without an increase in hypoglycaemia, and reduced the insulin dose requirement (139,140) (n=743, n=660).

- When added to metformin and sulfonylurea, alogliptin significantly reduced HbA1c, hypoglycaemia, CV death and all-cause mortality compared to placebo. The risk of CV death was higher in patients with a recent acute coronary syndrome, but remained similar between alogliptin and placebo(141) (n=1,398).

Insulin based treatments

We identified 26 studies (table 8) covering different types and dosages of insulin. These included 3 Cochrane reviews and 23 RCTs.

Short acting insulin analogues

A Cochrane review (142) (10 studies, n=2,751) assessed the effects of short acting insulin analogues compared to regular human insulin in adult, non-pregnant people with T2D. Overall, the incidence of severe hypoglycaemic events was low, and none of the trials showed a clear difference between the two intervention arms. The review found no clear benefits of short acting insulin analogues over regular human insulin.

An RCT (143) (n=412) found that metformin in combination with insulin analogues did not reduce carotid IMT despite a significant reduction in HbA1c, less weight gain, and smaller insulin dose compared with placebo plus insulin.

Insulin aspart

A further 6 RCTs compared the short acting analogue insulin aspart with other forms of insulin, and in combination with them. The results indicated that:

- Fast-acting insulin aspart was non-inferior to conventional insulin aspart for change in HbA1c and overall rates of hypoglycaemia, although worse for post meal hypoglycaemia (144) (n=689).

- When added to basal insulin, fast-acting insulin aspart improved glycaemic control but was worse for hypoglycaemia and change in body weight (145) (n=236).

- Stepwise intensification with biphasic insulin aspart from 1 to 3 times daily:

  - was superior to basal-bolus treatment for change in HbA1c and nocturnal severe or blood glucose confirmed hypoglycaemia (146) (n=335).

  - was superior to insulin aspart 3 times daily in combination with insulin detemir once daily, and insulin detemir alone once daily, but no different for change in carotid IMT and worse for weight gain (146,147) (n=335, n=412).

- Twice daily insulin degludec combined with insulin aspart was non-inferior to biphasic insulin aspart 30 for change in HbAlc and superior for reductions in fasting plasma glucose and incidence of overall and nocturnal confirmed hypoglycaemia (148) (n=394).

- A basal plus regimen of insulin glargine and glulisine was non-inferior to biphasic insulin aspart for change in HbA1c with a similar overall rate, but higher nocturnal rate, of hypoglycaemia (149) (n=335).

Long acting insulin analogues

A study based on the SWITCH 1 and 2 trials (150) assessed the cost effectiveness of degludec compared to glargine U100. Cost effectiveness was analysed over a 1-year time horizon based on the different rates of hypoglycaemia and actual doses of insulin used, rather than glycaemic control due to the treat-to-target trial design. It was estimated that quality of life was improved (0.0065 QALYs gain) with degludec compared with glargine U100 at an increased annual cost of £117 (incremental cost effectiveness ratio, £17,939), indicating that degludec would be cost effective relative to glargine U100.

A further analysis of the SWITCH 2 trial(151) (n=720) found insulin degludec improved hypoglycaemia over a 9 month period compared to insulin glargine, with no significant difference in HbA1c level.

A further 5 studies on degludec indicated that:

- Degludec was non-inferior to glargine for change in HbA1c and major CV events and superior for hypoglycaemia(152–154) (n=7,637, n=833, n=721).

- Insulin glargine 300 Units/mL was non-inferior to insulin degludec 100 Units/mL for change in HbA1c. Hypoglycaemia incidence and rates were comparable with both insulins during the full 24 week study period (155) (n=929).

- Insulin degludec and insulin aspart administered either as a twice daily co-formulation or as a basal-bolus regimen in multiple separate injections were both effective in improving HbA1c. The co-formulation resulted in a significantly lower total daily insulin dose, a

smaller change in body weight, and similar rates of confirmed hypoglycaemia (156) (n=274).

Glargine dosage

The EDITION 1, 2 and 3 studies compared glargine 300 U/ml (Gla-300) versus glargine 100 U/ml (Gla-100) in patients using basal plus meal-time insulin for 12 months. In EDITION 1 (157) (n=807) the higher dose was superior in terms of HbA1c levels and the rate of daytime or nocturnal confirmed severe hypoglycaemia. However, overall hypoglycaemia was similar.

In the EDITION 2 trial (158) (n=629), Gla-300 and Gla-100 were similar in terms of HbA1c levels for people with T2D using basal insulin and oral antihyperglycaemic drugs, but Gla-300 was superior for weight change and nocturnal or severe hypoglycaemia.

In the EDITION 3 trial (159) (n=878) Gla-300 was as effective as Gla-100 in reducing HbA1c in insulin-naïve people with T2D, but with a lower overall risk of hypoglycaemia.

The SENIOR study (160) (n=1,014) found that Gla-300 was as effective as Gla-100 in older people (65 years or older) in terms of HbA1c reduction and risk of hypoglycaemia, with a lower risk of hypoglycaemia in people over 75 years.

Biosimilars

The SORELLA 2 RCT (161) (n=505) found that the in-development biosimilar SAR342434 was non-inferior to Gla-100 in reducing HbA1c, with no differences in adverse events.

The INSTRIDE RCT (162) (n=560) found that MYL-1501D insulin biosimilar plus oral antidiabetic drugs (OAD) was non-inferior to insulin glargine plus OADs, with similar rates of hypoglycaemia.

NICE Evidence summary 64 on insulin glargine biosimilar Abasaglar has been published. This includes a review of the ELEMENT 2 trial (163) in people with T2D (n=756), where once-daily Abasaglar was non-inferior to once-daily insulin glargine Lantus (primary end point) in reducing HbA1c, demonstrating equivalent efficacy of both medicines. The safety profile of Abasaglar is comparable to that of Lantus.

Insulin analogues compared to human insulin

An RCT (164) (n=701) found that insulin glargine was not superior to NPH insulin in improving HbA1c, or in limiting nocturnal hypoglycaemia using a using a protocol designed to limit pre-breakfast and nocturnal hypoglycaemia.

Insulin strategies for hospitalised patients

A Cochrane review (165) (8 studies, n=1048) examined the effects of sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus. The main comparison was between sliding scale insulin and basal-bolus insulin therapy. Results indicated that basal-bolus insulin therapy may be associated with an increased risk of severe hypoglycaemic episodes (defined as blood glucose levels below 40 mg/dL). Sliding scale insulin was associated with higher blood glucose levels compared to basal-bolus insulin therapy. There were no significant differences in mean length of hospital stay and post-operative infections. The review was

inconclusive as to which insulin strategy (Sliding scale or basal-bolus insulin) is best. A basal-bolus insulin strategy in these patients might result in better short-term glycaemic control but could increase the risk for severe hypoglycaemic episodes.

Insulin monotherapy compared with the addition of OADs

A Cochrane review (166) (37 studies, n=3227) assessed the effects of insulin monotherapy compared with the addition of oral glucose-lowering agents (sulfonylureas, pioglitazone, alpha-glucosidase inhibitors, DPP-4 inhibitors, and metformin plus glimepiride) to insulin monotherapy for people with T2D already on insulin therapy and inadequate glycaemic control. The review found that the addition of all oral glucose-lowering agents in people with T2D and inadequate glycaemic control who are on insulin therapy had positive effects on glycaemic control and insulin requirements. The addition of sulfonylureas resulted in more hypoglycaemic events. Additional weight gain was only avoided by adding metformin to insulin.

Intelligence gathering

Drug treatment

SGLT-2 inhibitors and GLP-1 analogues

Topic experts indicated that the management of T2D has changed considerably since publication of the guideline, and it now needs to be updated as a priority with new CV and renal evidence for the SGLT-2 inhibitor and GLP-1 analogue classes of drugs. The lack of explicit consideration of CVD outcomes within the guideline is considered by experts to be a weakness. Practice is considered to be moving away from using DPP4 inhibitors as the first intensification option and the evidence is pointing towards SGLT2 inhibitors and GLP1 receptor agonists. Relevant CV outcome trials were highlighted including LEADER (liraglutide), DECLARE (dapagliflozin), EMPA-REG (empagliflozin), and CANVAS (Canagliflozin). It should be noted that several drugs in these classes, with the exception of liraglutide for CVD prevention, are covered by NICE TAs that are either undergoing review, have recently been reviewed, or are in development. The timeframe for topics under review is being synchronised with the surveillance review of NICE NG28 to align publication. Relevant evidence identified in the surveillance review has been passed to the NICE TA team for consideration in these topics.

In addition experts noted that the joint ADA and EASD guideline Management of Hyperglycemia in Type 2 Diabetes (2018) has moved to a risk stratification model of treating T2D taking into account CV risk. This is considered to promote a much more patient-centred approach to drug therapy. The ADA/EASD guideline was also stated to include more expensive treatment combinations which are not recommended by NICE. These include metformin in combination with SGLT2 inhibitors and DPP4i drugs and metformin in combination with SGLT-2 inhibitors and GLP-1 analogues.

Furthermore, experts considered there to be a barrier to using the newer medications earlier in the treatment pathway because these are not currently recommended by NICE.

In July 2017, NICE reviewed the evidence on the effectiveness and impact of drugs used to manage diabetes in people with a high risk of CVD. NICE found that there was insufficient evidence to make further recommendations, as trials had only reported on some of the drugs in the SGLT-2 and GLP-1 classes, with trials of others still ongoing. The recommendations remained unchanged.

However, text on SGLT-2 inhibitors was added to the section on initial drug treatment. The algorithm for blood glucose lowering therapy in adults with type 2 diabetes was also updated with links to relevant NICE guidance on SGLT-2 inhibitors, and new information on SGLT-2 inhibitors was also added to the box on action to take if metformin is contraindicated or not tolerated.

A new MHRA safety warning for SGLT-2 inhibitors was issued in 2019, covering reports of Fournier's gangrene.

Newer insulins

Newer insulins were also highlighted for consideration by experts, including the long acting insulin analogues Toujeo (glargine) and Tresiba (degludec). A related NICE Evidence summary has been published on Toujeo: Type 2 diabetes mellitus in adults: high-strength insulin glargine 300 units/ml (Toujeo) (December 2015) ESNM65.

