NICE National Institute for Health and Care Excellence

Surveillance proposal consultation document

2019 surveillance of 4 diabetes guidelines

Surveillance proposal

We propose to update the following guidelines on diabetes at this time:

- Type 1 diabetes in adults: diagnosis and management (NICE guideline NG17). The proposed update will focus on insulin therapy and management of complications.
- Type 2 diabetes in adults: management (NICE guideline NG28). The proposed update will focus on blood glucose management and management of complications.
- Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NICE guideline NG18). The proposed update will focus on measures to encourage screening for diabetic retinopathy and fluid and insulin therapy for diabetic ketoacidosis.

We propose to not update the guideline on Diabetic foot problems: prevention and management (NICE guideline NG19).

Reasons for the proposals

This section provides a summary of the reasons for the proposals.

Type 1 diabetes in adults: diagnosis and management

Blood glucose management

Telemedicine

Evidence was identified to support the use of telemedicine to manage blood glucose. Telemedicine interventions such as remote monitoring devices linked to clinicians for review, online education platforms and teleconference sessions were all found to significantly reduce HbA1c levels. 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.

Smartphone applications and online platforms

Evidence was identified to support the use of a smartphone application to enhance self-monitoring. This area is relevant 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 digital platforms as an area that is in need of review. Considering the ongoing work in this area, the new evidence on smartphone applications and the importance of digital platforms emphasised in the NHS Long-Term Plan, it is proposed that this area is reviewed.

Flash glucose monitoring

Evidence was identified to support the use of Flash glucose monitoring in people with well-controlled diabetes. Topic experts also highlighted this as an area in need of review. Currently the guideline does not contain any recommendations on Flash glucose monitoring, however some of the evidence identified has already been considered in the NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110) which covers people with type 1 and type 2 diabetes, as well as pregnant women with diabetes. This area is also relevant to a recent policy change in the NHS, ensuring access to Flash glucose monitoring on prescription in the NHS if patients meet various eligibility criteria such as: 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 with their clinician); as well as other criteria listed in this statement. The new evidence does not cover these populations because the studies only include people with well-controlled diabetes, however given that the evidence on this device has not yet been considered since this guideline was published, it is proposed that this area is reviewed.

Insulin therapy

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). Given the 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.

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 raised 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. In light of the new evidence, it is proposed that this area is reviewed.

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. 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 or weight loss.

Managing complications

Eye disease

New evidence was identified on the treatment of diabetic eye disease, including retinopathy and macular oedema. The evidence supports the use of anti-VEGF treatment and intravitreous injection of aflibercept for diabetic retinopathy and laser therapy for diabetic macular oedema. Currently the guideline has recommendations on screening and referral, but no recommendations on specific treatments. However, there are many treatments covered in NICE technology appraisal guidance, suggesting that there may be a gap in the recommendations of NICE guideline NG17. Given the growing evidence base and the related NICE technology appraisal guidance, we propose that this area is reviewed.

Topic experts also highlighted new evidence on the optimum frequency of diabetic eye screening. 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.

Areas not proposed for update

Evidence was identified on education and information, dietary management and control of cardiovascular risk which directly supports or is consistent with existing recommendations and therefore has no impact on NICE guideline NG17.

Evidence was also identified on care of adults with type 1 diabetes in hospital which indicates that while basal-bolus insulin might result in better short-term glycaemic control than sliding scale insulin, it could also increase the risk for severe hypoglycaemic episodes. However, the new evidence was inconclusive about which insulin strategy has the best patient outcomes so further research is required before any impact on the guideline, which recommends using the basal-bolus strategy, can be concluded.

Evidence was also identified on areas not currently covered in NICE guideline NG17 which supports the use of closed-loop insulin delivery systems and sensor-augmented pump therapy in adults with type 1 diabetes, however further evidence from larger randomised control trials, with long-term follow-up and examining safety outcomes is required to confirm these findings.

For further details and a summary of all evidence identified in surveillance, see appendix A1 (NG17- type 1 diabetes in adults evidence summary).

