Appendix A1: Summary of evidence from surveillance

2019 surveillance of Type 1 diabetes in adults: diagnosis and management (2015) NICE guideline NG17

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Evidence considered in surveillance

Search and selection strategy
We searched for new evidence related to the whole guideline.

We found 81 studies in a search for randomised controlled trials and Cochrane reviews published between 1 June 2014 and 7 December 2018.

We also included 5 studies identified in comments received during consultation on the 2019 surveillance review.

From all sources, we considered 86 studies to be relevant to the guideline.

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 strategies were taken to ensure only relevant studies were selected:

- Studies with a sample size lower than 50 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.
- Pilot or proof-of-concept studies were excluded.
- Single studies already included in a Cochrane review were excluded.
Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 8 studies 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:

- **Effectiveness of multimodal imaging for the evaluation of retinal oedema and new vessels in diabetic retinopathy**
- **Circulating biomarkers to detect sight-threatening diabetic retinopathy**
- **A comparison of standard laser with micropulse laser for the treatment of diabetic macular oedema**
- **DAFNEplus cluster randomised controlled trial**
- **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**
- **Masked performance check of the Abbott FreeStyle Libre Flash Glucose Monitoring System.**
- **Closing the Loop in Adults With Sub-optimally Controlled Type 1 Diabetes Under Free Living Conditions (AP@home04).**
- **Home Testing of Day and Night Closed Loop With Pump Suspend Feature (APCam11).**

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 the guideline.

We sent questionnaires to 20 topic experts and received 6 responses. The topic experts were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty.

Topic experts highlighted new evidence in relation to the following areas identified for update: smartphone applications and online platforms, flash glucose monitoring, insulin therapy, SGLT2 inhibitors. See [summary of evidence](#) from surveillance below.

In addition, one expert called for more guidance around CVD risk assessment in type 1 diabetes; this is being considered in the update of the NICE guideline on [lipid modification](#) and we will assess impact when it is published.
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.

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.

A full list of guideline recommendations can be found on the website at the following link: https://www.nice.org.uk/guidance/ng17

1.1 Diagnosis and early care plan

Surveillance proposal

This section of the guideline should be updated.

2019 surveillance summary

Diagnosing monogenic diabetes

An observational study (1) (n = 1407) examined the diagnostic accuracy of a biomarker-based screening pathway for detecting monogenic diabetes. Participants were diagnosed with type 1 diabetes at age 30 years or younger, and were younger than 50 years at the time of the study. The pathway included 3 stages: 1) Assessment of endogenous insulin secretion using urinary C-peptide/creatinine ratio (UCPCR); 2) if UCPCR was ≥0.2 nmol/mmol, measurement of GAD and IA2 islet autoantibodies; and 3) if negative for both autoantibodies, molecular genetic diagnostic testing for 35 monogenic diabetes subtypes. The results showed that an extra 17 cases of monogenic diabetes were confirmed in the study population using this pathway. The positive and negative predictive values of the screening pathway were 20% and 99.9% respectively.
Distinguishing between type 1 and type 2 diabetes

A cross-sectional analysis of the UK biobank population (2) (n = 379, 511) was identified which examined the frequency and phenotype of type 1 diabetes resulting from high genetic susceptibility in the first 6 decades of life. Findings indicate that genetically defined cases of type 1 diabetes were distributed across all ages. The clinical characteristics of type 1 diabetes for the group diagnosed after 30 years were similar to the group diagnosed when aged 30 years or younger. Individuals in both groups had a significantly lower BMI, significantly more likely to progress to insulin treatment, and were at significantly increased risk of diabetic ketoacidosis compared with participants with assumed type 2 diabetes.

An observational study (3) (n = 583) examined the prevalence and characteristics of type 1 diabetes after the age of 30 (late onset) and assessed whether these individuals are identified as having type 1 diabetes in practice. Type 1 diabetes in this case was defined as a development of severe endogenous insulin deficiency. Results indicated that people with late onset type 1 diabetes had similar clinical characteristics to those with young-onset type 1 diabetes. However, people with late-onset type 1 diabetes had a significantly higher islet autoantibody prevalence and were significantly less likely to be identified as having type 1 diabetes.

A systematic review (4) of 11 studies examined which clinical criteria could be used to discriminate type 1 and type 2 diabetes. Results indicated that age at diagnosis and time to insulin treatment were the most discriminatory criteria. Furthermore, BMI was found to add little to these two criteria.

An observational study (5) (n = 601) examined the diagnostic accuracy of the criteria in the Royal College of General Practitioners' (RCGP) UK Practical Classification Guidelines for Diabetes compared to the reference standard defined as "continuous insulin treatment within 3 years of diagnosis and absolute insulin deficiency (Urinary C-peptide creatinine ratio <0.2 nmol/mmol ≥5 years post-diagnosis)". The RCGP guideline uses age at diagnosis (less than 35 years) and time to commencing insulin treatment from diagnosis (at diagnosis or within 6 months afterwards) as its diagnostic criteria for type 1 diabetes. Results indicated that the RCGP’s criteria correctly classified 86% of participants, with 87 people being misclassified, when compared to the reference standard. Time to insulin and age at diagnosis performed best in predicting long-term endogenous insulin production (ROC AUC = 0.904 and 0.871); BMI was a less strong predictor of diabetes type (AUC = 0.824).

Intelligence gathering

One stakeholder highlighted new evidence on the diagnosis of type 1 diabetes using the C-peptide test. They noted that the new evidence showed that misclassification of late-onset diabetes is relatively common and that clinical criteria for diagnosis do not perform as well as C-peptide tests. They also noted that C-peptide testing is relatively cheap and can be used on a single non-fasting random blood or urine sample after people’s own meals, demonstrating ease of use.
Impact statement

Diagnosing monogenic diabetes

New evidence was identified to suggest that a 3-stage biomarker-based pathway may be beneficial in identifying people with monogenic diabetes, however the positive predictive value of the pathway is notably low. The negative predictive value is high (99.9%), however this is likely to be due to the low prevalence of monogenic diabetes in the population. Currently, the guideline only advises considering C peptide and/or diabetes-specific autoantibody titres if there are either atypical features in the presentation, clinical suspicion of monogenic diabetes, or classification is uncertain (recommendation 1.1.4). The study findings are limited by the small numbers of people with monogenic diabetes which limits the ability to evaluate diagnostic sensitivity. Furthermore, evidence reviewed during guideline development suggests that the C-peptide test has better discriminative value the longer the test is done after diagnosis, whereas the antibody test may be more effective at the time of diagnosis. The new evidence recommends using the tests at the same point in time, which is not supported by the large body of evidence considered during guideline development. As such, the guideline recommendations are unlikely to be impacted by the results of this study.

New evidence is unlikely to change guideline recommendations.

Distinguishing between type 1 and type 2 diabetes

New evidence was identified at stakeholder consultation to suggest that people with late-onset type 1 diabetes may be at risk of misclassifications and that clinical characteristics like BMI (currently mentioned in recommendation 1.1.1) may not be as accurate as C-peptide tests when distinguishing between diabetes types in people aged over 35 years. Stakeholders also highlighted the low cost of C-peptide testing and noted that it can be used on a single non-fasting random blood or urine sample after people’s own meals, demonstrating ease of use.

During the development of the original guideline, the committee noted that more evidence is required on the use and timing of urine C-peptide and urine C-peptide/creatine ratios before any further recommendations could be made on their use. They also added a research recommendation in this area (see research recommendations below). As the new evidence sheds some light on the risk of misclassification of late-onset type 1 diabetes, the limits of the clinical criteria currently listed in recommendation 1.1.1 and the benefits of using C-peptide tests, we propose that this area is reviewed.

New evidence identified that may change current recommendations.
1.2 Support and individualised care

Surveillance proposal
No new information was identified.
This section of the guideline should not be updated.

1.3 Education and information

Surveillance proposal
This section of the guideline should not be updated.

2019 surveillance summary
One randomised controlled trial (RCT) was identified on a training programme to enhance self-management skills in type 1 diabetes (table 1). A guided self-determination intervention (delivered by group training) was found to have no effect on HbA1c levels compared to care as usual but did significantly improve diabetes distress scores after 9 months. (6) (n = 178).

Intelligence gathering
A topic expert noted that there have been advances in online platforms, which could be offered as an alternative to the current structured education programmes referenced in the guideline.

An ongoing trial (DAFNEplus) was identified which is examining the effect of a 5-day training course for healthy eating in adults with type 1 diabetes. We have added the trial to our event tracker and will assess the impact of the results when they are available.

Impact statement
Evidence was identified to suggest that a guided self-determination intervention had no effect on HbA1c levels compared to care as usual. This is consistent with the guideline, which does not make any recommendations on self-determination interventions. Ongoing research was identified on the DAFNE trial, which the guideline currently recommends (recommendation 1.3.1). We will assess the impact of these results when they are available.

New evidence is unlikely to change guideline recommendations.
1.4 Dietary management

Surveillance proposal
This section of the guideline should not be updated.

2019 surveillance summary
We identified 1 RCT (7) \((n = 168)\) on dietary management interventions. The results indicate that carbohydrate counting with an automated bolus calculator (to estimate insulin requirements outside of meal-times) is more effective than mental calculations in lowering HbA1c levels (table 2).

Intelligence gathering
No intelligence was identified for this section of the guideline.

Impact statement
New evidence was identified to support the use of an automated bolus calculator in carbohydrate calculating compared to mental calculations. During guideline development, the committee noted that bolus calculators (to estimate one-off insulin requirements at meal-times) can be a useful addition to a patient’s own carbohydrate counting. However, they also highlighted that a bolus calculator’s effectiveness relies on carefully adjusted settings, ratios and blood glucose targets, and ability to carbohydrate count accurately. They noted that these are usually established with the help of skills learned in structured education, or in intensive one-to-one consultation with a suitably trained healthcare professional. As such, recommendations 1.4.1 and 1.4.2 advise carbohydrate counting training for adults with type 1 diabetes as part of structured education programmes (which may or may not cover the use of a bolus calculator). Therefore, no impact on the guideline is expected.

New evidence is unlikely to change guideline recommendations.

1.5 Physical activity

Surveillance proposal
No new information was identified.