Ongoing studies

The Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial was highlighted by topic experts, which aims to assess whether dulaglutide can reduce major cardiovascular events and other serious outcomes in people with type 2 diabetes, when added to their anti-hyperglycemic regimen. The preliminary results of this study have been announced through a press release, with full results expected to be presented in June 2019. The preliminary results suggest that, compared with placebo, dulaglutide reduced major adverse CV events in adults with T2D both with (31%) and without (69%) established CVD, over a median follow-up period of more than 5 years.

Costs and health economics

Experts indicated that the price of degludec has been reduced. Expert also noted that insulin glargine biosimilars are available, following expiry of the patent for insulin glargine. Further biosimilars are also in development.

Impact statement

Initial treatment

The guideline recommends metformin as the most cost-effective initial therapy for almost all patients with T2D. No new evidence was identified to signal the need to change to this advice. The evidence indicating that, for adults with T2D and advanced renal disease, metformin immediate-release had a significantly greater reduction in HbA1c than metformin delayed-release and placebo also indicated a 3-fold greater plasma metformin exposure. No evidence of safety for this form of metformin was identified through the surveillance review.

However, this section of the guideline should be updated to consider cardiovascular outcomes for initial therapy as part of the proposed broader review of the antidiabetic drug pathway.

New evidence identified that may change current recommendations.

First intensification

Clinical characteristics

Evidence indicates that important clinical characteristics need to inform the choice of first intensification medication, after failure to control blood glucose with metformin and lifestyle interventions. These include:

- The presence of established atherosclerotic CVD, for which there is now evidence to support the use of SGLT2 inhibitors and GLP1 agonist classes. However, some studies of individual drugs within these classes have demonstrated superiority over placebo (Harmony Outcomes [albiglutide], LEADER [liraglutide]) whereas others do not (ELIXA [lixisenatide] and EXSCEL [exenatide]) suggesting that this may not be a class effect. The risk-benefit profile of individual medicines should therefore be considered, including CV outcomes and risk of hypoglycaemia and weight gain.

- Other comorbidities, such as heart failure or CKD.

- Age and frailty level.

- Safety and tolerability.

Patient adherence

Patient adherence is also an important consideration; In the 2017 NICE review of newer agents, the committee noted that in current clinical practice, there is a patient-focused and individualised approach to the choice of single, or combination of, antidiabetic drugs. This is also reflected by the updated international ADA and EASD guideline. According to experts, patients take into account frequency of monitoring and how the drug is administered (injectable or oral) when considering adherence.

Cost effectiveness

At the time of the 2017 review, the committee noted that there were no cost effectiveness studies on SGLT-2 inhibitors or GLP-1 analogues based directly on CV outcomes reported in randomised trials. In the absence of robust cost effectiveness evidence, the committee agreed it would not be appropriate to make specific recommendations about the place of SGLT-2 inhibitors and GLP-1 mimetics in the diabetes management pathway, as to do so would involve a comparison to all the other available antidiabetic drug options, something that was not possible to do based on CV outcomes.

The committee therefore agreed it was appropriate that a larger scale update of the antidiabetic drug pathway in NICE NG28 be undertaken, and that this should be timed to also

take in to account the evidence from several large trials, which were ongoing at the time, so all the relevant drugs from these classes can be considered:

These key CV outcome trials have now published, including:

- DECLARE-TIMI 58 (dapagliflozin)

- HARMONY Outcomes (albiglutide)

- EXSCEL (exenatide)

- REWIND (dulaglutide – preliminary results).

Additional ongoing CV trials are due to publish soon, including VERTIS CV Study and PIONEER 6.

It is therefore proposed that a review be undertaken, of the antidiabetic drug pathway in NICE NG28. This should include:

- Clinical characteristics detailed above and the potential need to adopt a risk stratification approach to sequencing of treatment.

- Consideration of the concurrent review of related TAs and development of new TAs for SGLT-2 inhibitors. These will consider new evidence for canagliflozin, dapagliflozin, empagliflozin and ertugliflozin in the SGLT-2 class. Both dual and triple (second intensification) therapy are covered within the scope of these TAs.

- Consideration of DPP4 inhibitors for patients with renal impairment. This should take account of dose adjustment according to level of renal function. The forthcoming results of the CAROLINA trial should be considered in the review.

- The distinction between individual and fixed combinations of GLP-1 analogues and basal insulin.

- Timing of treatment intensification, to provide further information on the time a patient should spend at uncontrolled hyperglycaemia before treatment intensification.

- The need to consider individual drugs within classes as well as class level comparisons in terms of CV outcomes, safety and tolerability.

- A review of the body mass index threshold of 35 kg/m^2 prior to being able to receive a GLP-1 analogue.

- Safety and tolerability, taking into account the latest MHRA safety warning for SGLT-2 inhibitors.

- Patient adherence, taking into account frequency of monitoring and route of administration.

- Acquisition costs of individual drugs and cost effectiveness of drug combinations from different classes. The 2017 review committee noted that SGLT2 inhibitors had the same price per dose in 2017. No cost studies were identified on this class, but new evidence for

GLP-1 analogues is conflicting on the comparative cost effectiveness of liraglutide and exenatide. A review of the health economic model is proposed.

New evidence identified that may change current recommendations.

Second intensification

The guideline recommends that if dual therapy with metformin and another oral drug has not controlled HbA1c to below the person's individually agreed threshold for intensification, then triple therapy should be considered comprising metformin, a sulfonylurea and either a DPP-4 inhibitor or pioglitazone. Alternatively, insulin based treatments can be considered.

If this is not effective, not tolerated or contraindicated, a GLP-1 mimetic can be considered in combination with metformin and a sulfonylurea.

Insulin based treatments are advised if metformin is contraindicated or not tolerated, and if dual therapy with 2 oral drugs has not continued to control HbA1c to below the person's individually agreed threshold for intensification.

The guideline refers to DPP-4 inhibitors, GLP-1 mimetics and sulfonylureas at a class level in the recommendations, and to SGLT-2 inhibitors in additional text added since publication.

However, CV outcomes were not considered in the guideline and therefore the same rationale for a comprehensive review of the antidiabetic drug pathway applies to second intensification as for first intensification (as detailed above). The review of second intensification should also consider:

- The evidence indicating that SGLT-2 inhibitors as a class are cost-neutral or cost effective, with additional drug costs offset by diabetes-related complication decreases, leading to slightly lower direct medical costs. The weight loss benefits are an important consideration for patients for whom this is a priority outcome.

- Evidence supporting the use of GLP1 analogues for T2D prior to and in combination with insulin, particularly for improving glucose control, CV outcomes and weight loss.

New evidence identified that may change current recommendations.

Insulin based treatments

The guideline recommends that when insulin therapy is necessary, it should be started from a choice of a number of insulin types and regimens. NPH insulin injected once or twice daily according to need is the preferred option. Insulin detemir or insulin glargine can be considered as an alternative in certain circumstances (see recommendations 1.6.34 and 1.6.35 for details). There are several insulin glargine products available including Lantus, the biosimilar Abasaglar or high-strength Toujeo.

New evidence was identified showing that the biosimilar Abasaglar, and the in-development biosimilars SAR342434 and MYL-1501D, are non-inferior to glargine in reducing HbA1c, with similar safety profiles.

The price reduction of Tresiba (degludec) and evidence indicating its cost effectiveness, in addition to the emergence of cheaper biosimilars, following expiry of the patent for insulin glargine, have implications for the health economics of insulin-based treatments. Further biosimilars are also in development. The choice between these longer-acting basal insulins may be determined by factors such as access and cost, alongside clinical considerations, particularly the risk of hypoglycaemia.

There is a potential impact on the guideline to review the increasing range of biosimilar and analogue insulins now available. The acquisition costs, safety profiles and dosage conversions will need to be considered.

New evidence identified that may change current recommendations.

Insulin monotherapy compared with the addition of oral antidiabetic drugs

The new systematic review evidence supports the addition of several classes of oral glucose-lowering agents to insulin in T2D patients requiring insulin therapy, but that additional weight gain is only avoided by adding metformin. This is largely consistent with recommendation 1.6.33, which advises continuing to offer metformin with insulin therapy in adults with T2D, and to review the continuing need for other blood glucose lowering therapies.

The supplementary text stating that treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with T2D remains valid but should be reviewed as part of the proposed broader review of the antidiabetic drug pathway to clarify the sequencing of particular drug classes, and individual drugs.

New evidence identified that may change current recommendations.

Insulin strategies for hospitalised patients

NG28 does not make specific recommendations on hospitalised patients with T2D. The new systematic review evidence was inconclusive as to which insulin strategy (Sliding scale or basal-bolus insulin) is best for these patients. There is unlikely to be an impact on NG28 until further and more conclusive evidence is available.

New evidence is unlikely to change guideline recommendations.

1.7 Managing complications

Surveillance proposal

This section of the guideline should be updated.

Editorial amendments

Recommendation 1.7.25 is proposed for withdrawal, but a cross referral should be considered in its place by the update committee to the NHS Diabetic Eye screening programme.

2019 surveillance summary

We identified 8 Studies on managing complications (Table 9).

Eye disease

We identified 2 Cochrane reviews and 2 RCTs on interventions to manage eye disease in T2D. Additionally, 2 Cochrane reviews (167,168) and 5 RCTs (169–173) focused on the use of anti-vascular endothelial growth factor (anti-VEGF) for diabetic macular oedema which is covered by the NICE technology appraisal guidance on Ranibizumab for treating diabetic macular oedema (TA274). These studies have been passed to the NICE TA team for consideration in reviewing this guidance.

Treatment of proliferative diabetic retinopathy

A Cochrane review (174) (18 studies n=1005) examined the effectiveness and safety of anti-VEGF for proliferative diabetic retinopathy. The comparator in this case was panretinal photocoagulation (PRP) which is usual care. Results indicated that anti-VEGFs (bevacizumab, pegaptanib, ranibizumab) significantly improved visual acuity compared to no anti-VEGF treatment. Any anti-VEGF treatment was also associated with significantly reduced risk of vitreous or pre-retinal haemorrhage and risk of losing 3 or more lines of visual acuity. Authors noted that the evidence was of very low quality and further trials are needed to inform treatment decisions.

