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 odema 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 sub-optimal 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 hypocglycaemia (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 analogies 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/m^2 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.

This section of the guideline should not be updated.

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.

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.

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.

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 pre-retinal haemorrhage and risk of losing 3 or more lines of visual acuity. Authors noted that the evidence was of very low quality and further trials are needed to inform treatment decisions.

One RCT (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 odema 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

Research recommendation	Summary of findings
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?	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.

Research recommendation	Summary of findings
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? *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.*	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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)?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	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.
In adults with type 1 diabetes, what is clinical and cost effectiveness of bolus calculators used in conjunction with self-monitoring blood glucose meters?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Research recommendation	Summary of findings
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?	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.
Can a risk stratification tool be used to aid the setting of individualised HbA1c targets for adults with type 1 diabetes?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, is HbA1c measurement by laboratory analysis more cost-effective compared to site of care HbA1c testing?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, what is the clinical and cost effectiveness of post-prandial blood glucose monitoring?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	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.
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?	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.

Research recommendation	Summary of findings
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)?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes and a BMI of ≥25 kg/m^2, 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)?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	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.

Research recommendation	Summary of findings
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, what is the optimum injection site and injection site rotation regimen in terms of clinical and cost effectiveness?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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, forpreventing and treating impaired awareness of hypoglycaemia?	New evidence 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.
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Research recommendation	Summary of findings
In adults with type 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)?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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.	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.
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

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

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Mohn, J.; et al. 2017 (6)	RCT	178	Adults over 30	Guided self-determination by group training	Care as usual	Change in HbA1c	9 months	No significant difference between intervention and comparator
						Diabetes distress scale	9 months	Improved with intervention
Abbreviations: RCT, randomised controlled trial.								

Table 2. Dietary management

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Hommel, E.; et al. 2017 (7)	RCT	168	Patient with MDIs and HbA1c of 8-11.3%.	Advanced carbohydrate counting with automated bolus calculator	Advanced carbohydrate counting with mental calculations	Change in HbA1c	12 months	Improved with intervention
Abbreviations: RCT, randomised controlled trial; MDIs, multiple daily injections.								

Table 3. Blood glucose management

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Telemedicine								
Flodgren, G.; et al. 2015 (8)	Cochrane	16 (2768 on diabetes)	Adult (age not specified)	Interactive telemedicine	Usual care	Change in HbA1c	9 months	Improved with intervention
Di Bartolo, P.; et al. 2017 (10)	RCT	182	Young adults (average age of 17.7) with poorly controlled T1D and poorly compliant with	Telemedicine	Standard glucose monitoring	Change in HbA1c	6 months	No significant difference between intervention and comparator
						Achievement of compliance with SMBG	6 months	No significant difference between intervention and comparator

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
			self-monitoring of BG			Quality of life	6 months	No significant difference between intervention and comparator
Esmatjes, E.; et al. 2014 (9)	RCT	154	Adults with inadequate metabolic control	Internet-based telematic system (2 face-to-face and 5 internet sessions)	Control (7 face-to-face sessions)	Change in HbA1c	7 sessions	No significant difference between intervention and comparator
						Healthcare professional time	n/a	Significantly less with intervention
Smartphone applications and online platforms								
Zhou, W.; et al. 2016 (11)	RCT	100	Adults with HbA1c >=64 mmol/mol	Smartphone-based application "Welltang"	Usual care	Change in HbA1c	3 months	Improved with intervention
Flash glucose monitoring								
Oskarsson, P.; et al. 2018 IMPACT (13)	RCT	167	Adults with MDIs	Flash glucose monitoring	Self-monitoring of capillary blood glucose	Mean time in hypoglycaemia (<3.9 mmol/L [70 mg/dL])	6 months	Improved with intervention
Bolinder, J.; et al. 2016 IMPACT (12)	RCT	241	Adults with well-controlled T1D	Flash glucose monitoring	Self-monitoring of capillary blood glucose	Mean time in hypoglycaemia (<3.9 mmol/L [70 mg/dL])	6 months	Improved with intervention
Continuous glucose monitoring								
Beck, R. W.; et al. 2017 DIAMOND (14)	RCT	158	Adults with MDIs	Continuous glucose monitoring	Usual care	Change in HbA1c	24 weeks	Improved with intervention
Riddlesworth, Tonya;et al. 2017 DIAMOND (17)	RCT	158	Adults with MDIs	Continuous glucose monitoring	Usual care	Hypoglycaemic events	6 months	Improved with intervention
Polonsky, W. H.; et al. 2017 DIAMOND (16)	RCT	158	Adults with MDIs	Continuous glucose monitoring	Multiple daily injections	Diabetes distress scale	24 weeks	Improved with intervention
Lind, M.; et al. 2017 GOLD (15)	RCT	161	Adults with MDIs	Continuous glucose monitoring	Conventional treatment	Change in HbA1c	26 weeks + 17 week washout	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Heinemann, L.; et al. 2018 HypoDE (18)	RCT	149	Adults with MDIs and a history of impaired hypoglycaemia awareness or severe hypoglycaemia in previous year	Real time CGM (rtCGM) (unmasked)	Self-monitoring of capillary blood glucose (with masked rtCGM)	Mean number of hypoglycaemic events per 28 days (glucose less than 3.0mmol/L for more than 20 minutes)	26 weeks	Improved with intervention
Little, S. A.; et al. 2014 HypoCOMPaSS (19)	RCT	96	Adults with impaired awareness of hypoglycemia	Real time CGM (rtCGM) (unmasked)	Self-monitoring of blood glucose	Hypoglycaemia awareness	24 weeks	No significant difference between intervention and comparator
Little, S. A.; et al. 2018 HypoCOMPaSS (20)	RCT	96	Adults with impaired awareness of hypoglycemia	Real time CGM (rtCGM) (unmasked)	Self-monitoring of blood glucose	Hypoglycaemia awareness	2 years	No significant difference between intervention and comparator

Abbreviations: RCT, randomised controlled trial; CGM, continuous glucose monitoring; SMBG, self-monitoing of blood glucose; MDIs, multiple daily injections.