This section of the guideline should not be updated.
1.6 Blood glucose management

Surveillance proposal
This section of the guideline should be updated.

2019 surveillance summary

Telemedicine
One Cochrane review and 3 RCTs were identified which examined the effect of telemedicine interventions on blood glucose management (table 3).

The Cochrane review (8) included 93 trials (n = 22,047) which examined the effectiveness, acceptability and costs of interactive telemedicine as an alternative to, or in addition to, usual care (i.e. face-to-face care, or telephone consultation). Telemedicine in this circumstance was defined as “the use of telecommunication systems to deliver health care at a distance”. For the purposes of this surveillance review, only the impact on diabetes outcomes are summarised (16 studies; n = 2768). The telemedicine interventions included in these studies mainly consisted of remote monitoring devices that sent data to clinicians to review. Usually the remote monitoring was accompanied by additional education (delivered remotely) and/or a teleconference with the clinician. Results indicated that telemedicine was associated with significantly lower HbA1c levels at 9 months follow-up. Cholesterol and blood pressure were also found to significantly lower in people allocated to telemedicine interventions.

Later trials show more mixed results on telemedicine. An internet-based telematic system was found to be no different from face-to-face sessions in terms of the effect on HbA1c levels. The intervention required significantly less time investment from healthcare professionals (9) (n = 154). In contrast, one study in young adults found telemedicine to have no significant impact on HbA1c levels, self-monitoring compliance and quality of life, compared to standard glucose self-monitoring after 6 months (10) (n = 182).

Smart phone applications and online platforms
Results from one trial indicated that a smartphone application for self-monitoring was found to significantly reduce HbA1c levels compared to usual care after 3 months (11) (n = 100) (table 3).

Flash glucose monitoring
The IMPACT trial examined the effect of Flash glucose monitoring in people with well-controlled type 1 diabetes, compared to standard self-monitoring of capillary blood glucose (table 3). One study found that Flash glucose monitoring significantly reduced the time spent in hypoglycaemia (<3.9 mmol/L [70 mg/dL]), compared to standard monitoring (12) (n = 241). This effect was also found in adults using multiple daily injections insulin therapy (13) (n = 167).
Continuous glucose monitoring (CGM)

We identified evidence from 4 trials examining the use of CGM (table 3).

Both the DIAMOND and GOLD trials examined the effect of CGM in people who had suboptimal control of their diabetes and took multiple daily injections of insulin, compared to usual care (not specified in the abstracts). Results from both trials suggest that CGM significantly reduced HbA1c levels compared to usual care (14,15) (DIAMOND, n = 158; GOLD, n = 161). Further analyses found that the diabetes distress score (16) (DIAMOND, n = 158) and frequency of hypoglycaemic events (17) (DIAMOND, n = 158) were also improved with CGM compared to usual care.

Both the HypoDE and HypoCOMPaSS trials examined the effect of CGM on people who took multiple daily injections and had a history of impaired hypoglycaemia awareness or experienced severe hypoglycaemia in the previous year. Compared to self-monitoring of capillary blood glucose, CGM was found to significantly reduce the number of hypoglycaemic events at 26 weeks follow-up (18) (HypoDE, n = 149). However, another trial found there was no effect of CGM on hypoglycaemia awareness after 24 weeks (19) or at 2-year follow-up (20) (both HypoCOMPaSS, n = 96).

Intelligence gathering

Telemedicine

A key priority in the NHS Long Term Plan is the move to deliver more digitally-enabled care. It states that over the next 5 years, every patient will be able to access a GP digitally, and where appropriate, opt for a ‘virtual’ outpatient appointment. There is also mention of the NHS App which will link health records and have the potential to offer a ‘digital triage’ to help people find the most appropriate care. Virtual clinics are also discussed, as well as triaging for specialist referrals with the use of photographs and online questionnaires reviewed by a healthcare professional.

Smartphone applications and online platforms

A topic expert suggested that online platforms for education and self-management may be considered a suitable alternative to structured education programmes currently referenced in the guideline. In addition, the NHS England Test Bed programme brings NHS organisations and industry partners together to test combinations of digital technologies with pathway redesign in real-world settings. The programme has specific projects on diabetes (e.g. Diabetes Digital Coach) which are currently testing various digital platforms aimed to enhance self-management. There are no published findings yet available from this work, however the NHS Long Term Plan does mention expanding the NHS Test Bed programme as one its objectives.

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. This policy will be rolled out from April 2019 and is expected to address the regional variation in Freestyle Libre availability that some patients are experiencing. The eligibility criteria for this technology are detailed in a recent statement from NHS England. The criteria for eligibility include: people who are clinically indicated as requiring intensive monitoring (more than 8 times a day); people unable to self-monitor; those with recurrent severe hypoglycaemia (if they have ruled out other options recommended in NICE guideline NG17); as well as other criteria listed in the statement.

One of the trials (12) identified in this surveillance review has already been considered in the NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110). Whereas the rest of the evidence considered in the medtech innovation briefing was in people with type 2 diabetes or pregnant women with diabetes, so not relevant to NICE guideline NG17.

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 from April 2019, the formulation of the adhesive will be revised.

Topic experts also noted the change in policy around Freestyle Libre and highlighted the significant cost pressures that this may add to the NHS, calling for the guideline to be reviewed in this area.

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 when they are available.

CGM

Many stakeholders noted the importance of the GOLD and DIAMOND trials on the use of CGM. In light of the new evidence, they called for this to be offered as treatment option for those with sub-optimal glucose control (as well as those with hypoglycaemia problems).

Impact statement

Telemedicine

Evidence from a Cochrane review suggests that telemedicine interventions, such as remote monitoring devices linked to health records, online software for education and teleconferences with a clinician improve blood glucose management. Evidence published after the review is mostly consistent with these findings, with a smartphone application appearing to improve HbA1c levels and an internet-based telematic intervention was found to be as effective as face-to-face sessions with a healthcare professional in terms of HbA1c levels. Although one trial was identified which found no difference in HbA1c levels, self-monitoring compliance and quality of life, from a policy perspective, digital interventions that enable care to be delivered remotely feature heavily in the NHS Long-Term Plan. Currently
the guideline only mentions structured education as a way of empowering people to self-monitor (recommendation 1.6.16). Taken together, most of the evidence suggests there may be a benefit of telemedicine interventions in improving blood glucose management, which is consistent with the NHS Long Term Plan. Therefore, it is proposed that this area is reviewed.

New evidence identified that may change current recommendations.

**Smartphone applications and online platforms**

One study was identified to support the use of a smartphone application to enhance self-monitoring. This area relates to the diabetes work running in the NHS England Test Bed programme, where digital platforms are being evaluated in real-world settings to enhance self-management. There are no published findings yet available from this work, however the NHS Long Term Plan does mention expanding the NHS Test Bed programme as one its objectives. A topic expert also raised this as an area that is in need of review. Considering the ongoing work in this area and the importance of digital platforms emphasised in the NHS Long-Term Plan, it is proposed that this area is reviewed.

New evidence identified that may change current recommendations.

**Flash glucose monitoring**

New evidence was identified on the use of Flash glucose monitoring in people with well-controlled type 1 diabetes. Time spent in hypoglycaemia was significantly reduced with Flash glucose monitoring compared to standard self-monitoring of capillary blood glucose. This evidence relates to a recent policy change, which states that from April 2019, Freestyle Libre (a Flash glucose monitoring device) should be made available to patients on the NHS in England if they meet certain criteria. The NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110) emphasises all evidence (at the time of publication in 2017) was 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 shed more light on the long-term effectiveness of Freestyle Libre in patients with type 1 diabetes. We will review these results and assess impact on the guideline as soon as they are published. In the meantime, it is proposed that this area is reviewed to take into account the change in policy and the new evidence published since the release of the NICE medtech innovation briefing MIB110.

New evidence identified that may change current recommendations.

**CGM**

We identified new evidence which supports the use of CGM in people having multiple daily injection therapy, with and without impaired hypoglycaemia awareness or history of severe
hypoglycaemia, and in people with sub-optimal glucose control. The guideline currently recommends offering CGM only to adults with complete loss of hypoglycaemia awareness or history of severe hypoglycaemia (recommendation 1.6.22). Many stakeholders raised concerns in this area, calling for CGM eligibility criteria to be reconsidered in light of the new evidence. Given this feedback and the new evidence which suggests CGM could also benefit people with sub-optimal glucose control, we propose that this area is reviewed.

New evidence identified that may impact on the guideline.

1.7 Insulin therapy

Surveillance proposal
This section of the guideline should be updated.

2019 surveillance summary

Insulin therapy
We identified 1 Cochrane review and 15 RCTs comparing different insulin types and dosages (table 4).

We also identified evidence on insulin peglispro (21,22), however as this drug does not currently have a license to be used in the UK this evidence has not been considered in this surveillance review.

Insulin analogues compared to human insulins
A Cochrane review (23) of 9 studies (n = 2693) examined the effects of short-acting insulin analogues (such as insulin lispro, insulin aspart and insulin glulisine) compared to regular human insulin. Results indicated that HbA1c levels were significantly lower in the insulin analogue group but there was no significant difference between groups for the risk of severe hypoglycaemia. A further study in people with recurrent severe hypoglycaemia found insulin analogues (detemir/aspart) to significantly reduce the number of severe hypoglycaemic episodes, compared to human insulin (24) (n = 159).

Long-acting insulins
Two trials (25,26) found that insulin degludec, an ultra-long-lasting insulin, may be superior to insulin glargine in terms of glucose-lowering effect (25) (n = 57) and hypoglycaemia outcomes (26) (n = 501). Insulin degludec was also found to be non-inferior to insulin detemir for changes to HbA1c levels (27) (n = 455).
Biosimilar insulins

Four biosimilar insulins were found to be non-inferior to the original formation, including SAR342434 (lispro) (28), LY296316 (glargine) (29), MK-1293 (glargine) (30), MYL-1501D (glargine) (31) for changes to HbA1c levels.