Type 2 diabetes in adults

Blood glucose management

First intensification

Clinical characteristics

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

- The presence of established atherosclerotic cardiovascular disease (CVD), for which there is now evidence to support the use of SGLT2 inhibitors and GLP1 agonist classes. However, some studies of individual drugs within these classes have demonstrated superiority over placebo (Harmony Outcomes [albiglutide], LEADER [liraglutide]) whereas others have not (ELIXA [lixisenatide] and EXSCEL [exenatide] suggesting that this may not be a class effect.
- Other comorbidities, such as heart failure or chronic kidney disease
- Risk of specific adverse medicine effects, particularly hypoglycaemia and weight gain.
- Safety and tolerability.

Cost effectiveness

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

The committee therefore agreed it was appropriate that a larger scale update of the antidiabetic drug pathway in NICE NG28 be undertaken, and that this should be timed to also take in to account the evidence from several large trials, which were ongoing at the time, so all the relevant drugs from these classes can be considered:

These key CVD outcome trials, have now published:

DECLARE-TIMI 58 (dapagliflozin), HARMONY Outcomes (albiglutide),

EXSCEL (exenatide)

REWIND (dulaglutide – preliminary results).

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

- Consideration of the concurrent review of related technology appraisals (TAs) and ongoing development of new TAs for SGLT2 inhibitors and GLP1 analogues. These will incorporate new evidence for canagliflozin, dapagliflozin, empagliflozin and ertugliflozin in the SGLT-2 class, and semaglutide and dulaglutide in the GLP-1 class. Both dual (first intensification) and triple (second intensification) therapy are covered within the scope of these TAs.
- Clinical characteristics detailed above and the potential need to adopt a risk stratification approach to sequencing of treatment.
- Safety and tolerability, taking into account the latest MHRA safety warning for SGLT-2 inhibitors.
- Patient adherence, taking into account frequency of monitoring and route of administration.
- Acquisition costs of individual drugs and cost effectiveness of drug combinations from different classes. The 2017 review committee noted that SGLT2 inhibitors had the same price per dose in 2017. No cost studies were identified on this class, but new evidence for GLP-1 analogues is conflicting on the comparative cost effectiveness of liraglutide and exenatide. A review of the health economic model is proposed.

Second intensification

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

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

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

The guideline refers to DPP-4 inhibitors, GLP-1 mimetics and sulfonylureas at a class level in the recommendations, and to SGLT-2 inhibitors in additional text added since publication. However, cardiovascular outcomes were not considered in the guideline and therefore the same rationale for a comprehensive review of the antidiabetic drug pathway applies to second intensification as for first intensification (as detailed above). The review of second intensification should also consider:

- The evidence indicating that GLP-1 mimetics as a class may be cost effective, with additional drug costs offset by diabetes-related complication decreases, leading to slightly lower direct medical costs.
- Evidence supporting the use of liraglutide for T2D in combination with insulin, particularly for improving glucose control, cardiovascular outcomes and weight loss.

Insulin-based treatments

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

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

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

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

Insulin monotherapy compared with the addition of oral antidiabetic drugs

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

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

Managing complications

Eye disease

The same reason for updating and proposed review of recommendations for diabetic eye disease as stated for NG17 applies to NG28. New evidence was identified on the treatment of diabetic eye disease, including retinopathy and macular oedema. Given the growing evidence base and the related NICE technology appraisal guidance, we propose that this area is reviewed.

Areas not proposed for update

Evidence was identified on individualised care, patient education and antiplatelet therapy which directly supports or is consistent with existing recommendations and therefore has no impact on NICE guideline NG28.

New evidence was identified concerning dietary advice and the effectiveness of low or very low-calorie diets on short-term remission of type 2 diabetes in adults, however it is proposed that further evidence of long-term effectiveness of these diets is required before this is considered as an area for update. It is also felt that advising on low-calorie diets would not be at odds with the current recommendations to provide adults with type 2 diabetes individualised advice for carbohydrate intake and meal patterns.