Table 4. Insulin therapy

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Insulin analogues compared to human insulins								
Fullerton, B.; et al. 2016 (23)	Cochrane	9 studies (n = 2693)	Adult (age not specified)	Short-acting insulin analogues	Regular human insulins	Change in HbA1c	Mean 37 weeks	Improved with intervention
						Risk of severe hypoglycaemic events	Mean 37 weeks	No significant difference between intervention and comparator
Pedersen-Bjergaard, U.; et al. 2014 HypoAna (24)	RCT	159	Adults prone to recurrent severe hypoglycaemia	Insulin analogue (detemir/aspart)	Human insulin (NPH/regular)	Number of validated episodes of severe hypoglycaemia	2 years	Improved with intervention
Biosimilar insulins								
Heise, T.; et al. 2017 (25)	RCT	57	Adult (age not specified)	Insulin degludec (0.4 U/Kg) Insulin degludec	Insulin glargine (300 U/ml)	Glucose lowing effect - within day variability	12 days	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
					Insulin glargine (U100)	Glucose lowing effect - day-to-day variability	12 days	Improved with intervention
Lane, W.; et al. SWITCH-1 (26)	RCT	501	Adult (age not specified)	Insulin degludec (0.4 U/Kg)	Insulin glargine (300 U/ml)	Rate of hypoglycaemic events	32 weeks	Improved with intervention
						Rate of nocturnal hypoglycaemic events	32 weeks	Improved with intervention
						Proportion of patients with severe hypoglycaemia	32 weeks	Improved with intervention
Garg, S. K.; et al. 2017 SORELLA 1 (28)	RCT	507	Adult (age not specified)	Biosimilar of insulin lispro (SAR342434)	Insulin Lispro-Humalog	Change in HbA1c	6 months	Intervention non-inferior
						Hypoglycaemic events	6 months	No significant difference between intervention and comparator
						Adverse events	6 months	No significant difference between intervention and comparator
Davies, M. J.; et al. 2014 (27)	RCT	455	Adult (age not specified)	Insulin degludec	Insulin detemir	Change in HbA1c	26 weeks	Non-inferiority of intervention over comparator
						Rate of confirmed hypoglycaemia	26 weeks	No significant difference between intervention and comparator
Blevins, T. C.; et al. 2015 (29)	RCT	535	Adult (age not specified)	LY296316 insulin glargine	Insulin glargine (lantus)	Change in HbA1c	52 weeks	Intervention non-inferior
Home, Philip D.; et al. 2018 (30)	RCT	508	Adult (age not specified)	MK-1293 Insulin glargine (100U/ml)	Insulin glrgine (Lantus)	Change in HbA1c	52 weeks	Intervention non-inferior
Blevins, T. C.; et al. 2018 (31)	RCT	558	Adult (age not specified)	MYL-1501D (insulin glargine biosimilar)	Reference insulin glargine	Change in HbA1c	52 weeks	Intervention non-inferior
Russell-Jones, D.; et al. 2017 ONSET-1 (32)	RCT	1143	Adult (age not specified) already taking insulin detemir	Fast-acting insulin aspart (double blind mealtime or open label post meal)	Conventional insulin aspart	Change in HbA1c	26 weeks	Intervention non-inferior