Rapid acting insulins

Results from the ONSET trials indicated that a faster-acting version of insulin aspart was non-inferior to conventional insulin aspart at 26 weeks ((32) n = 1143; (33) n = 1024) but superior at 52 weeks (34) n = 381 for HbA1c levels. The same non-inferiority effect of faster-acting aspart was also found when delivered via a continuous subcutaneous insulin infusion (CSII), (35) (n = 472).

Dose comparisons

Results from the EDITION trial indicated that a higher dose of insulin glargine (300 units/ml) was non-inferior to a lower dose (100 units/ml) ((36) n = 243 (37) n = 549) in terms of HbA1c levels. However, a higher dose significantly reduced the rate of confirmed severe hypoglycaemic events ((38) n = 243).

Continuous subcutaneous insulin infusion or insulin pump therapy

Four studies (19,39–41) were identified which examined the effect of insulin pump therapy in adults with type 1 diabetes. These studies relate to the NICE technology appraisal guidance on continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (NICE technology appraisal guidance 151) and will not be considered in this surveillance review.

Adjuncts to insulin

We identified 13 RCTs examining the effect of adjunctive treatment alongside insulin in type 1 diabetes (table 4). The following studies relate to NICE technology appraisal guidance in development and will not be considered in this surveillance review:

- Three studies on sotagliflozin (42-44) (GID-TA10376)
- Three studies on empagliflozin (45–47) (GID-TA10375)
- Three studies on dapagliflozin (48–50)(GID-TA10374)

Results from one RCT (51) (n = 351) indicated that adjunctive treatment with canagliflozin significantly improved HbA1c levels and body weight compared to placebo.

Results from the ADJUNCT trials show adjunctive treatment with liraglutide significantly improved HbA1c levels and body weight compared to placebo after 26 weeks (52) (n =835) and 1 year (53) (n = 1398). For a subset of overweight participants with insufficient glycaemic control, there was no effect of liraglutide on HbA1c levels but there were significantly fewer hypoglycaemic events compared to placebo (54) (n = 100).

We also identified evidence on Subetta (55) as an add-on to insulin therapy, however as this drug does not currently have a license to be used in the UK this evidence has not been considered in this surveillance review.
Intelligence gathering

Many topic experts highlighted that new insulins have become available since the guideline was published. They advised that as many have different pharmacological features, such as ultra-long lasting and fast-acting, there are now more options available in insulin therapy that should be considered in the guideline. The increased availability of biosimilar insulins was also raised as an area to review as these are cheaper versions of the insulins currently recommended in the guideline.

An expert also noted that the guideline may need to be reviewed to consider the place of sodium-glucose cotransporter 2 (SGLT2) inhibitors in the treatment of type 1 diabetes.

A drug safety update was identified relating to high-strength, fixed-combination and biosimilar insulin products. This gives an overview of the new insulin products available and advises on ways to minimise the risk of medication errors.

Another drug safety update was identified which highlights the potential association between the use of SGLT2 inhibitors and Fournier’s gangrene (necrotising fasciitis of the genitalia or perineum) in people with type 2 diabetes. The report advises that treatment with SGLT2 inhibitors should be stopped if Fournier’s gangrene is suspected. It also states that warnings about Fournier’s gangrene will be added to the product information for all SGLT2 inhibitors and a letter has been sent to advise healthcare professionals of the risk.

Impact statement

Insulin therapy

Insulin analogues compared to human insulins

A Cochrane review and a further trial were identified which support the use of short-acting insulin analogues over human insulin. This is consistent with the guideline, which currently recommends offering rapid-acting insulin analogues before meals (recommendation 1.7.7) and has no recommendations on human insulin use. Therefore, no impact on the guideline is expected.

New evidence is unlikely to change guideline recommendations.

Long-acting insulin

Evidence was identified which supports the use of the ultra-long-lasting insulin degludec. This was also an area raised by topic experts, who highlighted that the evidence on new insulins needs reviewing. Whilst the original guideline committee noted that how insulins are used is more important than which specific insulin within class is used, there are still recommendations offering insulin detemir or insulin glargine in adults with type 1 diabetes (recommendation 1.7.4). In light of expert advice and the new evidence supporting ultra-long-lasting insulin, we propose this area is reviewed. The safety profiles and dosage conversions will also need careful consideration, given the advice in the corresponding drug safety update.
New evidence identified that may change current recommendations.

**Biosimilar insulins**

Evidence was identified to suggest that various biosimilar insulins may be non-inferior to original insulin formulations such as lispro and glargine. The guideline currently recommends offering insulin detemir or insulin glargine in adults with type 1 diabetes (recommendation 1.7.4). This was also an area highlighted by topic experts, who highlighted the potential cost savings available when switching to cheaper (but clinically comparable) insulins. Furthermore, recommendation 1.7.5 currently states “When choosing an alternative insulin regimen, take account of the person’s preferences and acquisition cost” which reinforces the need to review cheaper alternatives. It is proposed that this area is reviewed to consider the various biosimilar insulins now available.

New evidence identified that may change current recommendations.

**Rapid-acting insulin**

Results from one trial indicated that a faster-acting version of insulin aspart was non-inferior in the short term and superior in the long term to conventional insulin aspart. The guideline does not currently recommend using a particular type of rapid-acting insulin (recommendations 1.7.7-1.7.9), therefore it is unlikely that the guideline will be impacted.

New evidence is unlikely to change guideline recommendations.

**Dose comparisons**

Results from one trial suggest there may be some benefit to offering a higher dose of insulin glargine to improve hypoglycaemia outcomes. The guideline does not currently make any recommendations on dosage amounts, under the assumption that other NICE evidence sources (such as the British National Formulary) are up-to-date and can be used for such queries. Therefore, no impact on the guideline is expected.

New evidence is unlikely to change guideline recommendations.

**Adjuncts to insulin**

We identified several trials examining the effect of SGLT2 inhibitors as an adjunct to insulin therapy. Topic experts also highlighted this as a possible area for update, given the rise in research for this population. Many of the studies were related to NICE technology appraisals currently in development, so cannot be considered in this surveillance review. However, there was some evidence to suggest that canagliflozin significantly improved HbA1c levels and body weight compared to placebo. Canagliflozin is a SGLT2 Inhibitor currently licensed for use in type 2 (but not type 1) diabetes. Given that the guideline does not currently have any recommendations on offering SGLT2 inhibitors, we propose that the impact of the NICE technology appraisals is assessed when the decisions are finalised. However, careful
consideration will need to be given to the indication of adjunct therapy with SGLT2 inhibitors, whether this be glycaemic control, weight-loss or cardiovascular outcomes. The drug safety update should also be considered in the update, which highlights an association of SGLT2 inhibitors with Fournier's gangrene when used in type 2 diabetes.

Results from one trial suggest that adjunctive treatment with liraglutide may improve HbA1c levels and reduce body weight. However, the effect on HbA1c levels was not found in a subset of overweight participants with insufficient glycaemic control, despite improvement in hypoglycaemia outcomes. Liraglutide is a GLP-1 agonist currently licensed for use in type 2 diabetes. The guideline currently recommends adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m² or above and wants to improve their blood glucose control whilst minimising their effective insulin dose (recommendation 1.7.14). Given the lack of benefit of liraglutide on overweight adults with type 1 diabetes, the guideline is unlikely to be affected at this point.

**New evidence identified that may change current recommendations.**

1.8 **Insulin delivery**

**Surveillance proposal**

No new information was identified.

This section of the guideline should not be updated.

1.9 **Referral for islet or pancreas transplantation**

**Surveillance proposal**

No new information was identified.

This section of the guideline should not be updated.

1.10 **Awareness and management of hypoglycaemia**

**Surveillance proposal**

No new information was identified.
1.11 **Ketone monitoring and management of diabetic ketoacidosis (DKA)**

**Surveillance proposal**

No new information was identified.

This section of the guideline should not be updated.

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1.12 **Associated illness**

**Surveillance proposal**

No new information was identified.

This section of the guideline should not be updated.

**Editorial amendments**

**Recommendation 1.12.1:** This recommendation currently advises that markers for coeliac disease should be assessed in people with type 1 diabetes who have a low BMI or unexplained weight loss. However, NICE guideline NG20 advises that serological testing for coeliac disease should be offered for all people with type 1 diabetes at the point of diagnosis. To address this discrepancy, recommendation 1.12.1 should be amended accordingly.

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1.13 **Control of cardiovascular risk**

**Surveillance proposal**

This section of the guideline should not be updated.

**2019 surveillance summary**

We identified 3 reports of 2 trials which examined different interventions to control cardiovascular disease (CVD) risk in type 1 diabetes (table 5).

One analysis of the ASCEND trial (56) (n = 15480) found that taking daily aspirin appeared to prevent serious vascular events in people who had diabetes and no evident CVD at the time.
of trial entry. However, major bleeding events were significantly more common with aspirin compared to placebo. In the same trial, another analysis (57) (n = 15,480) found no effect of n-3 fatty acid supplementation on cardiovascular events over an average of 7.4 years, compared to an olive oil control.

One RCT (58) (n = 4732) found achieving a target systolic blood pressure of less than 120mmHg does not appear to mitigate risk of major adverse cardiovascular events whereas between 120-140mmHg does significantly reduce risk.

**Intelligence gathering**

A topic expert noted that further guidance on the cardiovascular risk assessment may be needed, particularly for younger adults with type 1 diabetes as the guidance advice on statins and angiotensin-converting-enzyme inhibitors is not appropriate for women of childbearing age.

**Impact statement**

Results from the ASCEND trial indicate that daily aspirin may prevent serious vascular events in people with type 1 diabetes and no current CVD, however aspirin also increased serious bleeding events. The guideline currently states “Do not offer aspirin for the primary prevention of cardiovascular disease to adults with type 1 diabetes” (recommendation 1.13.1). During guideline development, there was little evidence in this population however the committee noted that guidance from the MHRA suggests that the harms of aspirin for primary prevention outweigh the benefits. As mentioned in the study, the absolute benefits of aspirin in this case are largely counterbalanced by the bleeding hazard. Therefore, it is unlikely that the new evidence will impact the guideline. The guideline does contain other recommendations for the primary prevention of CVD, including recommendations on smoking cessation, lipid modification and lifestyle changes.