New evidence was also identified concerning the use of motivational interviewing techniques for changing diet in adults with type 2 diabetes, results of which were inconclusive, with variation in trial and interventions design (components and intensity) making it difficult to identify best practice strategies. There are currently no recommendations on motivational interviewing, but it is proposed that further research identifying the effective components of motivational interviewing would be required for this to be considered as an area for update.

For further details and a summary of all evidence identified in surveillance, see appendix A2 (NG28 – type 2 diabetes in adults).

Diabetes (type 1 and type 2) in children and young people

Diabetic retinopathy in children and young people with type 1 or type 2 diabetes

Evidence was identified indicating that compared with usual care, quality improvement initiatives incorporating behaviour change techniques such as goal-setting and additional social support lead to a substantial increase in diabetic retinopathy screening attendance and are likely to be cost effective. While uptake data for NICE guideline NG18 indicates that there have been annual increases between 2015 and 2017 in the percentage of children aged 12 years or older with type 1 diabetes having an eye screening or a referral for eye screening, there remains room for improvement with the figure in 2017 at 74.4%; and the uptake data for children aged 12 years or older who have type 2 diabetes indicates that only just over half (54.8%) attended an annual eye screening appointment in 2017. The current recommendations 1.2.1 to 1.2.11 and 1.3.1 to 1.3.7 on education and information for children and young people with type 1 or type 2 diabetes respectively, discuss the need to provide a continuing, tailored programme of education but do not mention any behaviour change techniques that may improve actions such as attendance at screening appointments. It is therefore proposed that investigating the effectiveness of incorporating behaviour change techniques into services for children with diabetes is an area for review.

Fluid and insulin therapy for diabetic ketoacidosis

Evidence was identified which indicates that rapid fluid infusion at volumes higher than those currently recommend in recommendation 1.4.31 is not associated with an increased risk of cerebral oedema in children and young people with diabetic ketoacidosis; and that in the case of severe diabetic ketoacidosis, more rapid fluid infusion rates may be associated with faster improvements in mental status. This evidence, along with international guidance reported by the International society for pediatric and adolescent diabetes (ISPAD) and topic expert opinion, indicates that this should be an area for review.

Areas not proposed for update

New evidence that directly supports or is consistent with existing recommendations and therefore has no impact on NICE guideline NG18 includes: evidence related to aspects of insulin therapy (offering multiple daily injections, basal-bolus insulin regimens from diagnosis, followed by offering continuous subcutaneous insulin infusion or pump if injections aren't appropriate), dietary management, blood glucose targets and monitoring, psychological and social issues in children and young people with type 1 diabetes; education and information and the use of metformin in children and young people with type 2 diabetes; service provision and transition from paediatric to adult care for children and young people with type 1 or type 2 diabetes.

Areas for which new evidence was identified, but the evidence base remains limited: the use of automated tools or systems to assist in the identification and diagnosis of type 2 diabetes in children and young people; insulin therapy for children and young people with type 1 diabetes which supports the use of the long-acting insulin in reducing HbA1c and the use of hybrid closed-loop therapy in controlling glucose and reducing the risk of hypoglycaemia; oral medicines for children and young people with type 1 diabetes which supports the use of metformin as an adjunct to insulin in improving HbA1c levels in the short-term. Further evidence from larger randomised control trials is required in order to consider whether these should be areas for update.

For further details and a summary of all evidence identified in surveillance, see appendix A3 (NG18 – Type 1 and type 2 diabetes in children evidence summary).

Diabetic foot problems

The majority of evidence was found to be consistent with the current guideline recommendations. Improvements were seen in the area of wound dressings for several wound healing outcomes, however there was a lack of comparison between interventions. The evidence found supports the use of wound dressings as an intervention rather than highlighting a specific product. Evidence for new treatment options was thinly spread across multiple products, with no evidence of product superiority found. This is in line with topic expert feedback which suggested the new trials available would be unlikely to impact the current guideline recommendations. We did not look for evidence relating to the use of systemic antibiotics for the treatment of diabetic foot infection as an antimicrobial prescribing guideline is in production in this area.