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
				Fast-acting insulin aspart (double blind mealtime)	Conventional insulin aspart	Change in HbA1c	26 weeks	Improved with intervention
Buse, John B.; et al. 2018 ONSET-8 (33)	RCT	1024	Adult (age not specified) already taking insulin degludec	Fast-acting insulin aspart (double blind mealtime or open label post meal)	Conventional insulin aspart	Change in HbA1c	26 weeks	Intervention non-inferior
				Fast-acting insulin aspart (double blind mealtime)	Conventional insulin aspart	Change in HbA1c	26 weeks	Improved with intervention
Mathieu, C.; et al. 2018 ONSET-1 (34)	RCT	381	Adult (age not specified) already taking insulin detemir	Fast-acting insulin aspart	Conventional insulin aspart	Change in HbA1c	52 weeks	Improved with intervention
						Hypoglycaemic events	52 weeks	No significant difference between intervention and comparator
Klonoff, David C.; et al. 2018 ONSET-5 (35)	RCT	472	Adult (age not specified)	Fast-acting insulin aspart used in CSII	Conventional insulin aspart used in CSII	Change in HbA1c	16 weeks	Intervention non-inferior
						Change in 1 hour postprandial glucose	16 weeks	Improved with intervention
Dose comparisons								
Matsuhisa, M.; et al. 2016 EDITION JP (36)	RCT	243	Adult (age not specified)	Insulin glargine (300 U/ml)	Insulin glargine (100 U/ml)	Change in HbA1c	6 months	Intervention non-inferior
						Rate of confirmed severe hypoglycaemic events	6 months	Improved with intervention
Home, P. D.; et al. 2015 EDITION 4 (37)	RCT	549	Adult (over 30)	Insulin glargine (300 U/ml)	Insulin glargine (100 U/ml)	Change in HbA1c	6 months	Intervention non-inferior
Adjuncts to insulin								
	RCT	351	Adult (age not specified)	Canagliflozin	Placebo	Change in HbA1c	18 weeks	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Henry, R. R.; et al. 2015 (51)						Percentage of people with no change in body weight	18 weeks	Improved with intervention
Ahren, B.; et al. 2016 ADJUNCT2 (52)	RCT	835	Adult (age not specified)	Liraglutide (1.8, 1.2, 0.6 mg)	Placebo	Change in HbA1c	26 weeks	Improved with intervention
						Body weight	26 weeks	Improved with intervention
Dejgaard, T. F.; et al. 2016 ADJUNCT 1 (54)	RCT	100	Overweight participants with insufficient glycaemic control	Liraglutide (0.6, 1.2, 1.8, mg gradually increasing doses)	Placebo	Change in HbA1c	24 weeks	No significant difference between intervention and comparator
						Change in hypoglycaemic events	24 weeks	Improved with intervention

Abbreviations: RCT, randomised controlled trial; CSII continuous subcutaneous insulin infusion.

Table 5. Control of cardiovascular risk

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

Abbreviations: RCT, randomised controlled trial.

Table 6. Care of adults with type 1 diabetes in hospital

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Colunga-Lozano, L. E.; et al. 2018 (59)	Cochrane	5 studies on T1D (n = 667)	Non-critically ill hospitalised adults with diabetes mellitus	Sliding scale insulin	Basal-bolus insulin	Severe hypoglycaemic episodes, defined as blood glucose levels below 40 mg/dL (2.2 mmol/L)	Not reported	Little or no benefit with intervention
						Mean blood glucose level	Not reported	Worse with intervention
Abbreviations: T1D, type 1 diabetes								

Table 7. Managing complications

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Eye disease								
Martinez-Zapata, M. J. 2014 (67)	Cochrane	1 study (n = 61)	Adult (age not specified)	Bevacizumab with panretinal photocoagulation	Panretinal photocoagulation	Risk of losing 3 or more lines of visual acuity	12 months	Improved with intervention
		5 studies (n = 373)	Adult (age not specified)	Treatment with either bevacizumab, pegaptanib or ranibizumab	No anti-VEGF treatment	Visual acuity	12 months	Improved with intervention
		3 studies (n = 342)	Adult (age not specified)	Any anti-VEGF treatment	No anti-VEGF treatment	Risk of vitreous or pre-retinal haemorrhage	12 months	Improved with intervention
		3 studies (n = 94)	Adult (age not specified)	Bevacizumab plus vitrectomy	Vitrectomy alone	Risk of losing 3 or more lines of visual acuity	12 months	Little or no benefit with intervention
Sivaprasad, S.; et al. 2017 CLARITY (68)	RCT	22 ophthalmic centres (n not reported in the abstract)	Adults with proliferative diabetic retinopathy	Intravitreous injection of aflibercept (2mg/0.05ml)	Photocoagulation	Change in BCVA	1 year	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Jorge, E. C.; et al. 2018 (70)	Cochrane Total includes = 24 studies (4422 eyes)	3703 eyes	Adult (age not specified)	Any type of focal/grid macular laser photocoagulation	No intervention	BCVA	1 year	Improvement with intervention
		29 eyes	Adult (age not specified)	Subthreshold photocoagulation	Standard photocoagulation	Resolution of macular oedema	1 year	No significant difference between intervention and comparator
		385 eyes	Adult (age not specified)	Subthreshold photocoagulation	Standard photocoagulation	Continuous BCVA	1 year	No significant difference between intervention and comparator
		385 eyes	Adult (age not specified)	Subthreshold photocoagulation	Standard photocoagulation	Change in central macular thickness	1 year	No significant difference between intervention and comparator
		773 eyes	Adult (age not specified)	Argon laser	Other type of laser	BCVA	1 year	No significant difference between intervention and comparator
		323 eyes	Adult (age not specified)	Modified ETDRS (mETDRS) grid technique	Mild macular grid technique	BCVA	1 year	Inconclusive
Friedman, S. M.; et al. 2015 (71)	RCT	125	Adult (age not specified)	Nepafenec (0.1%)	Placebo	Mean change in optical coherence tomography retinal volume	12 months	No significant difference between intervention and comparator
Diabetic kidney disease								
Lo, C.; et al. 2018 (72)	Cochrane	7 studies (n = 1092)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Change in HbA1c	Not reported	Improved with intervention
		5 studies (n = 855)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Fasting blood glucose	Not reported	Improved with intervention
		7 studies (n = 1198)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Systolic blood pressure	Not reported	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
		7 studies (n = 3086)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Genital infections	Not reported	Worse with intervention
		5 studies (n = 1029)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Weight	Not reported	Improved with intervention
		9 studies (n not reported)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Risk of cardiovascular death	Not reported	No significant difference between intervention and comparator
		9 studies (n not reported)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Hypoglycaemia	Not reported	No significant difference between intervention and comparator
		9 studies (n not reported)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Acute kidney injury	Not reported	No significant difference between intervention and comparator
		7 studies (n = 5897)	Adult (age not specified) with diabetes and chronic kidney disease	DPP-4 inhibitors	Placebo	Change in HbA1c	Not reported	Improved with intervention
		7 studies (n = 5897)	Adult (age not specified) with diabetes and chronic kidney disease	DPP-4 inhibitors	Placebo	Fasting blood glucose	Not reported	Little or no benefit with intervention
		7 studies (n = 5897)	Adult (age not specified) with diabetes and chronic kidney disease	DPP-4 inhibitors	Placebo	Cardiovascular death	Not reported	No significant difference between intervention and comparator
		2 studies (n = 210)	Adult (age not specified) with diabetes and chronic kidney disease	DPP-4 inhibitors	Placebo	Weight	Not reported	No significant difference between intervention and comparator