A topic expert highlighted the need for further guidance on cardiovascular risk assessment. Currently the guideline sign-posts to the NICE guideline on lipid modification for advice on tools for assessing risk of CVD in adults with type 1 diabetes (recommendation 1.13.3). The NICE guideline on lipid modification is currently undergoing update in the area of CVD risk assessment, following recent surveillance which identified new evidence on the QRISK3 tool to identify and assess CVD risk in people with type 1 diabetes. We will review this area and assess impact on NICE guideline NG17 once this evidence has been considered and the update has been published.

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New evidence is unlikely to change guideline recommendations.
1.14 Care of adults with type 1 diabetes in hospital

Surveillance proposal
This section of the guideline should not be updated.

2019 surveillance summary
A Cochrane review of 8 studies (59) (n = 1048) examined the effects of sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus (table 6). 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 authors concluded that the evidence was insufficient to draw any conclusions on the most effective insulin strategy in this population.

Intelligence gathering
No intelligence was identified for this section of the guideline.

Impact statement
We identified evidence that suggest basal-bolus insulin might result in better short-term glycaemic control but could increase the risk for severe hypoglycaemic episodes, compared to sliding scale insulin. The guideline currently recommends using the basal-bolus strategy (see recommendation 1.14.4). As the new evidence was inconclusive about which insulin strategy has the best patient outcomes, further research is required before any impact on the guideline can be assessed.

New evidence is unlikely to change guideline recommendations.

1.15 Managing complications

Surveillance proposal
This section of the guideline should be updated.

Editorial amendments
● Recommendation 1.15.43: The hyperlink to NG69 needs updating to link to the latest version of the guideline.
● **Recommendation 1.15.42**: The cross referral to NICE guideline CG113 should be changed to the most recent title: “Generalised anxiety disorder and panic disorder in adults: management”.

● Recommendations on screening and referral for diabetic eye disease should be withdrawn and replaced with a cross-referral to the NHS Diabetic Eye Screening Programme.

### 2019 surveillance summary

**Eye disease**

We identified 2 Cochrane reviews and 3 RCTs on interventions to manage eye disease in type 1 diabetes (table 7). Two Cochrane reviews (60,61) and 5 RCTs (62–66) focussed on the use of anti-vascular endothelial growth factor (anti-VEGF) for diabetic macular oedema which relate to the NICE technology appraisal guidance on Ranibizumab for treating diabetic macular oedema (TA274). Therefore, these studies will not be considered in this surveillance review.

**Treatment of proliferative diabetic retinopathy**

A Cochrane review (67) of 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) significantly improved visual acuity compared to no anti-VEGF treatment. Any anti-VEGF treatment was also associated with significantly reduced risk of vitreous or preretinal 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 (68) (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.

Evidence was identified on the use of sulodexide in patients with non-proliferative diabetic retinopathy (69), however as this drug does not currently have a license to be used in the UK this evidence has not been considered in this surveillance review.

**Treatment of diabetic macular oedema**

A Cochrane review (70) 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.

One RCT (71) (n = 125) found that compared to placebo, there was no effect of topical nepafenac on change in optical coherence tomography retinal volume.
Diabetic kidney disease

A Cochrane review of 44 studies (72) (128 records, 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 (table 7). Studies were identified examining the following interventions: 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 cardiovascular 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 cardiovascular death and weight. Compared to placebo, GLP-1 agonists may significantly reduce HbA1c. The evidence on glitazones was uncertain and no conclusions could be drawn.

A long-term follow-up study of the Diabetes Control and Complications Trial (DCCT) (73) (n = 1441) found that intensive treatment (involving target levels of glycaemia as close to non-diabetic range as safely possible) significantly reduced the risk of developing albuminuria after 18 years.

Chronic painful neuropathy

We identified 3 studies related to diabetic peripheral neuropathic pain (table 7). One RCT (74) (n = 303) found that duloxetine is non-inferior to pregabalin in lowering average pain scores in people with diabetic peripheral neuropathic pain. Another trial (75) (n = 270) found that there was no difference in pain scores in people treated with gabapentin or pregabalin. However, an additional RCT (76) (n = 620) found that, compared to placebo, there was no effect of pregabalin on average pain scores for people with painful diabetic peripheral neuropathy.

Evidence was also identified on the use of mirogabalin (77), however as this drug does not currently have a license to be used in the UK, this evidence has not been considered in this surveillance review.

Gastroparesis

We identified 1 RCT (78) (n = 56) which found a small particle size diet to significantly reduce gastroparetic symptoms compared to a control diet in adults with gastroparesis. Another study (79) (n = 89) found that metoclopramide nasal spray was more effective at symptom control than metoclopramide in oral tablet form (table 7).

Evidence was also identified on the use of Relamorelin (80), however as this drug does not currently have a license to be used in the UK this evidence has not been considered in this surveillance review.

Psychological problems

We identified 2 studies examining interventions to treat psychological problems in adults with type 1 diabetes (table 7). One RCT (81) (n = 94) found that both mindfulness-based cognitive behaviour therapy (CBT) and regular CBT significantly reduced depression.
compared to no treatment. Another study (82) (n = 200) found that a self-management intervention significantly reduced depressive symptoms in people with serious mental illness and diabetes, compared to usual care.

**Intelligence gathering**

One topic expert noted that there is new evidence on the optimum screening strategy for retinopathy in type 1 diabetes.

We were also made aware of restrictions in the use of SGLT-2 inhibitors in people with impaired renal function. For example, the summary of product characteristics for dapagliflozin advises that it should not be initiated in patients with a glomerular filtration rate [GFR] < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min.

We also identified several ongoing trials relevant to this section of the guideline which are detailed below:

- **Effectiveness of multimodal imaging for the evaluation of retinal oedema and new vessels in diabetic retinopathy**
- **Circulating biomarkers to detect sight-threatening diabetic retinopathy**
- **A comparison of standard laser with micropulse laser for the treatment of diabetic macular oedema**
- **Lowering Events in Non-proliferative retinopathy in Scotland**

These trials are being tracked and we will assess the impact of the results when they are published.

**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. The guideline currently only has recommendations on screening for diabetic retinopathy and referral criteria. During original guideline development, the committee only considered evidence on non-surgical treatment for diabetic retinopathy (which excludes the use of injections). Given the growing evidence base in this area and the related NICE technology appraisal guidance on treatments for diabetic macular oedema, we propose that this area is reviewed.

Topic experts also highlighted new evidence on the optimum frequency of screening for diabetic retinopathy. This area was not considered in the surveillance review because it 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. In response to stakeholder
concerns about losing this information, we will add in a cross referral to the screening programme so that this guidance can be more easily referred to.

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.

Diabetic kidney disease

New evidence was identified to support the use of glucose-lowering agents (SGLT2 inhibitors, DPP-4 inhibitors and GLP-1 agonists) in people with diabetes and chronic kidney disease. The guideline currently sign-posts to the NICE guideline on chronic kidney disease however it does not contain any recommendations on glucose-lowering agents for this population. The new evidence seems to suggest that SGLT2 could be effective in managing blood glucose levels in people with chronic kidney disease. However, the Cochrane review notes that the safety aspects of these treatments are uncertain and expert advice warns of the restrictions in using dapagliflozin in people with chronic kidney disease. Until there is further evidence on the safety of glucose-lowering agents in adults with diabetes and chronic kidney disease, it is unlikely that the guideline will be affected.

We identified evidence from a large long-term trial (DCCT) supporting the use of intensive diabetes treatment (with glycaemia targets) significantly reduced the risk of developing albuminuria at 18-year follow-up. The guideline currently recommends "Support adults with type 1 diabetes to aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications" (recommendation 1.6.6). During guideline development, the committee acknowledged the importance of the DCCT data as a large RCT of intensified therapy. After considering the results, they selected a target HbA1c value that is lower than the achieved HbA1c of the DCCT, recognising that achieving the value of 7%, as done in the DCCT, was more likely if the target was set lower than this. The new evidence supports the continued use of this target and therefore it is unlikely to impact recommendations.
New evidence is unlikely to change guideline recommendations.

**Chronic painful neuropathy**

We identified mixed evidence on the use of duloxetine, gabapentin and pregabalin for people with diabetic peripheral neuropathic pain. The guideline does not have any recommendations on pharmacological treatments for neuropathic pain, however it does signpost to the NICE guideline on neuropathic pain – pharmacological management (NICE guideline CG173) which recommends a choice of duloxetine, gabapentin or pregabalin as an initial treatment (recommendation 1.1.8). Whilst two of the identified trials were consistent with this recommendation, the third study found no effect of pregabalin on pain scores. Until further evidence is identified to confirm these findings, no impact is expected at this point.

New evidence is unlikely to change guideline recommendations.

**Gastroparesis**

We identified evidence supporting the adoption of a small particle size diet for people with diabetes and gastroparesis. This is in line with recommendation 1.15.25 in the guideline which states “Advise a small-particle-size diet (mashed or pureed food) for symptomatic relief for adults with type 1 diabetes who have vomiting caused by gastroparesis”. Evidence was also identified to suggest that metoclopramide as a nasal spray is more effective than oral tablets at controlling symptoms. The guideline does not currently have any recommendations on the use of metoclopramide for gastroparesis. Until there is further evidence in this area, the guideline will not be affected.

New evidence is unlikely to change guideline recommendations.

**Psychological problems**

We identified evidence to support the use of standard CBT, mindfulness-based CBT and a self-determination intervention in adults with diabetes and psychological problems. The guideline does not currently make any recommendations on interventions in this group, instead signposting to NICE guidelines on common mental health disorders, generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults and depression in adults with a chronic health problem. The new evidence is in line with the advice in these guidelines so no impact is expected.

New evidence is unlikely to change guideline recommendations.
Areas not currently covered in the guideline

In surveillance, evidence was identified for areas not covered by the guideline. This new evidence has been considered for possible addition as a new section of the guideline.

New section considered in surveillance

Closed-loop systems

Surveillance proposal

This section should be added.

Closed-loop insulin delivery

2019 surveillance summary

We identified 3 RCTs examining the effect of closed-loop insulin delivery systems (table 8).