One RCT (175) (n not reported in the abstract, 22 ophthalmic centres) found that intravitreous injection of aflibercept was more effective than standard care with photocoagulation at improving visual acuity. A related NICE TA covering aflibercept for treating diabetic macular oedema is available, but the scope does not cover diabetic retinopathy.

Treatment of diabetic macular oedema

A Cochrane review (176) of 24 studies (n= 4422 eyes) examined the efficacy and safety of laser photocoagulation as monotherapy in the treatment of diabetic macular oedema. Results indicated that compared to no intervention, those receiving laser treatment were significantly less likely to lose best-corrected visual acuity (BCVA) at one year. There was some indication that the less invasive laser techniques (e.g. subthreshold technique) may be as effective as standard laser therapy, however authors note that further evidence is required.

An RCT (177) (n=125) found that compared to placebo, there was no effect of topical nepafenac on change in optical coherence tomography retinal volume.

Treatment of periodontal disease

A Cochrane review(178) (35 studies, 33 targeting only T2D) investigated the effect of periodontal therapy on glycaemic control in people with diabetes mellitus. The review identified only low quality evidence that the treatment of periodontal disease by scaling and root planing improves glycaemic control in people with diabetes, but there was insufficient evidence that this was maintained beyond 4 months. There was no evidence to support that one periodontal therapy was more effective than any other in achieving glycaemic control.

An RCT(179) (n=264) found that, compared to control periodontal treatment, intensive periodontal treatment (IPT) reduced HbA1c in patients with type 2 diabetes and moderate-to-severe periodontitis after 12 months. IPT comprised whole mouth subgingival scaling, surgical periodontal therapy [if the participants showed good oral hygiene practice; otherwise dental cleaning again], and supportive periodontal therapy every 3 months until completion of the study).

Diabetes-related distress

A Cochrane review (180) (30 studies, n=9177) assessed the effects of psychological interventions for diabetes-related distress (DRD) in adults with T2D. The trials included a wide spectrum of interventions and were both individual- and group-based. Low-quality evidence showed that none of the psychological interventions would improve DRD more than usual care. Low-quality evidence showed improved self-efficacy and HbA1c after psychological interventions at 6 to 12 month follow-up.

Cognitive impairment and dementia

A Cochrane review (181) (7 studies, n=16,044) assessed the effects of different strategies for managing T2D on cognitive function and the incidence of dementia. The review found no good evidence that any specific treatment or treatment strategy for T2D can prevent or delay cognitive impairment. An intensive treatment strategy was more likely than standard treatment to cause hypoglycaemia, but there were no differences in death rates. The quality of the evidence for all outcomes to be low or moderate due to risk of bias in the included studies, small sample sizes, and imprecise estimates of the effects.

Intelligence gathering

Several stakeholders highlighted that periodontal disease has a bi-directional relationship with diabetes and that its effective management by the dental team has a role in prevention and treatment of diabetes.

Impact statement

Eye disease

Treatment of diabetic retinopathy

We identified new evidence on the treatment of proliferative diabetic retinopathy, supporting the use of anti-VEGF treatment, including intravitreous injection of aflibercept. The guideline currently only has recommendations on screening for diabetic retinopathy and referral criteria, incorporated from NICE's guideline on type 1 diabetes in adults. During original guideline development, the committee noted that management in this area was largely determined by practice for all people with diabetes and not just those with T2D. The committee concluded that recommendations for people with T2D should closely follow those for type 1 diabetes.

Given the growing evidence base in this area and the related NICE technology appraisal guidance on treatments for diabetic macular oedema, there may be a need for new recommendations to be developed with specialist ophthalmic input.

A topic expert also highlighted new evidence around diabetic eye screening. However, this was not considered in this surveillance review as this falls under the remit of the NHS Diabetic Eye Screening Programme who cover screening and referral criteria for people with diabetes. However, to avoid an overlap in guidance we plan to withdraw the recommendations on screening and referral. A cross reference to the Diabetic Eye Screening Programme will be retained for information.

Periodontal disease

The systematic review evidence to support treatment of periodontal disease by scaling and root planing to improves glycaemic control in people with diabetes is of a low quality and is limited to short term benefits up to 4 months. Results from a more recent RCT supporting the use of intensive periodontal treatment over 12 months may need to be substantiated by further studies to establish an impact on the guideline. NICE's guideline on type 1 and 2 diabetes in children and young people cross-refers to NICE's guideline on dental recall. This highlights diabetes as a risk factor for developing dental disease and notes that 'People with diabetes (both type I and type II) are at increased risk of developing destructive periodontal disease ... individuals with diabetes may need a more frequent recall. Inadequate plaque control and the presence of other risk factors will modify the recall interval further.' This issue will be put forward for consideration for scoping discussions for NICE guideline NG28 as expert input is required to determine an appropriate way of highlighting oral health in people with diabetes.

New evidence identified that may change current recommendations.

Treatment of diabetic macular oedema

We identified new evidence on the treatment of diabetic macular oedema. A Cochrane review supports the use of laser therapy compared to no intervention and suggested that less invasive techniques may be just as effective as the standard laser, however these results were highly uncertain. A further study found no effect of nepafenac on change in optical coherence tomography retinal volume. As mentioned above, the guideline currently only has recommendations on screening for diabetic retinopathy and referral criteria. There are no recommendations on diabetic macular oedema and the original guideline committee did not consider surgical evidence in this area. Given the growing evidence base in this area and the related NICE technology appraisal guidance on treatments for diabetic macular oedema, there may be a need for new recommendations to be developed.

New evidence identified that may change current recommendations.

Diabetes-related distress

There is uncertainty about the effects of psychological interventions on DRD, with only low quality evidence showing no difference to usual care, and therefore no impact on the guideline is anticipated.

New evidence is unlikely to change guideline recommendations.

Cognitive impairment and dementia

The systematic review in this area did not find any good quality evidence to support any specific treatment or strategy for T2D to prevent or delay cognitive impairment. NICE NG28 does not make recommendations in this area and in the absence of any high quality evidence, there is unlikely to be any impact.

New evidence is unlikely to change guideline recommendations.

Periodontal disease

Intelligence indicates the bidirectional association between periodontal disease and type 2 diabetes. Although the aetiology of diabetes is outside the scope of NICE guideline NG28, the NICE guideline on Dental recall will be considered for addition to the Type 2 diabetes pathway for information. This guideline highlights diabetes as a risk factor for developing dental disease. It also notes that 'People with diabetes (both type I and type II) are at increased risk of developing destructive periodontal disease. This may be due to an altered periodontal tissue response to plaque. Therefore, individuals with diabetes may need a more frequent dental recall. Inadequate plaque control and the presence of other risk factors will modify the recall interval further.' NICE's guideline on Oral health promotion also discusses risk factor control for people with diabetes and will be considered for addition to the Type 2

diabetes pathway for information. As the issues highlighted are covered by existing NICE guidelines, this will not be an area proposed for update.

> New evidence is unlikely to change guideline recommendations.

Research recommendations

Research recommendation	Summary of findings
What is the effectiveness of low carbohydrate diets in adults with type 2 diabetes?	New systematic review evidence was identified indicating that the benefits of low carbohydrate diets are evident only in the short term and are not maintained beyond 6 months. However, the DIRECT trial suggests that it is possible to achieve remission from type 2 diabetes by dieting, as evaluated over 2 years. It represents a promising relatively low resource intervention which is likely to be cost-saving in the long run if the results can be maintained. The longer-term results of the DIRECT study, and other longer term restricted diet studies are likely to be needed to establish any definite impact on the guideline.
What is the natural history of individuals who are diagnosed with type 2 diabetes in childhood in terms of long-term complications/consequences in adulthood?	The research recommendation would be answered by an observational study design that was not included in the search for the related section of the guideline.
What is the effectiveness of short-term self-monitoring of blood glucose during acute intercurrent illnesses in adults with type 2 diabetes?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Research recommendation	Summary of findings
What is the optimal frequency for self-monitoring of blood glucose in adults with type 2 diabetes?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What are the optimal blood glucose targets for self-monitoring in adults with type 2 diabetes?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 2 diabetes, what treatment combinations (for example, glucagon-like peptide-1 [GLP-1] mimetics and insulin, combination therapy with meglitinides) are most effective when initial drug treatment with non-metformin monotherapy fails to adequately control blood glucose levels?	New evidence was identified and an update to this section of the guideline is proposed. However, further evidence on cost effectiveness of treatment combinations may be needed to establish the cost implications for intensification after initial treatment failure.
In adults with type 2 diabetes, what are the effects of early use of insulin and glucagon-like peptide-1 (GLP-1) mimetics?	New evidence was identified to support the use of insulin and GLP-1 mimetics, including liraglutide, exenatide and lixisenatide in adults with T2D. Evidence indicates that, in combination with insulin, drugs in this class improve glycaemic control without an increased risk of hypoglycaemia, reduce body weight and blood pressure, and enable patients to lower their insulin doses. However, further research may be needed on longer term effects.
When third intensification of treatment is indicated, which blood glucose lowering therapies should be used to control blood glucose levels?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Research recommendation	Summary of findings
In adults with type 2 diabetes, what are the effects of stopping and/or switching drug treatments to control blood glucose levels, and what criteria should inform the decision?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 2 diabetes, what are the long-term effects of blood glucose lowering therapies such as dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium–glucose cotransporter 2 (SGLT-2) inhibitors and meglitinides?	No new evidence relevant to the long-term effects (defined as over 5 years in the research recommendation) was found and no ongoing studies were identified.
In adults with type 2 diabetes and chronic kidney disease, what is the safety and effectiveness of metformin?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 2 diabetes, what patient characteristics predict response or non-response to pharmacological blood glucose lowering therapies?	The research recommendation would be answered by an observational study design that was not included in the search for the related section of the guideline.
In adults with type 2 diabetes and multimorbidity, what are the optimal blood glucose lowering treatment strategies?	Although some new evidence was identified for certain comorbidities, including CVD and renal disease, the research recommendation proposed a systematic review to determine optimal treatment strategies for blood glucose control in adults with T2D and a range of comorbid conditions. The research recommendation therefore remains ongoing.