For further details and a summary of all evidence identified in surveillance, see appendix A4 (NG19 – diabetic foot problems).

Overview of 2019 surveillance methods

NICE's surveillance team checked whether recommendations in the following guidelines remain up to date:

- Type 1 diabetes in adults: diagnosis and management (NICE guideline NG17)
- Type 2 diabetes in adults: management (NICE guideline NG28)
- Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NICE guideline NG18)
- Diabetic foot problems: prevention and management (NICE guideline NG19)

For all guidelines, the surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- A search for new or updated Cochrane reviews.

- Examining related NICE guidance and quality standards and NIHR signals.
- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders (this document).

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in surveillance

Search and selection strategy

For details of the individual search and selection strategies used please refer to the following appendices:

- Appendix A1 (NG17 - Type 1 diabetes in adults)
- Appendix A2 (NG28 - Type 2 diabetes in adults)
- Appendix A3 (NG18 - Type 1 and type 2 diabetes in children)
- Appendix A4 (NG19 – Diabetic foot problems)

Intelligence gathered during surveillance

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to each of the 4 guidelines.

The following responses were received from 20 topic expert questionnaires sent for each guideline:

- NICE guideline NG17- Six responses were received, 5 of the experts felt an update was needed and 1 was unsure.
- NICE guideline NG28 – Seven responses were received, all 7 of the experts agreed that an update is needed.

- NICE guideline NG18 – Five responses were received, 4 of the experts felt an update was needed and 1 was unsure.
- NICE guideline NG19 – Seven responses were received, all 7 of the experts agreed that no update is required at this time.

For full details of the topic expert feedback for these 4 guidelines, please see appendices A1-A4.

Views of stakeholders

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Equalities

No equalities issues were identified during the surveillance process.

Editorial amendments

During surveillance of the guidelines we identified the following points in each of the 4 guidelines that should be amended.

Type 1 diabetes in adults

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".

Type 2 diabetes in adults

Antihypertensive drug treatment

NICE guideline CG127 on hypertension in adults, recommendation 1.6.15 states that low cost angiotensin II receptor blocker (ARB) should be used in preference to an ACE inhibitor in all African or Caribbean people because of the low risk of angioedema. However, NG28 Recommendation 1.4.8 currently states the first line treatment should be an ACE inhibitor for a person of African or Caribbean family origin. Recommendation 1.4.10 advises that for a person with continuing intolerance to an ACE inhibitor (other than renal deterioration or hyperkalaemia), substitute an ARB for the ACE inhibitor.

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

Cross-referrals

Recommendation 1.3.10: the cross referral to smoking: brief interventions and referrals and stop smoking services should be replaced with Stop smoking interventions and services. This should be done following the forthcoming review of the suite of NICE guidelines on smoking, to ensure the cross referral is current.

Recommendations 1.6.24 and 1.6.26: the following text will be added at the end to replace existing text cross referring to TAs: "Following the development of this guideline, new TAs are available that are relevant to this section. Please see the Type 2 diabetes in adults' pathway for further information."

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

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

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

Diabetes (type 1 and type 2) in children and young people

Recommendation 1.2.32 lists the 'sulphonylureas', these are now spelled 'sulfonylureas', so should be changed to this new spelling. 'glyburide' is listed but that name isn't used in the UK and is a synonym for 'glibenclamide', which is already listed. 'glyburide' should therefore be removed from this recommendation.

Recommendations 1.2.110 and 1.3.43 require the following footnote adding: "screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme."

Recommendation 1.3.14 the cross-referrals to NICE guideline NG7 on 'preventing excess weight gain' and NICE guideline CG189 on 'obesity: identification, assessment and management' should be replaced with cross-referrals to the NICE physical activity, obesity and diet pathways

Diabetic foot problems

Section 1, Recommendations: The text box highlighting the certainty of recommendations contains an incorrect hyperlink. The following link "See about this guideline for details" goes to 'changes after publication'. It should be updated to About this guideline.