One study (83) (n = 153), in hypoglycaemia prone adults with type 1 diabetes, found that after 6 months of using the Medtronic MiniMed 640G with SmartGuard, weekly hypoglycaemic events and severe hypoglycaemic events were significantly reduced compared to people using the MiniMed 640G pump with standard self-monitoring of blood glucose.

One study (84) (n = 86), in adults with sub-optimally controlled type 1 diabetes, found that 12 weeks of day and night hybrid closed-loop insulin delivery significantly reduced the risk of hypoglycaemia. The 'hybrid' nature of this intervention enabled participants to administer insulin boosts at meal times. Another trial (85) (n = 75) found that 4 nights of closed-loop control (used at home) significantly reduced the time spent in hypoglycaemia. The closed-loop device in this trial had no input from the participant. In both trials, the closed-loop delivery intervention was compared to sensor-augmented pump therapy. Although both therapies combine the use of CGM with an insulin pump, the closed-loop delivery is fully automatic, sometimes termed an “artificial pancreas” whereas the sensor-augmented pump therapy allows users to perform real-time adjustments to insulin therapy.

Intelligence gathering

NICE have produced guidance on:

- Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) (Diagnostics guidance DG21) which is scheduled for update in 2019. These systems combine continuous glucose monitoring and continuous subcutaneous insulin infusion, for people with type 1 diabetes.
MiniMed 640G system with SmartGuard for managing blood glucose levels in people with type 1 diabetes (Medtech innovation briefing MIB51). This integrated sensor-augmented pump therapy system with SmartGuard is a continuous glucose monitoring and insulin delivery system for people with type 1 diabetes. It can automatically suspend insulin delivery if blood glucose is predicted to drop below a pre-set level within 30 minutes (distinguishing it from traditional sensor-augmented pump systems, which allow real-time adjustments).

We are also tracking the progress of 2 ongoing trials in this area:

- **AP@home04** - trial examining the effectiveness of day and night home closed-loop over the medium term compared with sensor-augmented pump therapy in adults with type 1 diabetes and suboptimal glycaemic control.

- **APCam11** - trial examining the effectiveness of a 3-month day-and-night home closed-loop glucose control combined with a pump suspend feature, compared with sensor-augmented insulin pump therapy in youths and adults with suboptimally controlled type 1 diabetes.

**Impact statement**

New evidence was identified to suggest a benefit of closed-loop insulin delivery systems, particularly in people with a high risk of hypoglycaemia and those with sub-optimally controlled diabetes. A closed-loop system is an emerging therapeutic approach for people with type 1 diabetes, combining a linked continuous glucose monitor with an insulin pump. NICE have produced both diagnostic guidance and a medtech innovation briefing on these devices.

Taken together, the new evidence shows promising results for closed-loop systems in reducing the risk of hypoglycaemia during the night for people at risk of hypoglycaemia. Furthermore, no serious adverse effects were reported. Taking into account the new evidence, the ongoing trials and NICE guidance in this area, there may be a need to add new recommendations to the guideline.

**New evidence identified that may impact on the guideline.**

**New section considered in surveillance**

Sensor-augmented pump therapy

**Surveillance proposal**

This section should not be added.
Sensor-augmented pump therapy

2019 surveillance summary

We identified one study (86) (n = 60) which examined the effect of sensor-augmented pump (SAP) therapy in people with type 1 diabetes, a history of albuminuria and were on stable renin-angiotensin system inhibition (table 8). Glucose variability, HbA1c levels and urine albumin creatine ratio all improved with SAP therapy compared to multiple daily injections.

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

New evidence supports the use of SAP therapy over multiple daily injections in people with a history of albuminuria and taking renin-angiotensin system inhibitors. Whilst the trial shows promising results for this population, the sample size was relatively small and confirmation in a larger trial is needed before impact on the guideline can be assessed.

New evidence is unlikely to impact on the guideline.

New section considered in surveillance

Periodontal risk factors in type 1 diabetes

Surveillance proposal

This section should not be added.

Periodontal risk factors

2019 surveillance summary

We did not identify any new evidence in this area that met the inclusion criteria for this surveillance review.

Intelligence gathering

Many stakeholders noted the bi-directional nature of poor oral health and diabetes and requested further recommendations on maintaining oral health and treating complications of poor oral health in adults with type 1 diabetes.
Impact statement

Stakeholders noted the bi-directional nature of poor oral health and diabetes (that diabetes can cause oral health problems, and conversely, that poor oral health can increase the risk of diabetes). They requested further recommendations on maintaining oral health and treating complications of poor oral health in children with diabetes and adults with type 2 diabetes. The aetiology of diabetes is not within scope for NICE guideline NG17, NG18 or NG28 however NICE guideline NG18 cross-refers to NICE guideline CG19 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 as part of the scoping for the update of NICE guidelines NG17 and NG28 as expert input is required to determine an appropriate way of highlighting oral health in people with diabetes.

New evidence is unlikely to impact on the guideline.

Research recommendations

<table>
<thead>
<tr>
<th>Research recommendation</th>
<th>Summary of findings</th>
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</thead>
<tbody>
<tr>
<td>In adults with diabetes, are diagnostic tests (autoimmune markers and biochemical tests such as urine C-peptide and urine C-peptide/creatinine ratio) useful for defining type 1 diabetes, and if so, what is the optimal time in which they should be measured in order to make the diagnosis?</td>
<td>New evidence relating to this research recommendation was identified during surveillance. See section 1.1 above for a summary of findings and impact on guidance.</td>
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<td>Research recommendation</td>
<td>Summary of findings</td>
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<tr>
<td>In adults with type 1 diabetes, are diagnostic tests (autoimmune markers and biochemical tests such as urine C-peptide and urine C-peptide/creatinine ratio) good prognostic makers of the complications associated with the 1 diabetes and its treatments? <em>We exclude the use of these markers in trials of immune modulation therapy to alter the course of type 1 diabetes, as this is not a current therapeutic option and the literature was not reviewed by the committee in this revision.</em></td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what methods can be used to increase the uptake of structured education programmes and to improve their clinical outcomes (particularly achieving and sustaining blood glucose control targets)?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with newly diagnosed type 1 diabetes, what is the optimal timing and method of delivering structured education in terms of clinical and cost effectiveness?</td>
<td>No new evidence relevant to the research recommendation was found. However, an ongoing trial (DAFNEplus) was identified which is examining the effect of a 5-day training course for healthy eating in adults with type 1 diabetes may be relevant in future. We have added the trial to our event tracker and will assess the impact of the results when they are available.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what is clinical and cost effectiveness of bolus calculators used in conjunction with self-monitoring blood glucose meters?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what is the clinical and cost effectiveness of different types of diet and dietary constituents, particularly in terms of the effect on insulin requirement and blood glucose control?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
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<tr>
<td>Research recommendation</td>
<td>Summary of findings</td>
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<tr>
<td>What methods and interventions are effective in increasing the number of adults with type 1 diabetes who achieve the recommended HbA1c targets without risking severe hypoglycaemia or weight gain?</td>
<td>New evidence relating to this research recommendation was identified during surveillance. See section 1.6 above for a summary of findings and impact on guidance.</td>
</tr>
<tr>
<td>Can a risk stratification tool be used to aid the setting of individualised HbA1c targets for adults with type 1 diabetes?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, is HbA1c measurement by laboratory analysis more cost-effective compared to site of care HbA1c testing?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what is the clinical and cost effectiveness of post-prandial blood glucose monitoring?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes who have chronically poor control of blood glucose levels, what is the clinical and cost effectiveness of continuous glucose monitoring technologies?</td>
<td>New evidence relating to this research recommendation was identified during surveillance. See section 1.6 above for summary of the HypoDE and HypoCOMPaSS trials which examined the effect of CGM on people who took multiple daily injections and had a history of impaired hypoglycaemia awareness or experienced severe hypoglycaemia in the previous year.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what is the clinical and cost effectiveness of basal insulins with longer action profiles compared to existing regimens, particularly in terms of dose adjustment for flexible lifestyles, such as intermittent exercise or alcohol consumption, and their long-term safety data?</td>
<td>New evidence relating to this research recommendation was identified during surveillance. See section 1.7 above for summary of evidence on comparing different insulin types and dosages.</td>
</tr>
<tr>
<td>Research recommendation</td>
<td>Summary of findings</td>
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<tr>
<td>In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of different intensities of glycaemic control (for example, inpatient intravenous insulin management versus outpatient multiple daily dose insulin injection therapies)?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of using basal-bolus insulin regimens?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what modifications of rapid-acting insulin use (including but not limited to timing of administration, and the nature of the insulin) could be employed to improve glycaemic control around different meal compositions?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes and a BMI of ≥25 kg/m², what is the clinical and cost effectiveness of metformin as an adjunct to insulin, particularly in terms of glycaemic control and weight loss (or reduction in weight gain)?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what is the clinical and cost effectiveness of GLP-1 analogues and other potential pharmacological adjuncts to insulin therapy?</td>
<td>New evidence relating to this research recommendation was identified during surveillance. See section 1.7 above for a summary of the evidence on adjuncts to insulin therapy.</td>
</tr>
<tr>
<td>Research recommendation</td>
<td>Summary of findings</td>
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</tr>
<tr>
<td>In adults with type 1 diabetes, what are the optimum needle length and type for administration of exogenous insulin in terms of clinical and cost effectiveness?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what is the optimum injection site and injection site rotation regimen in terms of clinical and cost effectiveness?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>For adults with type 1 diabetes, what are the optimum technologies (such as insulin pump therapy and/or continuous glucose monitoring, partially or fully automated insulin delivery, and behavioural, psychological and educational interventions) and how are they best used, in terms of clinical and cost effectiveness, for preventing and treating impaired awareness of hypoglycaemia?</td>
<td><strong>New evidence</strong> relating to this research recommendation was identified during surveillance. See section 1.7 above for a summary of the new evidence on CSII or insulin pump therapy. See also the new evidence on closed-loop delivery and sensor augmented pump therapy.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the management of DKA?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the prevention of DKA?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of pre-empting admissions) of self-monitoring blood ketones compared to urine ketones?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>Research recommendation</td>
<td>Summary of findings</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>In adults with type 1 diabetes, what is the clinical and cost effectiveness of aspirin and other antiplatelet agents who are at high risk for vascular disease (for example, smokers, those with renal disease, those with other evidence of vascular disease)?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of optimal blood glucose control, patient-reported outcomes and experience, length of stay, and short-term complications) of closed-loop insulin delivery systems and automated insulin dose advisors during in-hospital care, and could the development of new systems and technologies improve on current clinical outcomes?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
<tr>
<td>In adults with type 1 diabetes, clinical and cost-effective treatments for diabetic gastroparesis are needed, together with further evidence for the clinical and cost effectiveness of existing treatments such as dopamine antagonists, insulin pump therapy, and gastric electrical stimulation.</td>
<td>New evidence relating to this research recommendation was identified during surveillance. See section 1.15 above for a summary of the new evidence on metoclopramide for the treatment of gastroparesis.</td>
</tr>
<tr>
<td>What is the clinical and cost effectiveness of constructing a national database and centralising supervision of the management of adults with type 1 diabetes who have painful neuropathy of rapid glycaemic control?</td>
<td>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</td>
</tr>
</tbody>
</table>

**Editorial amendments**

During surveillance of the guideline we identified the following points in the guideline that should be amended:

- **Recommendation 1.12.1**: This recommendation currently advises that markers for coeliac disease should be assessed in people with type 1 diabetes who have a low BMI or unexplained weight loss. However, NICE guideline NG20 advises that serological testing for coeliac disease should be offered for all people with type 1 diabetes at the point of
diagnosis. To address this discrepancy, recommendation 1.12.1 should be amended accordingly.