Research recommendation	Summary of findings
What is the optimal dosing of different phosphodiesterase-5 (PDE-5) inhibitors for people with type 2 diabetes and erectile dysfunction?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the effectiveness of pharmacological treatment strategies for people with type 2 diabetes and erectile dysfunction who do not respond to phosphodiesterase-5 (PDE-5) inhibitors, for example PDE-5 inhibitor plus prostaglandins?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the effectiveness of treatment strategies (pharmacological and non-pharmacological) for sexual dysfunction related to type 2 diabetes in women?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the effectiveness of treatment strategies (pharmacological and non-pharmacological) for sexual dysfunction in adults with type 2 diabetes in same-sex relationships?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Data summary tables

Table 1 Individualised care

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Kulzer, B.; et al. 2018 (1)	RCT	101 practices n=907	Adult (age not specified)	Integrated personalised diabetes management	Usual care	Change in HbA1c	12 months	Improved with intervention
Abbreviations: RCT – Randomised controlled trial Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated								

Table 2 Patient education

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Web-based self-management								
Murray E; et al. (2)	RCT	374	Adult (age not specified)	Web-based self-management programme (HeLP-Diabetes)	Control arm had access to simple information website	Change in HbA1c	12 months	Improved with intervention
						Diabetes mellitus-related distress (Problem Areas in Diabetes scale)	Not reported	No effect of intervention
						Plasma insulin level	25 weeks	Improved with intervention
						Glycaemic control (not defined)	25 weeks	Improved with intervention
						Insulin resistance	25 weeks	Improved with intervention
Structured education								
Attridge, M.; et al. 2014 (4)	Cochrane	33 RCTs (28 in meta-analysis, n=7453)	Adult (age not specified)	Culturally appropriate health education	Usual care	Change in HbA1c	3, 6, 12 months	Improved with intervention
						Knowledge scores	3, 6, 12 months	Improved with intervention
						CVD outcomes	3, 6, 12 months	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Bajaj, H. S.; et al. 2016 (3) INNOVATE	RCT	139	Adult (age not specified)	Insulin Glargine Titration Web Tool	Enhanced usual therapy diabetes education program	Composite of 4 out of 7 days FPG within 5-7.2 mmol/L plus mean for 3 consecutive days FPG within 5-7.2 mmol/L plus no severe hypoglycaemia	12 weeks	No effect of intervention
Bowen, M. E.; et al. 2016 (8)	RCT	150	Adult (age not specified)	Self-management education and support with carbohydrate gram counting	General health education	Change in HbA1c	6 months	No effect of intervention
				Self-management education and support with carbohydrate gram counting	General health education	Change in HbA1c (from baseline HbA1c 7-10%)	6 months	Improved with intervention
				Self-management education and support with modified plate method	General health education	Change in HbA1c	6 months	No effect of intervention
				Self-management education and support with modified plate method	General health education	Change in HbA1c (from baseline HbA1c 7-10%)	6 months	Improved with intervention
Cheng, L.; et al. (9)	RCT	242	Adult (age not specified)	Patient-centred, empowerment-based intervention programme	Health education classes and post-discharge follow-up	Change in HbA1c	20 weeks	No effect of intervention
						Blood glucose self-management	20 weeks	No effect of intervention
Dallosso, H. M.; et al. 2015 (5)	RCT	292 (from 75 practices)	Adult (age not specified)	Structured group education programme with module on SMBG	Structured group education programme with module on self-monitoring using urine glucose	Change in HbA1c	18 months	No effect of intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Guo, X. H.; et al. 2014 (7)	RCT	1289	Adult (age not specified)	Structured diabetes education plus insulin therapy	Usual care plus insulin therapy	Change in HbA1c	16 weeks	Improved with intervention
Hermanns, N.; et al. 2017 (6)	RCT	182	Adult (age not specified)	MEDIAS 2 BSC: self-management oriented education programme	Established education programme	Change in HbA1c	6 months	Improved with intervention

Abbreviations: RCT – Randomised controlled trial; CVD – Cardiovascular disease; FPG – fasting plasma glucose

Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated

Table 3 Dietary advice

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Low carbohydrate diet								
Carter, Sharayah; et al. 2018 (16)	RCT	137	Adults (age not specified)	Intermittent energy restriction (500-600 cal/day) (2 non-consecutive days per week, with usual diet 5 days per week)	Continuous energy restriction (1200-1500 cal/day) for 7 days per week	Change in HbA1c	12 months	Intervention non-inferior
						Change in body weight	12 months	No effect of intervention
						Hypoglycaemia	2 weeks	No effect of intervention
Huntriss, R.; et al. 2018 (11)	SR	18 RCTs (n=2204) included in total. 7 RCTs in meta-analysis of 1 year data	Adults (age not specified)	LCD	Usual care	CVD outcomes	1 year	Improved with intervention
Korsmo-Haugen, Henny-Kristine; et al. 2019 (12)	SR	23 studies (n=2178)	Adult (age not specified)	LCD	Higher carbohydrate diets	Change in HbA1c	NR	Improved with intervention
						Change in body weight	NR	No effect of intervention
						Blood pressure	NR	No effect of intervention
Lean, M.E.J; et al. 2019 (17,18) DIRECT	RCT	298	Adult (20-65 years)	Integrated structured weight-management programme (withdrawal of anti-diabetes and anti-hypertensive drugs, total diet replacement, stepped food reintroduction plus structured support for maintenance)	Best practice care in accordance with guidelines	Change in body weight (weight loss of 15 kg or more)	24 months	Improved with intervention
						Diabetes remission (HbA1c below 6.5% after withdrawal of anti-diabetes medications)	24 months	Improved with intervention
						Change in body weight	24 months	Improved with intervention
						Change in HbA1c	24 months	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Liu, Kai; et al. 2018 (13)	RCT	122	Adult (age not specified)	LCHP diet combined with omega-3 polyunsaturated fatty acid [PFU] (LHCP+omega-3)	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Change in HbA1c	12 weeks	No effect of intervention
				LCHP plus corn oil placebo	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Fasting glucose	12 weeks	No effect of intervention
				LCHP plus corn oil placebo	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Change in HbA1c	12 weeks	No effect of intervention
				Omega-3	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Change in HbA1c	12 weeks	No effect of intervention
				LCHP+omega-3	LCHP plus corn oil placebo	Change in HbA1c	12 weeks	Improved with intervention
				LCHP+omega-3	omega-3	Change in HbA1c	12 weeks	Improved with intervention
				LCHP+omega-3	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Fasting glucose at 4 weeks	4 weeks	Improved with intervention
				LCHP+omega-3	LCHP plus corn oil placebo	Fasting glucose at 12 weeks	12 weeks	Improved with intervention
				LCHP+omega-3	omega-3	Fasting glucose at 12 weeks	12 weeks	Improved with intervention
				LCHP diet combined with omega-3 polyunsaturated fatty acid [PFU] (LHCP+omega-3)	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Change in HbA1c	12 weeks	No effect of intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Meng, Y.; et al (11)	SR	9 studies (n=734)	Adult (age not specified)	LCD	Normal or High carbohydrate diet	Change in HbA1c	NR	Improved with intervention
						Short term weight loss	NR	Improved with intervention
Shakil-Ur-Rehman, Syed; et al. 2017 (21)	RCT	102	Adult (age not specified)	Supervised structured aerobic exercise training programme plus routine medication and dietary plan	Routine medication and dietary plan	Fasting blood glucose	25 weeks	Improved with intervention
Tay, J.; et al. 2015 (14)(15)	RCT	115	Adult (age not specified)	Very low carbohydrate, high unsaturated fat, low saturated fat diet, combined with supervised aerobic and resistance exercise	High carbohydrate, low-fat (energy-matched) diet, combined with supervised aerobic and resistance exercise	Change in HbA1c	Assessed at 24, 52 and 104 weeks	No effect of intervention
						Fasting blood glucose	Assessed at 24, 52 and 104 weeks	No effect of intervention
						Change in body weight	Assessed at 24, 52 and 104 weeks	No effect of intervention
						Blood pressure	Assessed at 24, 52 and 104 weeks	No effect of intervention
Vitamin D supplementation								
Krul-Poel, Y. H. M.; et al. 2015 (19) SUNNY	RCT	275	Adult (age not specified)	Vitamin D supplementation (50,000 IU/month) for 6 months	Placebo for 6 months	Change in HbA1c	6 months	No effect of intervention
Angellotti, E.; et al. 2018 (20)	RCT	127	Adults (mean age 60 years)	4000 units of vitamin D (cholecalciferol) daily for 48 weeks	Placebo daily for 48 weeks	Change in HbA1c	24 weeks	Improved with intervention
						Insulin secretion rate	24 weeks	No effect of intervention
						Change in HbA1c	Measured at 16, 24, 36, and 48 weeks	No effect of intervention
						Mean 25(OH)D levels	24 weeks	Direction of change not reported
Abbreviations: RCT – Randomised controlled trial; SR – systematic review; LCHP – low carbohydrate high protein; HCLP – high carbohydrate low protein Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated								