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
		7 studies (n = 867)	Adult (age not specified) with diabetes and chronic kidney disease	GLP-1 agonists	Placebo	Change in HbA1c	Not reported	Improved with intervention
		2 studies (n = 551)	Adult (age not specified) with diabetes and chronic kidney disease	Sitagliptin	Glipizide	Hypoglycaemia	Not reported	Improved with intervention
DCCT EDIC group 2014 (73)	RCT	1441	Adult (age not specified)	Intensive treatment (target levels of glycaemia as close to non-diabetic range as safely possible)	Conventional treatment (prevention of symptoms of hyperglycaemia and hypoglycaemia)	Incidence of microalbuminuria	18 years	Improved with intervention
Chronic painful neuropathy								
Enomoto, H.; et al. 2018 (74)	RCT	303	Adult (age not specified)	Duloxetine (40-60mg/day)	Pregabalin (300-600 mg/day)	Mean 24hr average pain score	12 weeks	Intervention non-inferior
Mimenza Alvarado, A.; Aguilar Navarro, S. (75)	RCT	270	Adult (age not specified)	Gabapentin plus complex B vitamins	Pregabalin	Pain intensity	12 weeks	No significant difference between intervention and comparator
Mu, Y.; et al. (76)	RCT	620	Adult (age not specified)	Pregabalin (300mg/day)	Placebo	Change in mean pain score	11 weeks	No significant difference between intervention and comparator
Gastroparesis								
Olausson, E. A.; et al. 2014 (78)	RCT	56	Adult (age not specified) with gastroparesis	Small particle sized diet	Control diet	Severity of gastroparetic symptoms	20 weeks	Improved with intervention
Parkman, H. P.; et al. (79)	RCT	89	Adult (age not specified) with gastroparesis	Metoclopramide nasal spray (10 or 20mg)	Oral metoclopramide (10mg)	Total symptom score	6 weeks	Improved with intervention
Psychological problems								
Tovote, K. A.; et al. 2014 (81)	RCT	94	Adult (age not specified) with T1D and	Mindfulness-based CBT	Waitlist control	Severity of depressive symptoms	3 months	Improved with intervention

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

Abbreviations: RCT, randomised controlled trial; T1D, type 1 diabetes; CBT, cognitive behavioural therapy; BCVA, best corrected visual acuity.

Table 8. Areas not covered in the guideline

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Closed-loop insulin delivery								
Bosi, E.; et al 2019 (83)	RCT	153	Adults with recent severe hypoglycaemia or hypoglycaemia unawareness	Insulin pump therapy with integrated CGM and a suspend-before-low feature (MiniMed 640G with SmartGuard)	Insulin pump therapy with integrated CGM (MiniMed 640G)	Mean number of sensor hypoglycaemic events	6 months (with 2-week lead-in)	Improved with intervention
Tauschmann, M.; et al. 2018 (84)	RCT	86	Adults with sub-optimally controlled T1D	Day and night hybrid closed-loop insulin delivery	SAP therapy	Proportion of time that BGC was within target range of 3.9-10 mmol/L	12 weeks	Improved with intervention
						Risk of hypoglycaemia	12 weeks	Improved with intervention
Nimri, R.; et al. (85)	RCT	75	Adults and children	Night time closed-loop control (MD Logic)	SAP therapy	Time spent in hypoglycaemia (glucose concentration below 70mg/dL)	4 nights	Improved with intervention
Sensor-augmented pump therapy								
Rosenlund, S.; et al. 2015 (86)	RCT	60	Adults with a history of albuminuria and	SAP therapy	Multiple daily injections	Change in urine albumin creatine ratio	1 year	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
			were on stable renin-angiotensin system inhibition			Change in HbA1c	1 year	Improved with intervention
						Glucose variability	1 year	Improved with intervention

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

References

1. Shields BM, Shepherd M, Hudson M, McDonald TJ, Colclough K, Peters J, et al. (2017) Population-Based Assessment of a Biomarker-Based Screening Pathway to Aid Diagnosis of Monogenic Diabetes in Young-Onset Patients. Diabetes care 40(8):1017–25

2. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT (2018) Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. The lancet. Diabetes & endocrinology 6(2):122–9

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

4. Shields BM, Peters JL, Cooper C, Lowe J, Knight BA, Powell RJ, et al. (2015) Can clinical features be used to differentiate type 1 from type 2 diabetes? A systematic review of the literature. BMJ Open 5(11):e009088