- **Recommendation 1.15.43**: The hyperlink to NG69 needs updating to link to the latest version of the guideline.

- **Recommendation 1.15.42**: The cross referral to NICE guideline CG113 should be changed to the most recent title: "Generalised anxiety disorder and panic disorder in adults: management".

- Recommendations on screening and referral for diabetic eye disease should be withdrawn and replaced with a cross-referral to the NHS Diabetic Eye Screening Programme.
## Data summary tables

### Table 1. Education and information

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>n</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Result</th>
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<tbody>
<tr>
<td>Mohn, J.; et al. 2017 (6)</td>
<td>RCT</td>
<td>178</td>
<td>Adults over 30</td>
<td>Guided self-determination by group training</td>
<td>Care as usual</td>
<td>Change in HbA1c</td>
<td>9 months</td>
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<td>Diabetes distress scale</td>
<td>9 months</td>
<td>Improved with intervention</td>
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Abbreviations: RCT, randomised controlled trial.

### Table 2. Dietary management

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<th>Outcome</th>
<th>Follow-up</th>
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<tr>
<td>Hommel, E.; et al. 2017 (7)</td>
<td>RCT</td>
<td>168</td>
<td>Patient with MDIs and HbA1c of 8-11.3%</td>
<td>Advanced carbohydrate counting with automated bolus calculator</td>
<td>Advanced carbohydrate counting with mental calculations</td>
<td>Change in HbA1c</td>
<td>12 months</td>
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Abbreviations: RCT, randomised controlled trial; MDIs, multiple daily injections.

### Table 3. Blood glucose management

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<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Result</th>
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<tr>
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<tr>
<td>Flodgren, G.; et al. 2015 (8)</td>
<td>Cochrane</td>
<td>16 (2768 on diabetes)</td>
<td>Adult (age not specified)</td>
<td>Interactive telemedicine</td>
<td>Usual care</td>
<td>Change in HbA1c</td>
<td>9 months</td>
<td>Improved with intervention</td>
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<tr>
<td>Di Bartolo, P.; et al. 2017 (10)</td>
<td>RCT</td>
<td>182</td>
<td>Young adults (average age of 17.7) with poorly controlled T1D and poorly compliant with Telemedicine</td>
<td>Standard glucose monitoring</td>
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<td>Change in HbA1c</td>
<td>6 months</td>
<td>No significant difference between intervention and comparator</td>
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<td></td>
<td>Achievement of compliance with SMBG</td>
<td>6 months</td>
<td>No significant difference between intervention and comparator</td>
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<th>Study</th>
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<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Result</th>
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<td>self-monitoring of BG</td>
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<td>Quality of life</td>
<td>6 months</td>
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<td>Esmatjes, E.; et al. 2014 (9)</td>
<td>RCT</td>
<td>154</td>
<td>Adults with inadequate metabolic control</td>
<td>Internet-based telematic system (2 face-to-face and 5 internet sessions)</td>
<td>Control (7 face-to-face sessions)</td>
<td>Change in HbA1c</td>
<td>7 sessions</td>
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<td>Healthcare professional time</td>
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<td>Smartphone applications and online platforms</td>
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<td>Zhou, W.; et al. 2016 (11)</td>
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<td>100</td>
<td>Adults with HbA1c &gt;=64 mmol/mol</td>
<td>Smartphone-based application “Welltang”</td>
<td>Usual care</td>
<td>Change in HbA1c</td>
<td>3 months</td>
<td>Improved with intervention</td>
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<td>Flash glucose monitoring</td>
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<td>Oskarsson, P.; et al. 2018 IMPACT (13)</td>
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<td>Adults with MDIs</td>
<td>Flash glucose monitoring</td>
<td>Self-monitoring of capillary blood glucose</td>
<td>Mean time in hypoglycaemia (&lt;3.9 mmol/L [70 mg/dL])</td>
<td>6 months</td>
<td>Improved with intervention</td>
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<td>Bolinder, J.; et al. 2016 IMPACT (12)</td>
<td>RCT</td>
<td>241</td>
<td>Adults with well-controlled T1D</td>
<td>Flash glucose monitoring</td>
<td>Self-monitoring of capillary blood glucose</td>
<td>Mean time in hypoglycaemia (&lt;3.9 mmol/L [70 mg/dL])</td>
<td>6 months</td>
<td>Improved with intervention</td>
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<td>Continuous glucose monitoring</td>
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<td>Beck, R. W.; et al. 2017 DIAMOND (14)</td>
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<td>158</td>
<td>Adults with MDIs</td>
<td>Continuous glucose monitoring</td>
<td>Usual care</td>
<td>Change in HbA1c</td>
<td>24 weeks</td>
<td>Improved with intervention</td>
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<td>Riddlesworth, Tonya; et al. 2017 DIAMOND (17)</td>
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<td>158</td>
<td>Adults with MDIs</td>
<td>Continuous glucose monitoring</td>
<td>Usual care</td>
<td>Hypoglycaemic events</td>
<td>6 months</td>
<td>Improved with intervention</td>
</tr>
<tr>
<td>Polonsky, W. H.; et al. 2017 DIAMOND (16)</td>
<td>RCT</td>
<td>158</td>
<td>Adults with MDIs</td>
<td>Continuous glucose monitoring</td>
<td>Multiple daily injections</td>
<td>Diabetes distress scale</td>
<td>24 weeks</td>
<td>Improved with intervention</td>
</tr>
<tr>
<td>Lind, M.; et al. 2017 GOLD (15)</td>
<td>RCT</td>
<td>161</td>
<td>Adults with MDIs</td>
<td>Continuous glucose monitoring</td>
<td>Conventional treatment</td>
<td>Change in HbA1c</td>
<td>26 weeks + 17 week washout</td>
<td>Improved with intervention</td>
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<td>Study</td>
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<td>n</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcome</td>
<td>Follow-up</td>
<td>Result</td>
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<td>Heinemann, L.; et al. 2018</td>
<td>RCT</td>
<td>149</td>
<td>Adults with MDIs and a history of impaired hypoglycaemia or severe hypoglycaemia in previous year</td>
<td>Real time CGM (rtCGM) (unmasked)</td>
<td>Self-monitoring of capillary blood glucose (with masked rtCGM)</td>
<td>Mean number of hypoglycaemic events per 28 days (glucose less than 3.0mmol/L for more than 20 minutes)</td>
<td>26 weeks</td>
<td>Improved with intervention</td>
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<tr>
<td>Little, S. A.; et al. 2014</td>
<td>RCT</td>
<td>96</td>
<td>Adults with impaired awareness of hypoglycaemia</td>
<td>Real time CGM (rtCGM) (unmasked)</td>
<td>Self-monitoring of blood glucose</td>
<td>Hypoglycaemia awareness</td>
<td>24 weeks</td>
<td>No significant difference between intervention and comparator</td>
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<tr>
<td>Little, S. A.; et al. 2018</td>
<td>RCT</td>
<td>96</td>
<td>Adults with impaired awareness of hypoglycaemia</td>
<td>Real time CGM (rtCGM) (unmasked)</td>
<td>Self-monitoring of blood glucose</td>
<td>Hypoglycaemia awareness</td>
<td>2 years</td>
<td>No significant difference between intervention and comparator</td>
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Abbreviations: RCT, randomised controlled trial; CGM, continuous glucose monitoring; SMBG, self-monitoring of blood glucose; MDIs, multiple daily injections.