Table 4 Self-monitoring of blood glucose

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
SMBG specific studies								
Sodipo, O. O.; et al. (23)	RCT	120	Adult (age not specified)	SMBG	No SMBG	Change in HbA1c	8 months	No effect of intervention
Continuous glucose monitoring								
Beck, R. W.; et al. (24)	RCT	158	Adult (mean age 60 years)	Continuous Glucose Monitoring	Usual care	Change in HbA1c	6 months	Improved with intervention
Flash glucose monitoring								
Haak, Thomas; et al. (25)	RCT	224	Adult (age not specified)	Flash glucose-sensing technology (FreeStyle Libre TM Flash Glucose Monitoring System)	Self-monitoring of blood glucose (FreeStyle Lite TM)	Hypoglycaemia	12 months (6 months treatment, 6 months open access)	Improved with intervention
Yaron M; et al. 2019 (26)	RCT	101	T2D Age unspecified	flash glucose monitoring	Usual care	Change in HbA1C	10 weeks	Improved with intervention
						Patient satisfaction	10 weeks	Improved with intervention
Remote monitoring								
Young, L. A.; et al. (27)	RCT	450	Adult (30 years and older)	SMBG	No SMBG	Change in HbA1c	52 weeks	No effect of intervention
Grady, Mike; et al. (28)	RCT	128	Adult (age not specified)	Blood glucose meter plus mobile app	Blood glucose meter only	Change in HbA1c	12 weeks	No effect of intervention
Hansen, C. R.; et al. (29)	RCT	165	Adult (age not specified)	Telemedicine intervention added to clinic-based care (8 month duration)	Clinic-based care	Change in HbA1c	At completion of 8 month intervention	Improved with intervention
						Change in HbA1c	6 month follow-up	No effect of intervention
Bollyky, J. B.; et al. (31)	RCT	330	Adult (age not specified)	Lifestyle coaching plus a connected glucose meter	Usual care	Change in HbA1c	12 weeks	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Wild, S. H.; et al. (30)	RCT	285	Adult (age not specified)	Supported telemonitoring intervention (self-measurement and transmission to secure website of twice weekly morning and evening glucose for clinician review)	Usual care (with at least annual review, more frequent review for those with poor glycaemic or blood pressure control)	Systolic blood pressure	Assumed 9 months. Outcome: ambulatory systolic blood pressure	Improved with intervention
						Diastolic blood pressure	Assumed 9 months. Outcome: ambulatory diastolic blood pressure	Improved with intervention
						Change in HbA1c	9 months	Improved with intervention
Kempf, K.; et al. (32)	RCT	202	Adult (age not specified)	Telemedical Lifestyle intervention Program TeLiPro	Routine care	Change in HbA1c	12 weeks	Improved with intervention
						10-year CVD risk	12 weeks	Improved with intervention
						quality of life	12 weeks	Improved with intervention
Lindberg, Inger; et al. (33)	RCT	166	Adult (age not specified)	Telemonitoring and health counselling	Usual care	Change in HbA1c	19 months	No effect of intervention
						Quality of life	19 months	No effect of intervention
Parsons, S. N.; et al. (34)	RCT	446	Adult (age not specified)	Structured SMBG	Usual care	Change in HbA1c	12 months	Improved with intervention

Abbreviations: RCT – Randomised controlled trial; CVD – cardiovascular disease; SMBG – self-monitoring of blood glucose

Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated

Table 5 Drug treatment: Initial therapy

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Henry, Robert R.; et al. (35)	RCT	571	Adults and CKD	Metformin delayed-release	Placebo	Change in HbA1c	16 weeks	Improved with intervention
				Metformin immediate release	Placebo or metformin delayed-release	Change in HbA1c	16 weeks	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Park, J.; et al. (45)	RCT	160	Adult (age not specified)	Evogliptin	Placebo	Change in HbA1c	24 weeks	Improved with intervention
Lim, S.; et al. (46) INICOM	RCT	433	Adult (age not specified)	Initial combination therapy with gemigliptin and metformin	Gemigliptin or metformin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
Ross, S. A.; et al. (47)	RCT	316	Adult (age not specified)	Linagliptin 5 mg once daily and metformin twice daily	Linagliptin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
Abbreviations: RCT – Randomised controlled trial; CKD - Chronic kidney disease Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated								

Table 6 Drug treatment: First intensification

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Class level comparisons								
Alfayez, Osamah M.;et al. 2019 (48)	SR	9 studies (n=87,162)	Adult (age not specified)	DPP4-inhibitors	Placebo	CVD outcomes	NR	No effect of intervention
				GLP-1 agonists	Placebo	CVD outcomes	NR	Improved with intervention
				GLP-1 agonists	Placebo	CV or all-cause death	NR	Improved with intervention
				SGLT-2 inhibitors	Placebo	Hospitalisation for heart failure	NR	Improved with intervention
Zelniker, T. A.; et al. (45)	SR	34,322	Adult (age not specified)	SGLT2 inhibitors	Placebo	CVD outcomes	NR	Improved with intervention
						Renal outcomes	NR	Improved with intervention
						Hospitalisation for heart failure	NR	Improved with intervention
Lo, C.; et al. 2018 (50)	Cochrane	7 studies n=1092	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Change in HbA1c	NR	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
		5 studies n=855	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Fasting blood glucose	NR	Improved with intervention
		7 studies n=1198	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Systolic blood pressure	NR	Improved with intervention
		7 studies n=3086	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Genital infections	NR	Worse with intervention
		5 studies n=1029	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Weight	NR	Improved with intervention
		9 studies n=Not reported	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Risk of cardiovascular death	NR	No effect of intervention
		9 studies n=Not reported	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Hypoglycaemia	NR	No effect of intervention
		9 studies n=Not reported	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Acute kidney injury	NR	No effect of intervention
		2 studies n=5897	Adult (age not specified) and CKD	DPP-4 inhibitors	Placebo	Cardiovascular death	NR	No effect of intervention
		2 studies n=210	Adult (age not specified) and CKD	DPP-4 inhibitors	Placebo	Weight	NR	No effect of intervention
		7 studies n=867	Adult (age not specified) and CKD	GLP-1 agonists	Placebo	Change in HbA1c	NR	Improved with intervention
		2 studies n=551	Adult (age not specified) and CKD	Sitagliptin	Glipizide	Hypoglcaemia	NR	Improved with intervention
SGLT-2 inhibitors								
Shestakova, M. V.; et al. 2018 (71)	RCT	165	Adult (age not specified)	Ipragliflozin	Placebo	Change in HbA1c	12 weeks	Improved with intervention
						Change in body weight	12 weeks	Improved with intervention
GLP-1 analogues								

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Hernandez, A. F.; et al. 2018 (84) Harmony Outcomes	RCT	9,463	Adult (over 40 years)	Albiglutide	Placebo	CVD outcomes	1.6 years	Improved with intervention
Chuang, L. H.; et al. 2016 (94)	Cost study		Adult (age not specified)	Exenetide 2mg twice weekly	liraglutide 1.2 mg and 1.8 mg once daily	Cost effectiveness		Intervention cost-effective
					lixisenatide 20 μg	Cost effectiveness		Intervention cost-effective
Wysham, C. H.; et al. 2018 (91)	RCT	375	Adult (age not specified)	Exenetide once-weekly (autoinjected)	Exenetide twice daily	Change in HbA1c	28 weeks	Improved with intervention
						Change in body weight	28 weeks	Intervention non-inferior
Gadde, K. M.; et al. 2017 (92)	RCT	365	Adult (age not specified)	Exenetide once-weekly	Sitagliptin	Change in HbA1c	28 weeks	Improved with intervention
					Placebo	Change in HbA1c	28 weeks	Improved with intervention
Holman, R. R.; et al. 2017 (93)	RCT	14,752	Adult (age not specified)	Exenatide	Placebo	CVD outcomes	Median 3.2 years	Intervention non-inferior
Xu, W.; et al. 2015 (95)	RCT	416	Adult (age not specified)	Exenatide	Insulin	Change in HbA1c	48 weeks	Intervention non-inferior
					Pioglitazone	Change in HbA1c	48 weeks	Improved with intervention
Hunt, Barnaby; et al. 2017 (96)	Cost		Adults (age unspecified)	Liraglutide	Exenatide, lixisenatide	Cost effectiveness	NR	Intervention cost effective
Mann, J. F. E.; et al. 2017 (97)	RCT	9,340	Adults (age unspecified)	Liraglutide	Placebo	Renal outcomes	Median 3.84 years	Improved with intervention
D'Alessio, D.; et al. 2015 (98)	RCT	489	Adult (age not specified)	Insulin glargine	Liraglutide	Change in body weight	24 weeks	Worse with intervention
						Adverse events	24 weeks	Improved with intervention
						Hypoglycaemia	24 weeks	Worse with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Ahmann, A. J.; et al. 2018 (72)	RCT	813	Adult (age not specified)	Once weekly 1.0 mg semaglutide	Exenatide extended release 2.0 mg	Change in HbA1c	56 weeks	Improved with intervention
						Change in body weight	56 weeks	Improved with intervention
Ahren, B.; et al. 2017 (73)	RCT	1225	Adults T2D	Subcutaneous semaglutide 0.5 mg once weekly plus oral sitagliptin placebo once daily	Oral sitagliptin 100 mg once daily plus subcutaneous semaglutide placebo 0.5 mg or 1.0 mg once weekly	Change in HbA1c	56 weeks	Improved with intervention
						Change in body weight	56 weeks	Improved with intervention
				Subcutaneous semaglutide 1.0 mg once weekly plus oral sitagliptin placebo once daily		Change in HbA1c	56 weeks	Improved with intervention
						Change in body weight	56 weeks	Improved with intervention
Aroda, V. R.; et al. 2017 (74)	RCT	1089	Adults T2D	0.5 mg weekly semaglutide	Daily titrated insulin glargine	Change in HbA1c	30 weeks	Improved with intervention
						Change in body weight	30 weeks	Improved with intervention
						Hypoglycaemia	30 weeks	Improved with intervention
				1.0 mg weekly semaglutide		Change in HbA1c	30 weeks	Improved with intervention
						Change in body weight	30 weeks	Improved with intervention
						Hypoglycaemia	30 weeks	Improved with intervention
Blonde, L.; et al 2015. (85)	RCT	591	Adults T2D	Dulaglutide 1.5 mg + prandial insulin lispro	Insulin glargine + prandial insulin lispro	Change in HbA1c	26 weeks	Improved with intervention
				Dulaglutide 0.75 mg + prandial insulin lispro	Insulin glargine + prandial insulin lispro	Change in HbA1c		Improved with intervention