5. Hope S V, Wienand-Barnett S, Shepherd M, King SM, Fox C, Khunti K, et al. (2016) Practical Classification Guidelines for Diabetes in patients treated with insulin: a cross-sectional study of the accuracy of diabetes diagnosis. The British journal of general practice : the journal of the Royal College of General Practitioners 66(646):e315

6. Mohn J, Graue M, Assmus J, Zoffmann V, Thordarson H, Peyrot M, et al. (2017) The effect of guided self-determination on self-management in persons with type 1 diabetes mellitus and HbA$_{1c}$ >=64 mmol/mol: a group-based randomised controlled trial. BMJ Open 7(6):e013295

7. Hommel E, Schmidt S, Vistisen D, Neergaard K, Gribhild M, Almdal T, et al. (2017) Effects of advanced carbohydrate counting guided by an automated bolus calculator in Type 1 diabetes mellitus (StenoABC): a 12-month, randomized clinical trial. Diabetic Medicine 34(5):708–15

8. Flodgren G, Rachas A, Farmer AJ, Inzitari M, Shepperd S (2015) Interactive telemedicine: effects on professional practice and health care outcomes. Cochrane Database of Systematic Reviews (9)

9. Esmatjes E, Jansa M, Roca D, Perez-Ferre N, del Valle L, Martinez-Hervas S, et al. (2014) The efficiency of telemedicine to optimize metabolic control in patients with type 1 diabetes mellitus: Telemed study. Diabetes Technology & Therapeutics 16(7):435–41

10. Di Bartolo P, Nicolucci A, Cherubini V, Iafusco D, Scardapane M, Rossi MC (2017) Young patients with type 1 diabetes poorly controlled and poorly compliant with self-monitoring of blood glucose: can technology help? Results of the i-NewTrend randomized clinical trial. Acta Diabetologica 54(4):393–402

11. Zhou W, Chen M, Yuan J, Sun Y (2016) Welltang - A smart phone-based diabetes management application - Improves blood glucose control in Chinese people with diabetes. Diabetes Research & Clinical Practice 116:105–10

12. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R (2016) Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 388(10057):2254–63

13.   Oskarsson P, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R, Bolinder J (2018) Impact of flash glucose monitoring on hypoglycaemia in adults with type 1 diabetes managed with multiple daily injection therapy: a pre-specified subgroup analysis of the IMPACT randomised controlled trial. Diabetologia 61(3):539–50

14.   Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. (2017) Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA 317(4):371–8

15.   Lind M, Polonsky W, Hirsch IB, Heise T, Bolinder J, Dahlqvist S, et al. (2017) Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. JAMA 317(4):379–87

16.   Polonsky WH, Hessler D, Ruedy KJ, Beck RW, Group DS (2017) The Impact of Continuous Glucose Monitoring on Markers of Quality of Life in Adults With Type 1 Diabetes: Further Findings From the DIAMOND Randomized Clinical Trial. Diabetes Care 40(6):736–41

17.   Riddlesworth T, Price D, Cohen N, Beck RW (2017) Hypoglycemic Event Frequency and the Effect of Continuous Glucose Monitoring in Adults with Type 1 Diabetes Using Multiple Daily Insulin Injections. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 8(4):947–51

18.   Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, et al. (2018) Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 391(10128):1367–77

19.   Little SA, Leelarathna L, Walkinshaw E, Tan HK, Chapple O, Lubina-Solomon A, et al. (2014) Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 x 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). Diabetes Care 37(8):2114–22

20.   Little SA, Speight J, Leelarathna L, Walkinshaw E, Tan HK, Bowes A, et al. (2018) Sustained Reduction in Severe Hypoglycemia in Adults With Type 1 Diabetes Complicated by Impaired Awareness of Hypoglycemia: Two-Year Follow-up in the HypoCOMPaSS Randomized Clinical Trial. Diabetes Care 41(8):1600–7

21.   Garg S, Dreyer M, Jinnouchi H, Mou J, Qu Y, Hartman ML, et al. (2016) A randomized clinical trial comparing basal insulin peglispro and insulin glargine, in combination with prandial insulin lispro, in patients with type 1 diabetes: IMAGINE 1. Diabetes, Obesity & Metabolism 18suppl2:25–33

22.   Bergenstal RM, Lunt H, Franek E, Travert F, Mou J, Qu Y, et al. (2016) Randomized, double-blind clinical trial comparing basal insulin peglispro and insulin glargine, in combination with prandial insulin lispro, in patients with type 1 diabetes: IMAGINE 3. Diabetes, Obesity & Metabolism 18(11):1081–8

23.   Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A, et al. (2016) Short?acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus. Cochrane Database of Systematic Reviews (6)

24.   Pedersen-Bjergaard U, Kristensen PL, Beck-Nielsen H, Norgaard K, Perrild H,

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

25.   Heise T, Norskov M, Nosek L, Kaplan K, Famulla S, Haahr HL (2017) Insulin degludec: Lower day-to-day and within-day variability in pharmacodynamic response compared with insulin glargine 300 U/mL in type 1 diabetes. Diabetes, Obesity & Metabolism 19(7):1032–9

26.   Lane W, Bailey TS, Gerety G, Gumprecht J, Philis-Tsimikas A, Hansen CT, et al. (2017) Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA 318(1):33–44