Overall surveillance proposal

After considering all evidence and other intelligence and the impact on current recommendations, we propose the following guidelines should be updated:

- Type 1 diabetes in adults: diagnosis and management (NICE guideline NG17).
- Type 2 diabetes in adults: management (NICE guideline NG28).
- Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NICE guideline NG18).

We propose to not update the guideline on Diabetic foot problems: prevention and management (NICE guideline NG19).

Appendix A2: Summary of evidence from surveillance

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

Contents:

- Evidence considered in surveillance
- Intelligence gathered during surveillance
- Summary of evidence from surveillance

Evidence considered in surveillance

Search and selection strategy

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

- Dietary advice
- Blood glucose management:
  - Self-monitoring of blood glucose
  - Drug treatment

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

We found 170 studies in a search for RCTs and systematic reviews published between 1 June 2014 and 12 February 2019.

See summary of evidence from surveillance below for details of all evidence considered, and references.

Selecting relevant studies

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

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

- Studies that included both type 1 and type 2 diabetes were excluded if they did not distinguish between the populations in the results.
- Post-hoc, pilot and secondary analysis studies were excluded unless prespecified in study protocols
- Single studies already included in a Cochrane review were excluded.
- Non-Cochrane systematic reviews were only included for priority areas and if they had a publication date of 2018 or later.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 16 were assessed as having the potential to change recommendations; therefore we plan to check the publication status regularly, and evaluate the impact of the results on current recommendations as quickly as possible. These studies are:

- Preventing cardiovascular and renal complications in patients with type 2 diabetes and microalbuminuria: the GP-Prompt study
- Can a new method of monitoring improve the control of blood glucose levels in patient with Type II diabetes who have had a heart attack?
- Glucose Lowering through Weight Management (GLoW)
- Effectiveness of multimodal imaging for the evaluation of retinal odema and new vessels in diabetic retinopathy
- TriMaster - a research study to help improve treatment of type 2 diabetes, by learning how individuals respond to different blood sugar-lowering drugs
- Embedding Diabetes Education (RCT)
- Circulating biomarkers to detect sight-threatening diabetic retinopathy
- Impact of a community based social prescribing intervention on people with type 2 diabetes in an ethnically diverse area of high socio-economic deprivation. Exploiting a natural experiment to evaluate effects on health and health care utilisation with economic assessment and ethnographic observation
- A comparison of standard laser with micropulse laser for the treatment of diabetic macular oedema
- Optimising cardiac surgery outcomes in people with diabetes
- Lowering Events in Non-proliferative retinopathy in Scotland
- Performance Check of the Abbott FreeStyle Libre Flash Glucose Monitoring System
- Education programme (DESMOND-ID) for the self-management of type 2 diabetes for adults with intellectual disabilities (ID)

- Implementation intentions for creating and breaking habits in care provided to patients with type 2 diabetes: a dual process approach
- Masked performance check of the Abbott FreeStyle Libre Flash Glucose Monitoring System
- Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND).

Intelligence gathered during surveillance

Views of topic experts

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

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

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

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

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

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

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

Other sources of information

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

Summary of evidence from surveillance

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

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

1.1 Individualised care

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

Integrated personalised management

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

Intelligence gathering

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

Impact statement

The new evidence on personalised diabetes management for T2D in adults is consistent with recommendation 1.1.1, which recommends an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with type 2 diabetes, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy.

New evidence is unlikely to change guideline recommendations.

1.2 Patient education

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

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

Web-based self-management

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

prespecified subgroup analysis of participants who had been more recently diagnosed with diabetes showed a beneficial impact of the intervention in this group.

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

Structured education

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

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

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

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

- Structured education with a module on self-monitoring for either blood or urine glucose were both effective for change in HbA1c at 18 months(5) (n=292).
- An education programme (MEDIAS 2 BSC) of non-intensive insulin treatment regimens was more effective in reducing HbA1c than an established education programme over 6 months(6) (n=182).
- Structured diabetes education plus insulin therapy compared to usual care improved HbA1c in insulin treated patients with T2D(7) (n=1289).
- Certified diabetes educator-delivered diabetes self-management and support with carbohydrate gram counting or a modified plate method improved glycaemic control in patients with an initial HbA1c between 7% and 10% compared to general health education (8) (n=150).
- A 6-week patient-centred, empowerment-based intervention programme was not superior to health education classes and post-discharge follow-up in reducing HbA1c, at 20 week follow-up (9).