Study	Type	N	Population	Intervention	Comparator	Outcome	Timepoint	Result
Davies, M.; *et al.* 2017 (75)	RCT	632	T2D Age unspecified	Once daily oral semaglutide (range 2.5 mg – 40 mg)	Placebo	Change in HbA1c	26 weeks	Improved with intervention
						Change in body weight	26 weeks	Improved with intervention
				Once weekly subcutaneous semaglutide 1.0 mg		Change in HbA1c	26 weeks	Improved with intervention
						Change in body weight	26 weeks	Improved with intervention
Lingvay, I.; *et al.* 2018 (76)	RCT	705	T2D Age unspecified	Once-daily semaglutide (range 0.05 - 0.3 mg)	Once daily liraglutide (range 0.3 - 1.8 mg)	Change in HbA1c	26 weeks	Improved with intervention
					Placebo	Change in HbA1c	26 weeks	Improved with intervention
Ludvik, B.; *et al* 2018 (86)	RCT	424	Adults T2D	Once-weekly dulaglutide 0.75 mg + SGLT2 inhibitor	Placebo + SGLT2 inhibitor	Change in HbA1c	24 weeks	Improved with intervention
						Adverse events	24 weeks	Worse with intervention
				Once-weekly dulaglutide 1.5 mg + SGLT2 inhibitor		Change in HbA1c	24 weeks	Improved with intervention
						Adverse events	24 weeks	Worse with intervention
Marso, S; *et al.* 2016 (82)	RCT	3297	T2D Age unspecified	Once-weekly semaglutide (0.5 mg or 1.0 mg)	Placebo	CVD outcomes	104 weeks	Intervention non-inferior
Nauck, M.; *et al.* 2014 (182)	RCT	1098	Adults T2D	Once-weekly dulaglutide 0.75 mg	100 mg sitagliptin	Change in HbA1c	52 weeks	Improved with intervention
						Change in body weight	52 weeks	Improved with intervention
				Once-weekly dulaglutide 1.5 mg		Change in HbA1c	52 weeks	Improved with intervention
						Change in body weight	52 weeks	Improved with intervention
Pozzilli, P.; *et al* 2017 (89)	RCT	300	Adults T2D	Weekly dulaglutide 1.5 mg injection + titrated daily glargine	Placebo + titrated daily glargine	Change in HbA1c	28 weeks	Improved with intervention
						Change in body weight	28 weeks	Improved with intervention
						Increases in mean glargine dose from baseline	28 weeks	Improved with intervention

Pratley, R. E.; et al. 2018 (77)	RCT	1201	Adults T2D	Semaglutide 0.5 mg once a week	Dulaglutide 0.75 mg once a week	Change in HbA1C	40 weeks	Improved with intervention
						Change in body weight	40 weeks	Improved with intervention
				Semaglutide 1.0 mg once a week	Dulaglutide 1.5 mg once a week	Change in HbA1C	40 weeks	Improved with intervention
						Change in body weight	40 weeks	Improved with intervention
Rodbard, H. W.; et al. 2018 (78) SUSTAIN 5	RCT	397	T2D Age unspecified	Subcutaneous semaglutide 0.5 mg once weekly (add on to basal insulin)	Placebo	Change in HbA1C	30 weeks	Improved with intervention
						Change in body weight	30 weeks	Improved with intervention
						Hypoglycaemia	30 weeks	No effect of intervention
				Subcutaneous semaglutide 1.0 mg once weekly (add on to basal insulin)		Change in HbA1C	30 weeks	Improved with intervention
						Change in body weight	30 weeks	Improved with intervention
						Hypoglycaemia	30 weeks	No effect of intervention
Rosenstock J; et al. 2019 (79)	RCT	1864	Adults T2D	Oral semaglutide 3 mg once daily	Sitagliptin 100 mg	Change in HbA1C	26 weeks	No effect of intervention
						Change in body weight	26 weeks	Result not stated
				Oral semaglutide 7 mg once daily		Change in HbA1C	26 weeks	Improved with intervention
						Change in body weight	26 weeks	Improved with intervention
				Oral semaglutide 14 mg once daily		Change in HbA1C	26 weeks	Improved with intervention
						Change in body weight	26 weeks	Improved with intervention
Sorli, C.; et al. 2017 (80)	RCT	387	Adults T2D	Subcutaneous semaglutide 0.5 mg once weekly	Placebo	Change in HbA1C	30 weeks	Improved with intervention
						Change in body weight	30 weeks	Improved with intervention

				Subcutaneous semaglutide 1.0 mg once weekly	Placebo	Change in HbA1C	30 weeks	Improved with intervention
						Change in body weight	30 weeks	Improved with intervention
Tuttle, Katherine R.; et al. 2018 (90)	RCT	384	T2D and CKD	Dulaglutide 0.75 mg + insulin lispro (once weekly)	Insulin glargine + insulin lispro (daily)	Change in HbA1C	26 weeks	Intervention non-inferior
						eGFR	52 weeks	Improved with intervention
						UCAR reduction	52 weeks	No effect of intervention
						Adverse events	52 weeks	No effect of intervention
		387		Dulaglutide 1.5 mg + insulin lispro (once weekly)		Change in HbA1C	26 weeks	Intervention non-inferior
						eGFR	52 weeks	Improved with intervention
						UCAR reduction	52 weeks	No effect of intervention
						Adverse events	52 weeks	No effect of intervention
Viljoen A; et al 2019. (83)	Cost	Not stated	T2D Age unspecified	Subcutaneous semaglutide 0.5 mg once weekly	Dulaglutide 1.5 mg once weekly	QALY	40 weeks	Improved with intervention
						Lifetime cost savings	40 weeks	Improved with intervention
				Subcutaneous semaglutide 1.0 mg once weekly		QALY	40 weeks	Improved with intervention
						Lifetime cost savings	40 weeks	Improved with intervention
Weinstock, R. S.; et al. 2015 (88)	RCT	657	T2D Age unspecified	Once-weekly dulaglutide 0.75 mg	100 mg sitagliptin	Change in HbA1C	104 weeks	Improved with intervention
						Change in body weight	104 weeks	No effect of intervention
				Once-weekly dulaglutide 1.5 mg		Change in HbA1C	104 weeks	Improved with intervention
						Change in body weight	104 weeks	Improved with intervention
Zinman B; et al 2019. (81)	RCT	301	Adults T2D			Change in HbA1C	30 weeks	Improved with intervention

SUSTAIN 9				Subcutaneous semaglutide 1.0 mg	Volume matched placebo	Change in body weight	30 weeks	Improved with intervention
DPP-4 inhibitors								
Moses, R. G.; et al. 2016 (99)	RCT	427	Adult (age not specified)	Sitagliptin and metformin fixed-dose combination	Placebo	Change in HbA1c	NR	Improved with intervention
Wang, W.; et al. 2017 (100)	RCT	381	Adult (age not specified)	Sitagliptin	Placebo	Change in HbA1c	24 weeks	Improved with intervention
Kim, S. S.; et al. 2017 (101)	RCT	292	Adult (18 years and over)	Sitagliptin and metformin fixed-dose combination	Glimepiride	Change in HbA1c	30 weeks	Improved with intervention
						Hypoglycaemia	30 weeks	Improved with intervention
						Fasting plasma glucose	30 weeks	Improved with intervention
						Change in body weight	30 weeks	Improved with intervention
Frias, Juan Pablo; et al. 2019 (102) CompoSIT-M	RCT	458	Adult (age not specified)	Sitagliptin plus metformin up-titration	Metformin up-titration alone	Change in HbA1c	20 weeks	Improved with intervention
Hartley, P.; et al. 2015 (103)	RCT	388	Elderly	Sitagliptin	Glimepiride	Change in HbA1c	30 weeks	Intervention non-inferior
						Hypoglycaemia	30 weeks	Intervention non-inferior
Jameshorani, M.; et al. 2017 (104)	RCT	160	Adult (age not specified)	Sitagliptin	Pioglitazone	Change in HbA1c	12 weeks	No effect of intervention
						Change in body weight	12 weeks	Improved with intervention
Buse, J. B.; et al. 2017 (105) TECOS	RCT	14,671	Adults and CVD	Sitagliptin	Placebo	Acute pancreatitis and pancreatic cancer	3 years	Intervention non-inferior
Josse, R. G.; et al. 2017 (106) TECOS	RCT	14,671	Adults (mean age 65.5 years)	Sitagliptin	Placebo	Fracture incidence	3 years	Intervention non-inferior
Green, J. B.; et al. 2015 (107) TECOS	RCT	14,671	Adult (age not specified)	Sitagliptin	Placebo	CVD outcomes	Median 3 years	Intervention non-inferior

Hong, S. M.; et al. 2017 (108)	RCT	222	Adult (age not specified)	Evogliptin	Sitagliptin	Change in HbA1c	24 weeks	Intervention non-inferior
Jin, S. M.; et al. 2015 (109)	RCT	180	Adult (age not specified)	Anagliptin	Sitagliptin	Change in HbA1c	24 weeks	Intervention non-inferior
Gu, Tianwei; et al. 2018 (110) SPECIFY	RCT	388	Adult (age not specified)	Saxagliptin	Glimepiride	Change in HbA1c	48 weeks	Improved with intervention
						Change in body weight	48 weeks	Improved with intervention
						Hypoglycaemia	48 weeks	Improved with intervention
Schernthaner, G.; et al. 2015 (111) GENERATION	RCT	720	Adult (65 years and older)	Saxagliptin	Glimepiride	Change in HbA1c	NR	Intervention non-inferior
Chen, Y.; et al. 2018 (112) SUPER	RCT	462	Adult (age not specified)	saxagliptin	Placebo	Change in HbA1c	NR	Improved with intervention
Du, J.; et al. 2017 (113) SMART	RCT	488	Adult (age not specified)	Saxagliptin	Acarbose	Change in HbA1c	24 weeks	Intervention non-inferior
Leiter, L. A.; et al. 2015 (114) SAVOR-TIMI 53	RCT	16,492	Adult (65 years and older)	Saxagliptin	Placebo	CVD outcomes	Median 2.1 years	Intervention non-inferior
Scirica, B. M.; et al. 2014 (115) SAVOR-TIMI 53	RCT	16,492	Adult (age not specified)	saxagliptin	Placebo	Heart failure	NR	Worse with intervention
Groop, P. H.; et al. 2017 (116) MARLINA-T2D	RCT	360	Adults and CKD	Linagliptin	Placebo	Change in HbA1c	NR	Improved with intervention
						urinary albumin-to-creatinine ratio	NR	No effect of intervention
Ji, L.; et al. 2015 (117)	RCT	689	Adult (age not specified)	Linagliptin plus low dose metformin	High dose metformin	Change in HbA1c	14 weeks	Intervention non-inferior
Rosenstock, Julio; et al. 2018 (118) CARMELINA	RCT	6,979	Elderly	Linagliptin	Placebo	CVD outcomes	Median 2.2 years	Intervention non-inferior
Gordon, Jason; et al. 2016 (119)	RCT	2,639	Adult (age not specified)	Alogliptin	Sulfonylurea	Cost effectiveness	2 years	Intervention cost effective