### Table 4. Insulin therapy

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<th>Study</th>
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<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
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<td>Insulin analogues compared to human insulins</td>
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<td>Fullerton, B.; et al. 2016</td>
<td>Cochrane</td>
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<td>Adult (age not specified)</td>
<td>Short-acting insulin analogues</td>
<td>Regular human insulins</td>
<td>Change in HbA1c</td>
<td>Mean 37 weeks</td>
<td>Improved with intervention</td>
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<td>(23)</td>
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<td>studies (n = 2693)</td>
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<td>Pedersen-Bjergaard, U.; et al. 2014</td>
<td>RCT</td>
<td>159</td>
<td>Adults prone to recurrent severe hypoglycaemia</td>
<td>Insulin analogue (detemir/aspart)</td>
<td>Human insulin (NPH/regular)</td>
<td>Number of validated episodes of severe hypoglycaemia</td>
<td>2 years</td>
<td>Improved with intervention</td>
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<td>HypoAna (24)</td>
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Biosimilar insulins

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<th>Study</th>
<th>Type</th>
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<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
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<tr>
<td>Heise, T.; et al. 2017</td>
<td>RCT</td>
<td>57</td>
<td>Adult (age not specified)</td>
<td>Insulin degludec (0.4 U/Kg)</td>
<td>Insulin glargine (300 U/ml)</td>
<td>Glucose lowing effect - within day variability</td>
<td>12 days</td>
<td>Improved with intervention</td>
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<tr>
<td>(25)</td>
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<td>Study</td>
<td>Type</td>
<td>n</td>
<td>Population</td>
<td>Intervention</td>
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<td>Follow-up</td>
<td>Result</td>
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<td>Lane, W.; et al.</td>
<td>RCT</td>
<td>501</td>
<td>Adult (age not specified)</td>
<td>Insulin degludec (0.4 U/Kg)</td>
<td>Insulin glargine (300 U/ml)</td>
<td>Rate of hypoglycaemic events</td>
<td>32 weeks</td>
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<td>Rate of nocturnal hypoglycaemic events</td>
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<td>Proportion of patients with severe</td>
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<td>Garg, S. K.; et al. 2017</td>
<td>RCT</td>
<td>507</td>
<td>Adult (age not specified)</td>
<td>Biosimilar of insulin lispro (SAR342434)</td>
<td>Insulin Lispro-Humalog</td>
<td>Change in HbA1c</td>
<td>6 months</td>
<td>Intervention non-inferior</td>
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<td>Hypoglycaemic events</td>
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<td>Davies, M. J.; et al. 2014</td>
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<td>Insulin degludec</td>
<td>Insulin detemir</td>
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<td>Rate of confirmed hypoglycaemia</td>
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<td>Blevins, T. C.; et al. 2015</td>
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<td>535</td>
<td>Adult (age not specified)</td>
<td>LY296316 insulin glargine</td>
<td>Insulin glargine (lantus)</td>
<td>Change in HbA1c</td>
<td>52 weeks</td>
<td>Intervention non-inferior</td>
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<td>Home, Philip D.; et al. 2018</td>
<td>RCT</td>
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<td>Adult (age not specified)</td>
<td>MK-1293 Insulin glargine (100U/ml)</td>
<td>Insulin glargine (Lantus)</td>
<td>Change in HbA1c</td>
<td>52 weeks</td>
<td>Intervention non-inferior</td>
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<tr>
<td>Blevins, T. C.; et al. 2018</td>
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<td>Adult (age not specified)</td>
<td>MYL-1501D (insulin glargine biosimilar)</td>
<td>Reference insulin glargine</td>
<td>Change in HbA1c</td>
<td>52 weeks</td>
<td>Intervention non-inferior</td>
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<td>Russell-Jones, D.; et al. 2017</td>
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<td>1143</td>
<td>Adult (age not specified)</td>
<td>Fast-acting insulin aspart (double blind mealtime or open label post meal)</td>
<td>Conventional insulin aspart</td>
<td>Change in HbA1c</td>
<td>26 weeks</td>
<td>Intervention non-inferior</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>n</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcome</td>
<td>Follow-up</td>
<td>Result</td>
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<td>Buse, John B.; et al. 2018 ONSET-8 (33)</td>
<td>RCT</td>
<td>1024</td>
<td>Adult (age not specified) already taking insulin degludec</td>
<td>Fast-acting insulin aspart (double blind mealtime)</td>
<td>Conventional insulin aspart</td>
<td>Change in HbA1c</td>
<td>26 weeks</td>
<td>Improved with intervention</td>
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<tr>
<td>Mathieu, C.; et al. 2018 ONSET-1 (34)</td>
<td>RCT</td>
<td>381</td>
<td>Adult (age not specified) already taking insulin detemir</td>
<td>Fast-acting insulin aspart (double blind mealtime)</td>
<td>Conventional insulin aspart</td>
<td>Change in HbA1c</td>
<td>52 weeks</td>
<td>Improved with intervention</td>
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<td>Klonoff, David C.; et al. 2018 ONSET-5 (35)</td>
<td>RCT</td>
<td>472</td>
<td>Adult (age not specified)</td>
<td>Fast-acting insulin aspart used in CSII</td>
<td>Conventional insulin aspart used in CSII</td>
<td>Change in HbA1c</td>
<td>16 weeks</td>
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<td>Dose comparisons</td>
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<td>Matsuhisa, M.; et al. 2016 EDITION JP (36)</td>
<td>RCT</td>
<td>243</td>
<td>Adult (age not specified)</td>
<td>Insulin glargine (300 U/ml)</td>
<td>Insulin glargine (100 U/ml)</td>
<td>Change in HbA1c</td>
<td>6 months</td>
<td>Intervention non-inferior</td>
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<tr>
<td>Home, P. D.; et al. 2015 EDITION 4 (37)</td>
<td>RCT</td>
<td>549</td>
<td>Adult (over 30)</td>
<td>Insulin glargine (300 U/ml)</td>
<td>Insulin glargine (100 U/ml)</td>
<td>Change in HbA1c</td>
<td>6 months</td>
<td>Intervention non-inferior</td>
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<td>Adjuncts to insulin</td>
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<td>RCT</td>
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<td>Adult (age not specified)</td>
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<td>Placebo</td>
<td>Change in HbA1c</td>
<td>18 weeks</td>
<td>Improved with intervention</td>
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## Table 5. Control of cardiovascular risk

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<th>Study</th>
<th>Type</th>
<th>n</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hartaigh; et al. 2018 (58)</td>
<td>RCT</td>
<td>4732</td>
<td>Adult (over 30)</td>
<td>Intensive systolic blood pressure target (&lt;120mmHg)</td>
<td>Standard systolic blood pressure target (less than 140mmHg)</td>
<td>Risk of major adverse cardiovascular events</td>
<td>~5 years</td>
<td>Improvement in control group but not intervention group (no between group comparison reported)</td>
</tr>
<tr>
<td>ASCEND Study Collaborative; et al. 2018 ASCEND (56)</td>
<td>RCT</td>
<td>15480</td>
<td>Adult (age not specified)</td>
<td>Daily aspirin (100mg)</td>
<td>Placebo</td>
<td>First serious vascular event</td>
<td>mean 7.4 years</td>
<td>Improved with intervention</td>
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<tr>
<td></td>
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<td></td>
<td>First major bleeding event</td>
<td>mean 7.4 years</td>
<td>Worse with intervention</td>
</tr>
<tr>
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<td></td>
<td>Incidence of gastrointestinal cancer</td>
<td>mean 7.4 years</td>
<td>No significant difference between intervention and comparator</td>
</tr>
<tr>
<td>ASCEND Study Collaborative; et al. 2018 ASCEND (57)</td>
<td>RCT</td>
<td>15480</td>
<td>Adult (age not specified)</td>
<td>Fatty acid supplementation</td>
<td>Placebo (olive oil)</td>
<td>First serious vascular event</td>
<td>mean 7.4 years</td>
<td>No significant difference between intervention and comparator</td>
</tr>
</tbody>
</table>

Abbreviations: RCT, randomised controlled trial.
Table 6. Care of adults with type 1 diabetes in hospital

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<tr>
<th>Study</th>
<th>Type</th>
<th>n</th>
<th>Population</th>
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<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Result</th>
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<tbody>
<tr>
<td>Colunga-Lozano, L. E.; et al. 2018 (59)</td>
<td>Cochrane</td>
<td>5 studies on T1D (n = 667)</td>
<td>Non-critically ill hospitalised adults with diabetes mellitus</td>
<td>Sliding scale insulin</td>
<td>Basal-bolus insulin</td>
<td>Severe hypoglycaemic episodes, defined as blood glucose levels below 40 mg/dL (2.2 mmol/L)</td>
<td>Not reported</td>
<td>Little or no benefit with intervention</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Mean blood glucose level</td>
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<td></td>
<td></td>
<td></td>
<td>Not reported</td>
<td></td>
<td>Worse with intervention</td>
</tr>
</tbody>
</table>

Abbreviations: T1D, type 1 diabetes

Table 7. Managing complications

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>n</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Result</th>
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<tbody>
<tr>
<td>Eye disease</td>
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<td>Martinez-Zapata, M. J. 2014 (67)</td>
<td>Cochrane</td>
<td>1 study (n = 61)</td>
<td>Adult (age not specified)</td>
<td>Bevacizumab with panretinal photocoagulation</td>
<td>Panretinal photocoagulation</td>
<td>Risk of losing 3 or more lines of visual acuity</td>
<td>12 months</td>
<td>Improved with intervention</td>
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<td></td>
<td>Visual acuity</td>
<td>12 months</td>
<td>Improved with intervention</td>
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<td>Risk of vitreous or pre-retinal haemorrhage</td>
<td>12 months</td>
<td>Improved with intervention</td>
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<td></td>
<td>Risk of losing 3 or more lines of visual acuity</td>
<td>12 months</td>
<td>Little or no benefit with intervention</td>
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<tr>
<td>Sivaprasad, S.; et al. 2017 CLARITY (68)</td>
<td>RCT</td>
<td>22 ophthalmic centres (n not reported in the abstract)</td>
<td>Adults with proliferative diabetic retinopathy</td>
<td>Intravitreous injection of aflibercept (2mg/0.05ml)</td>
<td>Photocoagulation</td>
<td>Change in BCVA</td>
<td>1 year</td>
<td>Improved with intervention</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>n</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcome</td>
<td>Follow-up</td>
<td>Result</td>
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<tr>
<td>Jorge, E. C.; et al. 2018 (70)</td>
<td>Cochrane</td>
<td>3703</td>
<td>Adult (age not specified)</td>
<td>Any type of focal/grid macular laser</td>
<td>No intervention</td>
<td>BCVA</td>
<td>1 year</td>
<td>Improvement with intervention</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>photocoagulation</td>
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<td></td>
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<tr>
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<td></td>
<td>29</td>
<td>Adult (age not specified)</td>
<td>Subthreshold photocoagulation</td>
<td>Standard photocoagulation</td>
<td>Resolution of macular oedema</td>
<td>1 year</td>
<td>No significant difference between intervention and comparator</td>
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<tr>
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<td>385</td>
<td>Adult (age not specified)</td>
<td>Subthreshold photocoagulation</td>
<td>Standard photocoagulation</td>
<td>Continuous BCVA</td>
<td>1 year</td>
<td>No significant difference between intervention and comparator</td>
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<td>385</td>
<td>Adult (age not specified)</td>
<td>Subthreshold photocoagulation</td>
<td>Standard photocoagulation</td>
<td>Change in central macular thickness</td>
<td>1 year</td>
<td>No significant difference between intervention and comparator</td>
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<td>773</td>
<td>Adult (age not specified)</td>
<td>Argon laser</td>
<td>Other type of laser</td>
<td>BCVA</td>
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<td></td>
<td>323</td>
<td>Adult (age not specified)</td>
<td>Modified ETDRS (mETDRS) grid technique</td>
<td>Mild macular grid technique</td>
<td>BCVA</td>
<td>1 year</td>
<td>Inconclusive</td>
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<tr>
<td>Friedman, S. M.; et al. 2015 (71)</td>
<td>RCT</td>
<td>125</td>
<td>Adult (age not specified)</td>
<td>Nepafenec (0.1%)</td>
<td>Placebo</td>
<td>Mean change in optical coherence tomography retinal volume</td>
<td>12 months</td>
<td>No significant difference between intervention and comparator</td>
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</table>