27.   Davies MJ, Gross JL, Ono Y, Sasaki T, Bantwal G, Gall MA, et al. (2014) Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: a 26-week randomized, open-label, treat-to-target non-inferiority trial. Diabetes, Obesity & Metabolism 16(10):922–30

28.   Garg SK, Wernicke-Panten K, Rojeski M, Pierre S, Kirchhein Y, Jedynasty K (2017) Efficacy and Safety of Biosimilar SAR342434 Insulin Lispro in Adults with Type 1 Diabetes Also Using Insulin Glargine-SORELLA 1 Study. Diabetes Technology & Therapeutics 19(9):516–26

29.   Blevins TC, Dahl D, Rosenstock J, Ilag LL, Huster WJ, Zielonka JS, et al. (2015) Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. Diabetes, Obesity & Metabolism 17(8):726–33

30.   Home PD, Lam RLH, Carofano WL, Golm GT, Eldor R, Crutchlow MF, et al. (2018) Efficacy and safety of MK-1293 insulin glargine compared with originator insulin glargine (Lantus) in type 1 diabetes: A randomized, open-label clinical trial. Diabetes, Obesity & Metabolism 20(9):2220–8

31.   Blevins TC, Barve A, Sun B, Ankersen M (2018) Efficacy and safety of MYL-1501D vs insulin glargine in patients with type 1 diabetes after 52 weeks: Results of the INSTRIDE 1 phase III study. Diabetes, Obesity & Metabolism 20(8):1944–50

32.   Russell-Jones D, Bode BW, De Block C, Franek E, Heller SR, Mathieu C, et al. (2017) Fast-Acting Insulin Aspart Improves Glycemic Control in Basal-Bolus Treatment for Type 1 Diabetes: Results of a 26-Week Multicenter, Active-Controlled, Treat-to-Target, Randomized, Parallel-Group Trial (onset 1). Diabetes Care 40(7):943–50

33.   Buse JB, Carlson AL, Komatsu M, Mosenzon O, Rose L, Liang B, et al. (2018) Fast-acting insulin aspart versus insulin aspart in the setting of insulin degludec-treated type 1 diabetes: Efficacy and safety from a randomized double-blind trial. Diabetes, Obesity & Metabolism 20(12):2885–93

34.   Mathieu C, Bode BW, Franek E, Philis-Tsimikas A, Rose L, Graungaard T, et al. (2018) Efficacy and safety of fast-acting insulin aspart in comparison with insulin aspart in type 1 diabetes (onset 1): A 52-week, randomized, treat-to-target, phase III trial. Diabetes, Obesity & Metabolism 20(5):1148–55

35.   Klonoff DC, Evans ML, Lane W, Kempe H-P, Renard E, DeVries JH, et al. (2018) A randomized, multicentre trial evaluating the efficacy and safety of fast-acting insulin aspart in continuous subcutaneous insulin infusion in adults with type 1 diabetes (onset 5). Diabetes, Obesity & Metabolism 09:9

36.	Matsuhisa M, Koyama M, Cheng X, Takahashi Y, Riddle MC, Bolli GB, et al. (2016) New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1). Diabetes, Obesity & Metabolism 18(4):375–83

37.	Home PD, Bergenstal RM, Bolli GB, Ziemen M, Rojeski M, Espinasse M, et al. (2015) New Insulin Glargine 300 Units/mL Versus Glargine 100 Units/mL in People With Type 1 Diabetes: A Randomized, Phase 3a, Open-Label Clinical Trial (EDITION 4). Diabetes Care 38(12):2217–25

38.	Matsuhisa M, Koyama M, Cheng X, Sumi M, Riddle MC, Bolli GB, et al. (2016) Sustained glycaemic control and less nocturnal hypoglycaemia with insulin glargine 300U/mL compared with glargine 100U/mL in Japanese adults with type 1 diabetes (EDITION JP 1 randomised 12-month trial including 6-month extension). Diabetes Research & Clinical Practice 122:133–40

39.	Heller S, White D, Lee E, Lawton J, Pollard D, Waugh N, et al. (2017) A cluster randomised trial, cost-effectiveness analysis and psychosocial evaluation of insulin pump therapy compared with multiple injections during flexible intensive insulin therapy for type 1 diabetes: the REPOSE Trial. Health Technology Assessment (Winchester, England) 21(20):1–278

40.	Beck RW, Riddlesworth TD, Ruedy KJ, Kollman C, Ahmann AJ, Bergenstal RM, et al. (2017) Effect of initiating use of an insulin pump in adults with type 1 diabetes using multiple daily insulin injections and continuous glucose monitoring (DIAMOND): a multicentre, randomised controlled trial. The Lancet Diabetes & Endocrinology 5(9):700–8

41.	Freckmann G, Arndt S, Fieselmann A, Klausmann G, Pralle K, Kunsting T, et al. (2017) Randomized Cross-Over Study Comparing Two Infusion Sets for CSII in Daily Life. Journal of Diabetes Science & Technology 11(2):253–9

42.	Garg SK, Henry RR, Banks P, Buse JB, Davies MJ, Fulcher GR, et al. (2017) Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. New England Journal of Medicine 377(24):2337–48