Mita, T.; et al. 2016 (120) SPEAD-A	RCT	341	Adult (age not specified)	Alogliptin	Placebo	Mean change in carotid IMT	24 months	Improved with intervention
White, W. B.; et al. 2016 (121) EXAMINE	RCT	5,380	Adults and recent acute coronary syndrome	Alogliptin	Placebo	CV mortality	Median 18 months	Intervention non-inferior
Hong, A. R.; et al. 2015 (122) VISUAL	RCT	344	Adult (age not specified)	Vidalgiptin	Sulfonylurea dose increasing	Change in HbA1c	24 weeks	Improved with intervention
Forst, T.; et al. 2015 (123)	RCT	162	Adult (age not specified)	Vildagliptin	NPH insulin	Change in HbA1c	24 weeks	Intervention non-inferior

Abbreviations: RCT – Randomised controlled trial; SR – systematic review; NR – not reported in abstract; CKD – Chronic kidney disease; CVD – cardiovascular disease

Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated

Table 7 – Drug treatment: Second intensification

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
SGLT-2 inhibitors								
Pawaskar, Manjiri; et al. 2018 (124)	Cost	NR	Adult (age not specified)	SGLT-2 inhibitors	NPH insulin	Cost effectiveness		Cost-neutral or cost-effective
GLP-1 analogues								
Guja, C.; et al. 2018 (125) DURATION-7	RCT	464	Adult (age not specified)	Exenetide plus insulin glargine	Placebo	Change in HbA1c	28 weeks	Improved with intervention
						Change in body weight	28 weeks	Improved with intervention
						postprandial glucose	28 weeks	Improved with intervention
Diamant, M.; et al. 2014 (126)	RCT	627	Adult (age not specified)	Exenetide plus insulin glargine	Insulin lispro plus insulin glargine	Change in HbA1c	30 weeks	Intervention non-inferior
Aroda, V. R.; et al. 2016 (127)	RCT	736	Adult (age not specified)	Insulin glargine plus lixisenatide	Insulin glargine	Change in HbA1c	30 weeks	Improved with intervention
						Change in body weight	30 weeks	Improved with intervention
	RCT	1,170	Adult (age not specified)	Insulin glargine plus lixisenatide		Change in HbA1c	30 weeks	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Rosenstock, J.; et al. 2016 (128) LixiLan-O					Insulin glargine or lixisenatide	Change in body weight	30 weeks	Improved with intervention
Rosenstock, J.; et al. 2016 (129)	RCT	323	Adult (age not specified)	Lixisenatide and Insulin glargine	Insulin glargine	Change in HbA1c	24 weeks	Intervention non-inferior
Gough, S. C.; et al. 2014 (130)	RCT	1663	Adult (age not specified)	Insulin degludec plus liraglutide	Insuline degludec or liraglutide alone	Change in HbA1c	26 weeks	Intervention non-inferior
Lingvay, I.; et al. 2016 (131) DUAL V	RCT	557	Adult (age not specified)	Insulin degludec plus liraglutide	Insulin glargine	Change in HbA1c	26 weeks	Improved with intervention
						Change in body weight	26 weeks	Improved with intervention
						Hypoglycaemia	26 weeks	Improved with intervention
Aroda, V. R.; et al. 2016 (132) BEGIN: ADD TO GLP-1	RCT	346	Adult (age not specified)	Insulin degludec plus liraglutide	Placebo plus liraglutide	Change in HbA1c	26 weeks	Improved with intervention
						Hypoglycaemia	26 weeks	Worse with intervention
Ahmann, A.; et al. 2015 (134)	RCT	451	Adult (age not specified)	Basal insulin plus liraglutide	Basal insulin plus placebo	Change in HbA1c	26 weeks	Improved with intervention
Lind, M.; et al. 2015 (135)	RCT	124	Adult (age not specified)	Liraglutide	Placebo	Change in HbA1c	24 weeks	Improved with intervention
						Change in body weight	24 weeks	Improved with intervention
						Hypoglycaemia	24 weeks	Intervention non-inferior
Rodbard, H. W.; et al. 2017 (136)	RCT	435	Adult (age not specified)	Insulin degludec plus liraglutide	Placebo	Change in HbA1c	26 weeks	Improved with intervention
Harris, S. B.; et al. 2017 (137) DUAL VI	RCT	420	Adult (age not specified)	Insulin degludec plus liraglutide once-weekly titration	Insulin degludec plus liraglutide twice weekly titration	Change in HbA1c	32 weeks	Intervention non-inferior

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Philis-Tsimkas A et al 2019 (133) DUAL IX	RCT	420	Adults T2D	Insulin degludec/liraglutide (IDegLira)	Insulin glargine 100 units/mL (IGlar U100)	Change in HbA1c	26 weeks	Intervention non-inferior
								Improved with intervention
						Body weight decrease	26 weeks	Improved with intervention
						Severe hypoglycaemia	26 weeks	Improved with intervention
						Total daily insulin dose	26 weeks	Improved with intervention
DPP-4 inhibitors								
Linjawi, S.; et al. 2015 (138) Sit2Mix	RCT	582	Adult (age not specified)	Once- and twice daily biphasic insulin aspart 30 with sitagliptin	Twice daily biphasic insulin aspart 30 without sitagliptin	Change in HbA1c	24 weeks	Improved with intervention
Roussel, Ronan; et al. 2018 (139) CompoSIT-I	RCT	743	Adult (age not specified)	Sitagliptin plus insulin glargine	Insulin glargine alone	Change in HbA1c	30 weeks	Improved with intervention
Mathieu, Chantal; et al. 2015 (140)	RCT	660	Adult (age not specified)	Sitagliptin	Placebo	Change in HbA1c	24 weeks	Improved with intervention
						Hypoglycaemia	24 weeks	Improved with intervention
White, W. B.; et al. 2018 (141) EXAMINE	RCT	1,398	Adults and recent acute coronary syndrome	Alogliptin plus baseline metformin and sulfonylurea	Placebo	Change in HbA1c	Up to 40 months (median 18 months)	Improved with intervention
						CVD outcomes	Up to 40 months (median 18 months)	Improved with intervention

Abbreviations: RCT – Randomised controlled trial; SR – systematic review; NR – not reported

Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated

Table 8 Drug treatment: Insulin-based treatments

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Short acting insulin analogues								
Fullerton, Birgit; et al. 2018 (142)	SR	10 studies n=2751	Adult (age not specified)	Short acting insulin analogues	Human insulin	Change in HbA1c	Not reported	Intervention non-inferior
						Hypoglycaemia	Not reported	Intervention non-inferior
						All-cause mortality	Not reported	Intervention non-inferior
Lundby-Christensen, L.; et al. 2016 (143) (147)	RCT	412	Adult (age not specified)	Metformin in combination with insulin	Placebo	Change in HbA1c	18 months	Improved with intervention
				Metformin in combination with insulin	Placebo	Mean carotid IMT	18 months	No effect of intervention
				Metformin in combination with insulin	Placebo	Change in body weight	18 months	Improved with intervention
				Metformin in combination with insulin	Placebo	Hypoglycaemia	18 months	Improved with intervention
				biphasic insulin aspart	Insulin aspart 3 times daily in combination with insulin detemir	Mean carotid IMT	18 months	No effect of intervention
				biphasic insulin aspart	Insulin aspart 3 times daily in combination with insulin detemir, or insulin detemir alone	Change in HbA1c	18 months	Improved with intervention
Bowering, K.; et al. 2017 (144)	RCT	689	Adult (age not specified)	Fast-acting insulin aspart	Insulin aspart	Change in HbA1c	26 weeks	Intervention non-inferior
						Hypoglycaemia	26 weeks	Worse with intervention
	RCT	236	Adult (age not specified)	Fast-acting insulin aspart	Basal only insulin	Change in HbA1c	18 weeks	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Rodbard, H. W.; et al. 2017 (145)				plus basal insulin		Change in body weight	18 weeks	Worse with intervention
Linjawi, Sultan; et al. 2018 (146)	RCT	335	Adult (age not specified)	Biphasic insulin aspart	Basal-bolus insulin	Change in HbA1c	32 weeks	Improved with intervention
						Hypoglycaemia	32 weeks	Improved with intervention
Franek, E.; et al. 2016 (148)	RCT	394	Adult (age not specified)	Insulin degludec plus insulin aspart	Biphasic insulin aspart	Change in HbA1c	26 weeks	Intervention non-inferior
						Fasting plasma glucose	26 weeks	Intervention non-inferior
Vora, J.; et al. 2015 (149)	RCT	335	Adult (age not specified)	Insulin glargine plus insulin glulisine	Insulin aspart plus aspart protamine	Change in HbA1c	24 weeks	Intervention non-inferior
Long acting insulin analogues								
Evans, M.; et al. 2018 (150)	Cost	Not applicable	Age and type not specified	Degludec	Glargine U100	Cost effectiveness based on rates of hypoglycaemia	NR	Intervention cost effective
Marso, S. P.; et al. 2017 (152)	RCT	7,637	Adult (age not specified)	Degludec	Glargine U100	CVD outcomes	NR	Intervention non-inferior
Pan, C.; et al. 2016 (153)	RCT	833	Adult (age not specified)	Insulin degludec	Insulin glargine	Change in HbA1c	26 weeks	Intervention non-inferior
Wysham, C.; et al. 2017 (154) SWITCH 2	RCT	721	Adult (age not specified)	Insulin degludec	Insulin glargine	Hypoglycaemia	32 weeks	Improved with intervention
Rosenstock, J.; et al. 2018 (155) BRIGHT	RCT	929	Adult (age not specified)	Insulin glargine 300 units/mL	Insulin degludec	Change in HbA1c	24 weeks	Intervention non-inferior
Rodbard, H. W.; et al. 2017 (156)	RCT	274	Adult (age not specified)	Insulin degludec plus insulin aspart	Insulin degludec	Change in HbA1c	26 weeks	No effect of intervention
Heller, SR et al 2019 (151)	RCT	720	T2D Age unspecified	Insulin degludec	Insulin glargine	Hypoglycaemia	32 weeks	Improved with intervention
						Change in HbA1c	32 weeks	No effect of intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Glargine dosage								
Riddle, M. C.; et al. 2015 (157) EDITION 1	RCT	807	Adult (age not specified)	Insulin glargine 300 units/mL	Insulin glargine 100 units/mL	Change in HbA1c	12 months	Improved with intervention
						Hypoglycaemia	12 months	Improved with intervention
Yki-Jarvinen, H.; et al. 2014 (158) EDITION 2	RCT	811	Adult (age not specified)	Insulin glargine 300 units/mL	Insulin glargine 100 units/mL	Change in HbA1c	12 months plus 6 month safety extension	Intervention non-inferior
						Hypoglycaemia	12 months plus 6 month safety extension	Improved with intervention
						Change in body weight	12 months plus 6 month safety extension	Improved with intervention
Bolli, G. B.; et al. 2017 (159) EDITION 3	RCT	878	Adult (age not specified)	Insulin glargine 300 units/mL	Insulin glargine 100 units/mL	Change in HbA1c	12 months	Intervention non-inferior
						Hypoglycaemia	12 months	Improved with intervention
Ritzel, R.; et al. 2018 (160) SENIOR	RCT	1,014	Adult (65 years and older)	Insulin glargine 300 units/mL	Insulin glargine 100 units/mL	Change in HbA1c	26 weeks	Intervention non-inferior
Biosimilars								
Derwahl, K. M.; et al. 2018 (161) SORELLA 2	RCT	505	Adult (age not specified)	SAR342434 insulin lispro biosimilar	Insulin lispro	Change in HbA1c	26 weeks	Intervention non-inferior
Blevins, T.; et al. 2018 (162) INSTRIDE 2	RCT	560	Adult (age not specified)	MYL-1501D insulin biosimilar plus oral antidiabetic drugs	Insulin glargine plus oral antidiabetic drugs	Change in HbA1c	24 weeks	Intervention non-inferior
Rosenstock, J.; et al. 2015 (163) ELEMENT 2	RCT	756	Adult (age not specified)	LY2963016 insulin glargine	Insulin glargine	Change in HbA1c	24 weeks	Intervention non-inferior
						Fasting plasma glucose	24 weeks	Intervention non-inferior
Insulin analogues compared to human insulin								