**Diabetic kidney disease**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>n</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>Lo, C.; et al. 2018 (72)</td>
<td>Cochrane</td>
<td>7 studies (n = 1092)</td>
<td>Adult (age not specified) with diabetes and chronic kidney disease</td>
<td>SGLT-2 inhibitors</td>
<td>Placebo</td>
<td>Change in Hba1c</td>
<td>Not reported</td>
<td>Improved with intervention</td>
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<tr>
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<td>5 studies (n = 855)</td>
<td>Adult (age not specified) with diabetes and chronic kidney disease</td>
<td>SGLT-2 inhibitors</td>
<td>Placebo</td>
<td>Fasting blood glucose</td>
<td>Not reported</td>
<td>Improved with intervention</td>
</tr>
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<td>7 studies (n = 1198)</td>
<td>Adult (age not specified) with diabetes and chronic kidney disease</td>
<td>SGLT-2 inhibitors</td>
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<td>Systolic blood pressure</td>
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<td>Improved with intervention</td>
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<td>Study</td>
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<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcome</td>
<td>Follow-up</td>
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<td>7 studies (n = 3086)</td>
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<td>SGLT-2 inhibitors</td>
<td>Placebo</td>
<td>Genital infections</td>
<td>Not reported</td>
<td>Worse with intervention</td>
</tr>
<tr>
<td>5 studies (n = 1029)</td>
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<td></td>
<td>Adult (age not specified) with diabetes and chronic kidney disease</td>
<td>SGLT-2 inhibitors</td>
<td>Placebo</td>
<td>Weight</td>
<td>Not reported</td>
<td>Improved with intervention</td>
</tr>
<tr>
<td>9 studies (n not reported)</td>
<td></td>
<td></td>
<td>Adult (age not specified) with diabetes and chronic kidney disease</td>
<td>SGLT-2 inhibitors</td>
<td>Placebo</td>
<td>Risk of cardiovascular death</td>
<td>Not reported</td>
<td>No significant difference between intervention and comparator</td>
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<tr>
<td>9 studies (n not reported)</td>
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<td>Adult (age not specified) with diabetes and chronic kidney disease</td>
<td>SGLT-2 inhibitors</td>
<td>Placebo</td>
<td>Hypoglycaemia</td>
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<td>9 studies (n not reported)</td>
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<td>Adult (age not specified) with diabetes and chronic kidney disease</td>
<td>SGLT-2 inhibitors</td>
<td>Placebo</td>
<td>Acute kidney injury</td>
<td>Not reported</td>
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<tr>
<td>7 studies (n = 5897)</td>
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<td>Adult (age not specified) with diabetes and chronic kidney disease</td>
<td>DPP-4 inhibitors</td>
<td>Placebo</td>
<td>Change in HbA1c</td>
<td>Not reported</td>
<td>Improved with intervention</td>
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<tr>
<td>7 studies (n = 5897)</td>
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<td>Adult (age not specified) with diabetes and chronic kidney disease</td>
<td>DPP-4 inhibitors</td>
<td>Placebo</td>
<td>Fasting blood glucose</td>
<td>Not reported</td>
<td>Little or no benefit with intervention</td>
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<tr>
<td>7 studies (n = 5897)</td>
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<td>DPP-4 inhibitors</td>
<td>Placebo</td>
<td>Cardiovascular death</td>
<td>Not reported</td>
<td>No significant difference between intervention and comparator</td>
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<td>2 studies (n = 210)</td>
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<td>DPP-4 inhibitors</td>
<td>Placebo</td>
<td>Weight</td>
<td>Not reported</td>
<td>No significant difference between intervention and comparator</td>
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<td>Study</td>
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<td>n</td>
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<td>Outcome</td>
<td>Follow-up</td>
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<tr>
<td>7 studies (n = 867)</td>
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<td>Adult (age not specified) with diabetes and chronic kidney disease</td>
<td>GLP-1 agonists</td>
<td>Placebo</td>
<td>Change in HbA1c</td>
<td>Not reported</td>
<td>Improved with intervention</td>
</tr>
<tr>
<td>2 studies (n = 551)</td>
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<td>Adult (age not specified) with diabetes and chronic kidney disease</td>
<td>Sitagliptin</td>
<td>Glipizide</td>
<td>Hypoglycaemia</td>
<td>Not reported</td>
<td>Improved with intervention</td>
</tr>
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<td>DCCT EDIC group 2014 (73)</td>
<td>RCT</td>
<td>1441</td>
<td>Adult (age not specified)</td>
<td>Intensive treatment</td>
<td>Conventional treatment</td>
<td>Incidence of microalbuminuria</td>
<td>18 years</td>
<td>Improved with intervention</td>
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<td>Chronic painful neuropathy</td>
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<tr>
<td>Enomoto, H.; et al. 2018 (74)</td>
<td>RCT</td>
<td>303</td>
<td>Adult (age not specified)</td>
<td>Duloxetine (40-60mg/day)</td>
<td>Pregabalin (300-600 mg/day)</td>
<td>Mean 24hr average pain score</td>
<td>12 weeks</td>
<td>Intervention non-inferior</td>
</tr>
<tr>
<td>Mimenza Alvarado, A.; Aguilar Navarro, S. (75)</td>
<td>RCT</td>
<td>270</td>
<td>Adult (age not specified)</td>
<td>Gabapentin plus complex B vitamins</td>
<td>Pregabalin</td>
<td>Pain intensity</td>
<td>12 weeks</td>
<td>No significant difference between intervention and comparator</td>
</tr>
<tr>
<td>Mu, Y.; et al. (76)</td>
<td>RCT</td>
<td>620</td>
<td>Adult (age not specified)</td>
<td>Pregabalin (300mg/day)</td>
<td>Placebo</td>
<td>Change in mean pain score</td>
<td>11 weeks</td>
<td>No significant difference between intervention and comparator</td>
</tr>
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<td>Gastroparesis</td>
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<td>Olausson, E. A.; et al. 2014 (78)</td>
<td>RCT</td>
<td>56</td>
<td>Adult (age not specified) with gastroparesis</td>
<td>Small particle sized diet</td>
<td>Control diet</td>
<td>Severity of gastroparetic symptoms</td>
<td>20 weeks</td>
<td>Improved with intervention</td>
</tr>
<tr>
<td>Parkman, H. P.; et al. (79)</td>
<td>RCT</td>
<td>89</td>
<td>Adult (age not specified) with gastroparesis</td>
<td>Metoclopramide nasal spray (10 or 20mg)</td>
<td>Oral metoclopramide (10mg)</td>
<td>Total symptom score</td>
<td>6 weeks</td>
<td>Improved with intervention</td>
</tr>
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<td>Psychological problems</td>
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<tr>
<td>Tovote, K. A.; et al. 2014 (81)</td>
<td>RCT</td>
<td>94</td>
<td>Adult (age not specified) with T1D and</td>
<td>Mindfulness-based CBT</td>
<td>Waitlist control</td>
<td>Severity of depressive symptoms</td>
<td>3 months</td>
<td>Improved with intervention</td>
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</tbody>
</table>
### Table 8. Areas not covered in the guideline

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
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<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Result</th>
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<tbody>
<tr>
<td></td>
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<td>CBT</td>
<td>Waitlist control</td>
<td>Severity of depressive symptoms</td>
<td>3 months</td>
<td>Improved with intervention</td>
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<tr>
<td>Sajatovic, M.; et al. 2017 (82)</td>
<td>RCT</td>
<td>200</td>
<td>Adult (age not specified) with T1D and serious mental illness</td>
<td>Self-management intervention</td>
<td>Usual care</td>
<td>Depressive symptoms</td>
<td>60 weeks</td>
<td>Improved with intervention</td>
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</tbody>
</table>

**Abbreviations:** RCT, randomised controlled trial; T1D, type 1 diabetes; CBT, cognitive behavioural therapy; BCVA, best corrected visual acuity.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>n</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>were on stable renin-angiotensin system inhibition</td>
<td>Change in HbA1c</td>
<td>1 year</td>
<td>Improved with intervention</td>
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<td>Glucose variability</td>
<td>1 year</td>
<td>Improved with intervention</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RCT, randomised controlled trial; BGC, blood glucose control; CGM, continuous glucose monitoring; SAP therapy, sensor-augmented pump therapy
References


3. Thomas NJ, Lynam AL, Hill A V, Weedon MN, Shields BM, Oram RA, et al. (2019) Type 1 diabetes defined by severe insulin deficiency occurs after 30 years of age and is commonly treated as type 2 diabetes. Diabetologia


Christiansen JS, et al. (2014) Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): a prospective, randomised, open-label, blinded-endpoint crossover trial. The Lancet Diabetes & Endocrinology 2(7):553–61


46. Famulla S, Pieber TR, Eilbracht J, Neubacher D, Soleymanlou N, Woerle HJ, et al. (2017) Glucose Exposure and Variability with Empagliflozin as Adjunct to Insulin in Patients with Type 1 Diabetes: Continuous Glucose Monitoring Data from a 4-Week, Randomized, Placebo-Controlled Trial (EASE-1). Diabetes Technology & Therapeutics 19(1):49–60


glucose-lowering agents for treating people with diabetes and chronic kidney disease. Cochrane Database of Systematic Reviews (9)


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