43.	Danne T, Cariou B, Banks P, Brandle M, Brath H, Franek E, et al. (2018) HbA$_{1c}$ and Hypoglycemia Reductions at 24 and 52 Weeks With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: The European inTandem2 Study. Diabetes Care 41(9):1981–90

44.	Buse JB, Garg SK, Rosenstock J, Bailey TS, Banks P, Bode BW, et al. (2018) Sotagliflozin in Combination With Optimized Insulin Therapy in Adults With Type 1 Diabetes: The North American inTandem1 Study. Diabetes Care 41(9):1970–80

45.	Pieber TR, Famulla S, Eilbracht J, Cescutti J, Soleymanlou N, Johansen OE, et al. (2015) Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). Diabetes, Obesity & Metabolism 17(10):928–35

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

47.   Rosenstock J, Marquard J, Laffel LM, Neubacher D, Kaspers S, Cherney DZ, et al. (2018) Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials. Diabetes Care 41(12):2560–9

48.   Dandona P, Mathieu C, Phillip M, Hansen L, Griffen SC, Tschope D, et al. (2017) Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. The Lancet Diabetes & Endocrinology 5(11):864–76

49.   Dandona P, Mathieu C, Phillip M, Hansen L, Tschope D, Thoren F, et al. (2018) Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes: The DEPICT-1 52-Week Study. Diabetes Care 41(12):2552–9

50.   Mathieu C, Dandona P, Gillard P, Senior P, Hasslacher C, Araki E, et al. (2018) Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes (the DEPICT-2 Study): 24-Week Results From a Randomized Controlled Trial. Diabetes Care 41(9):1938–46

51.   Henry RR, Thakkar P, Tong C, Polidori D, Alba M (2015) Efficacy and Safety of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-on to Insulin in Patients With Type 1 Diabetes. Diabetes Care 38(12):2258–65

52.   Ahren B, Hirsch IB, Pieber TR, Mathieu C, Gomez-Peralta F, Hansen TK, et al. (2016) Efficacy and Safety of Liraglutide Added to Capped Insulin Treatment in Subjects With Type 1 Diabetes: The ADJUNCT TWO Randomized Trial. Diabetes Care 39(10):1693–701

53.   Mathieu C, Zinman B, Hemmingsson JU, Woo V, Colman P, Christiansen E, et al. (2016) Efficacy and Safety of Liraglutide Added to Insulin Treatment in Type 1 Diabetes: The ADJUNCT ONE Treat-To-Target Randomized Trial. Diabetes Care 39(10):1702–10

54.   Dejgaard TF, Frandsen CS, Hansen TS, Almdal T, Urhammer S, Pedersen-Bjergaard U, et al. (2016) Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. The Lancet Diabetes & Endocrinology 4(3):221–32

55.   Mkrtumyan A, Romantsova T, Vorobiev S, Volkova A, Vorokhobina N, Tarasov S, et al. (2018) Efficacy and safety of Subetta add-on therapy in type 1 diabetes mellitus: The results of a multicenter, double-blind, placebo-controlled, randomized clinical trial. Diabetes Research & Clinical Practice 142:1–9

56.   Group ASC, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, et al. (2018) Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. New England Journal of Medicine 379(16):1529–39

57.   Group ASC, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, et al. (2018) Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus. New England Journal of Medicine 379(16):1540–50

58.   B OH, Szymonifka J, Okin PM (2018) Achieving target SBP for lowering the risk of major adverse cardiovascular events in persons with diabetes mellitus. Journal of Hypertension 36(1):101–9

59.   Colunga?Lozano LE, Gonzalez Torres FJ, Delgado?Figueroa N, Gonzalez?Padilla DA, Hernandez A V, Roman Y, et al. (2018) Sliding scale insulin for non?critically ill hospitalised adults with diabetes mellitus. Cochrane Database of Systematic Reviews

(11)

60. Mehta H, Hennings C, Gillies MC, Nguyen V, Campain A, Fraser?Bell S (2018) Anti?vascular endothelial growth factor combined with intravitreal steroids for diabetic macular oedema. Cochrane Database of Systematic Reviews (4)

61. Virgili G, Parravano M, Evans JR, Gordon I, Lucenteforte E (2018) Anti?vascular endothelial growth factor for diabetic macular oedema: a network meta?analysis. Cochrane Database of Systematic Reviews (10)

62. Wiley HE, Thompson DJ, Bailey C, Chew EY, Cukras CA, Jaffe GJ, et al. (2016) A Crossover Design for Comparative Efficacy: A 36-Week Randomized Trial of Bevacizumab and Ranibizumab for Diabetic Macular Edema. Ophthalmology 123(4):841–9

63. Berger A, Sheidow T, Cruess AF, Arbour JD, Courseau AS, de Takacsy F (2015) Efficacy/safety of ranibizumab monotherapy or with laser versus laser monotherapy in DME. Canadian Journal of Ophthalmology 50(3):209–16

64. Do D V, Sepah YJ, Boyer D, Callanan D, Gallemore R, Bennett M, et al. (2015) Month-6 primary outcomes of the READ-3 study (Ranibizumab for Edema of the mAcula in Diabetes-Protocol 3 with high dose). Eye (Basingstoke) 29(12):1538–44

65. Gale JD, Berger B, Gilbert S, Popa S, Sultan MB, Schachar RA, et al. (2018) A CCR2/5 Inhibitor, PF-04634817, Is Inferior to Monthly Ranibizumab in the Treatment of Diabetic Macular Edema. Investigative Ophthalmology & Visual Science 59(6):2659–69