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Home, P. D.; et al. 2015 (164)	RCT	701	Adult (mean age of 57 years)	Insulin glargine	Neutral protamine Hagedorn insulin	Change in HbA1c	36 weeks	Intervention non-inferior
Insulin strategies for hospitalised patients								
Colunga-Lozano, L. E.; et al. 2018 (165)	Cochrane	8 studies n=1048	Adult (age not specified)	Sliding scale insulin	Basal insulin, basal-bolus insulin, correction dose insulin	All-cause mortality	NR	No effect of intervention
						Hypoglycaemia	NR	No effect of intervention
Insulin monotherapy compared with the addition of OADs								
Vos, R. C.; et al. 2016 (166)	Cochrane	9 studies n=316	Adult (age not specified)	Insulin-sulfonylurea combination	Insulin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
		9 studies n=698	Adult (age not specified)	Insulin metformin	Insulin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
		3 studies n=448	Adult (age not specified)	Insulin plus alpha-glucosidase inhibitors	Insulin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
		2 studies n=265	Adult (age not specified)	Insulin plus DPP-4 inhibitors	Insulin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
		7 studies n=220	Adult (age not specified)	Insulin-sulfonylurea combination	Insulin monotherapy	Hypoglycaemia	24 weeks	Worse with intervention
		7 studies n=615	Adult (age not specified)	Insulin metformin	Insulin monotherapy	Change in body weight	24 weeks	Improved with intervention
		2 studies n=362	Adult (age not specified)	Insulin plus DPP-4 inhibitors	Insulin monotherapy	Change in body weight	24 weeks	Worse with intervention
Insulin glargine and liraglutide								
D'Alessio, D.; et al. 2015 (98)	RCT	489	Adult (age not specified)	Insulin glargine	Liraglutide	Change in HbA1c	24 weeks	No effect of intervention
Billings, L. K.; et al. 2018 (183)	RCT	695	Adult (age not specified)	Insulin degludec plus liraglutide	Basal insulin	Change in HbA1c	Not reported	Intervention non-inferior
						Change in body weight	Not reported	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
						Hypoglycaemia	Not reported	Improved with intervention
Buse, J. B.; et al. 2014 (184)	RCT	413	Adult (age not specified)	Insulin degludec and liraglutide	Insulin degludec	Change in HbA1c	26 week	Improved with intervention
						Change in body weight	26 week	Improved with intervention

Abbreviations: RCT – Randomised controlled trial; SR – systematic review; NR – not reported in abstract

Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated

Table 9 Managing complications

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Treatment of proliferative diabetic retinopathy								
Martinez-Zapata, M. J. 2014 (174)	Cochrane	1 study (n = 61)	Adult (age not specified)	Bevacizumab with panretinal photocoagulation	Panretinal photocoagulation	Risk of losing 3 or more lines of visual acuity	12 months	Improved with intervention
		5 studies (n = 373)	Adult (age not specified)	Treatment with either bevacizumab, pegaptanib or ranibizumab	No anti-VEGF treatment	Visual acuity	12 months	Improved with intervention
		3 studies (n = 342)	Adult (age not specified)	Any anti-VEGF treatment	No anti-VEGF treatment	Risk of vitreous or pre-retinal haemorrhage	12 months	Improved with intervention
		3 studies (n = 94)	Adult (age not specified)	Bevacizumab plus vitrectomy	Vitrectomy alone	Risk of losing 3 or more lines of visual acuity	12 months	Little or no benefit with intervention
Sivaprasad, S.; et al. 2017 (175) CLARITY	RCT	22 ophthalmic centres (n not reported in the abstract)	Adults with proliferative diabetic retinopathy	Intravitreous injection of aflibercept (2mg/0.05ml)	Photocoagulation	Change in BCVA	1 year	Improved with intervention
Treatment of diabetic macular oedema								

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Jorge, E. C.; et al. 2018 (176)	Cochrane Total includes = 24 studies (4422 eyes)	3703 eyes	Adult (age not specified)	Any type of focal/grid macular laser photocoagulation	No intervention	BCVA	1 year	Improvement with intervention
		29 eyes	Adult (age not specified)	Subthreshold photocoagulation	Standard photocoagulation	Resolution of macular oedema	1 year	No significant difference between intervention and comparator
		385 eyes	Adult (age not specified)	Subthreshold photocoagulation	Standard photocoagulation	Continuous BCVA	1 year	No significant difference between intervention and comparator
		385 eyes	Adult (age not specified)	Subthreshold photocoagulation	Standard photocoagulation	Change in central macular thickness	1 year	No significant difference between intervention and comparator
		773 eyes	Adult (age not specified)	Argon laser	Other type of laser	BCVA	1 year	No significant difference between intervention and comparator
		323 eyes	Adult (age not specified)	Modified ETDRS (mETDRS) grid technique	Mild macular grid technique	BCVA	1 year	Inconclusive
Friedman, S. M.; et al. 2015 (177)	RCT	125	Adult (age not specified)	Nepafenec (0.1%)	Placebo	Mean change in optical coherence tomography retinal volume	12 months	No significant difference between intervention and comparator
Treatment of periodontal disease								
Simpson, T. C.; et al. 2015 (178)	Cochrane	14 RCTs (N=1499)	Adult (age not specified)	Periodontal therapy	No active intervention/ usual care	Change in HbA1c	3 to 4 months post-treatment	Improved with intervention
		5 RCTs (N=826)	Adult (age not specified)	Periodontal therapy	No active intervention/ usual care	Change in HbA1c	6 months	No effect of intervention
		12 RCTs (N=450)	Adult (age not specified)	Scaling and root planing plus antimicrobial	Scaling and root planing	Change in HbA1c	3 to 4 months post-treatment	No effect of intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
D'Aiuto F et al.	RCT	264	Adult (age not specified)	Intensive periodontal treatment (whole mouth subgingival scaling, surgical periodontal therapy, and supportive periodontal therapy every 3 months until completion of the study)	Control periodontal treatment (CPT; supra-gingival scaling and polishing)	Change in HbA1c	12 months	Improved with intervention
Diabetes-related distress								
Chew, B. H.; et al. 2017 (180)	Cochrane	5 RCTs (N=1932)	Adult (18 and over)	Psychological intervention	Usual care	Health-related quality of life	Median 12 months (range 0 to 12 months)	No effect of intervention
		3 RCTs (N=1376)	Adult (18 and over)	Psychological intervention	Usual care	All-cause mortality	Median 12 months (range 0 to 12 months)	No effect of intervention
		3 RCTs (N=438)	Adult (18 and over)	Psychological intervention	Usual care	Adverse events	Median 12 months (range 0 to 12 months)	No effect of intervention
		6 RCTs (N=2675)	Adult (18 and over)	Psychological intervention	Usual care	Self-efficacy	6-12 months	Improved with intervention
		11 RCTs (N=3165)	Adult ((18 and over)	Psychological intervention	Usual care	Change in HbA1c	6-12 months	Improved with intervention
		12 RCTs (N=3315)	Adult (18 and over)	Psychological intervention	Usual care	Diabetes-related distress	Median 12 months (range 0 to 12 months)	No effect of intervention
Cognitive impairment and dementia								
Areosa Sastre, A.; et al. 2017 (181)	SR	1 RCT, n=11,140	Adult (age not specified)	Intensive glycaemic control	Standard glycaemic control	Incidence of dementia	NR	No effect of intervention
		1 RCT, n=2794	Adult (age not specified)	Intensive glycaemic control	Standard glycaemic control	MMSE score	40 months	No effect of intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
		2RCTs, n=12,827	T2D Age unspecified	Intensive glycaemic control	Standard glycaemic control	Hypoglycaemia	NR	Worse with intervention
		3 RCTs, 15,888	Adult (age not specified)	Intensive glycaemic control	Standard glycaemic control	All-cause mortality	NR	No effect of intervention
		1 RCT, n=156	Adult (age not specified)	Glibenclamide (glyburide)	Repaglinide	MMSE score	12 months	Improved with intervention
		1 RCT, n=11,140	Adult (age not specified)	Intensive glycaemic control	Standard glycaemic control	Decline by 3 points or more on Mini Mental State Examination (1 study)	NR	No effect of intervention

Abbreviations: RCT – Randomised controlled trial; SR – systematic review; NR – not reported in abstract; CKD – chronic kidney disease

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