66. Campochiaro PA, Khanani A, Singer M, Patel S, Boyer D, Dugel P, et al. (2016) Enhanced Benefit in Diabetic Macular Edema from AKB-9778 Tie2 Activation Combined with Vascular Endothelial Growth Factor Suppression. Ophthalmology 123(8):1722–30

67. Martinez?Zapata MJ, Mart??Carvajal AJ, Sol? I, Pijo?n JI, Buil?Calvo JA, Cordero JA, et al. (2014) Anti?vascular endothelial growth factor for proliferative diabetic retinopathy. Cochrane Database of Systematic Reviews (11)

68. Sivaprasad S, Prevost AT, Vasconcelos JC, Riddell A, Murphy C, Kelly J, et al. (2017) Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, n. Lancet 389(10085):2193–203

69. Song JH, Chin HS, Kwon OW, Lim SJ, Kim HK, Group DR (2015) Effect of sulodexide in patients with non-proliferative diabetic retinopathy: diabetic retinopathy sulodexide study (DRESS). Graefes Archive for Clinical & Experimental Ophthalmology 253(6):829–37

70. Jorge EC, Jorge EN, Botelho M, Farat JG, Virgili G, El Dib R (2018) Monotherapy laser photocoagulation for diabetic macular oedema. Cochrane Database of Systematic Reviews (10)

71. Friedman SM, Almukhtar TH, Baker CW, Glassman AR, Elman MJ, Bressler NM, et al. (2015) Topical nepafenec in eyes with noncentral diabetic macular edema. Retina 35(5):944–56

72. Lo C, Toyama T, Wang Y, Lin J, Hirakawa Y, Jun M, et al. (2018) Insulin and

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

73.   group DE research (2014) Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. The Lancet Diabetes & Endocrinology 2(10):793–800

74.   Enomoto H, Yasuda H, Nishiyori A, Fujikoshi S, Furukawa M, Ishida M, et al. (2018) Duloxetine in patients with diabetic peripheral neuropathic pain in Japan: A randomized, double-blind, noninferiority comparative study with pregabalin. Journal of Pain Research 11:1857–68

75.   Mimenza Alvarado A, Aguilar Navarro S (2016) Clinical trial assessing the efficacy of gabapentin plus B complex (B1/B12) versus pregabalin for treating painful diabetic neuropathy. Journal of Diabetes Research 2016(no pagination)

76.   Mu Y, Liu X, Li Q, Chen K, Liu Y, Lv X, et al. (2018) Efficacy and safety of pregabalin for painful diabetic peripheral neuropathy in a population of Chinese patients: A randomized placebo-controlled trial. Journal Of Diabetes 10(3):256–65

77.   Baba M, Matsui N, Kuroha M, Wasaki Y, Ohwada S (2019) Mirogabalin for the Treatment of Diabetic Peripheral Neuropathic Pain: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study in Asian Patients. Journal of Diabetes Investigation 23:23

78.   Olausson EA, St?rsrud S, Grundin H, Isaksson M, Attvall S, Simr?n M (2014) A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. American journal of gastroenterology 109(3):375–85

79.   Parkman HP, Carlson MR, Gonyer D (2014) Metoclopramide nasal spray is effective in symptoms of gastroparesis in diabetics compared to conventional oral tablet. Neurogastroenterology & Motility 26(4):521–8

80.   Camilleri M, McCallum RW, Tack J, Spence SC, Gottesdiener K, Fiedorek FT (2017) Efficacy and Safety of Relamorelin in Diabetics With Symptoms of Gastroparesis: A Randomized, Placebo-Controlled Study. Gastroenterology 153(5):1240–1250.e2

81.   Tovote KA, Fleer J, Snippe E, Peeters AC, Emmelkamp PM, Sanderman R, et al. (2014) Individual mindfulness-based cognitive therapy and cognitive behavior therapy for treating depressive symptoms in patients with diabetes: results of a randomized controlled trial. Diabetes Care 37(9):2427–34

82.   Sajatovic M, Gunzler DD, Kanuch SW, Cassidy KA, Tatsuoka C, McCormick R, et al. (2017) A 60-Week Prospective RCT of a Self-Management Intervention for Individuals With Serious Mental Illness and Diabetes Mellitus. Psychiatric Services 68(9):883–90

83.   Bosi E, Choudhary P, de Valk HW, Lablanche S, Castañeda J, de Portu S, et al. (2019) Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): an open-label randomised controlled trial. The lancet. Diabetes & endocrinology 7(6):462–72

84.   Tauschmann M, Thabit H, Bally L, Allen JM, Hartnell S, Wilinska ME, et al. (2018) Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet 392(10155):1321–9

85.   Nimri R, Bratina N, Kordonouri O, Avbelj Stefanija M, Fath M, Biester T, et al. (2017) MD-Logic overnight type 1 diabetes control in home settings: A multicentre, multinational, single blind randomized trial. Diabetes, Obesity & Metabolism 19(4):553–61

86.   Rosenlund S, Hansen TW, Rossing P, Andersen S (2015) Effect of Sensor-Augmented Pump Treatment Versus Multiple Daily Injections on Albuminuria: A 1-Year Randomized Study. Journal of Clinical Endocrinology & Metabolism 100(11):4181–8