Intelligence gathering

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

Impact statement

The guideline recommends offering structured education to adults with T2D and their family members or carers, that is evidence based and suits the needs of the person. As alluded to by topic expert feedback, the new studies identified on web-based self-management and structured education reflect a growing body of evidence that is consistent with these evidence based principles. The interventions are very diverse so the optimal intervention duration, provider, or contact hours are not clear. The specific interventions proposed for various contexts are broadly encompassed under the general recommendations and therefore no impact on the guideline is anticipated.

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

New evidence is unlikely to change guideline recommendations.

1.3 Dietary advice and bariatric surgery

Surveillance proposal

This section of the guideline should not be updated.

Editorial amendments

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

2019 surveillance summary

Dietary advice

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

Low carbohydrate diet (LCD)

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

- LCD significantly reduced HbA1c, triglyceride concentration and HDL cholesterol concentration relative to normal or HCDs, but that the difference in HbA1c was evident only in studies with a duration of 6 months or less and with a high risk of bias.
- LCD was not associated with a decreased level of total or LDL cholesterol or diastolic blood pressure.
- LCD led to short term weight loss, but this was not maintained over longer term periods of more than 6 months.
- Dietary adherence was considered to be a barrier in most studies, and definitions of LCD varied between studies.

The DIRECT (13,14) (n=298) assessed remission of T2D during a primary care-led LCD weight-management programme. The intervention consisted of withdrawal of anti-diabetes and anti-hypertensive drugs, total diet replacement (825-853 kcal per day formula diet for 12-20 weeks), stepped food reintroduction (2-8 weeks), and then structured support for weight loss maintenance. The primary outcomes, analysed hierarchically in the intention-to-treat population at 24 months, were weight loss of at least 15 kg, and remission of diabetes, defined as HbA1c less than 6·5% (48 mmol/mol) after withdrawal of anti-diabetes drugs at baseline.

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

A further 3 RCTs(15–17) were identified on LCD for T2D in adults, the findings of which indicated that:

- A low carbohydrate high protein diet combined with omega-3 polyunsaturated fatty acid supplementation diet provided greater effects on HbA1c and fasting glucose and faster effects on fasting glucose than either dietary component alone(15) (n=122).
- A very-low-carbohydrate, high unsaturated fat, low-saturated fat (LC) diet and a high carbohydrate, low-fat (HC) diet achieved similar outcomes in weight loss, reduced HbA1c and fasting glucose. However the LC diet provided significantly better lipid profile, blood glucose stability, and reductions in diabetes medication requirements(16) (n=115).
- Intermittent energy restriction (2 days per week) was non-inferior to continuous energy restriction for the reduction of HbA1c and weight loss over 12 months (17) (n=137).

An additional RCT found that supervised structured aerobic exercise training compared to a routine medication and dietary plan improved fasting blood glucose, plasma insulin level, glycaemic control and insulin resistance(18) (n=102).

Vitamin D supplementation

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

Intelligence gathering

The Diabetes Remission Clinical Trial

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

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

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

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

Motivational interviewing

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

Impact statement

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

New systematic review evidence indicates that benefits of LCDs are evident only in the short term and are not maintained beyond 6 months. However, the DIRECT trial suggests that it is possible to achieve remission from type 2 diabetes through a low calorie diet, as evaluated over 2 years. It represents a promising relatively low resource intervention which is likely to be cost-saving in the long run if the results can be maintained. The longer-term results of the DIRECT study, and other longer-term LCD studies are likely to be needed to establish any definite impact on the guideline.

Motivational interviewing

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

New evidence is unlikely to change guideline recommendations.

1.4 Blood pressure management

Surveillance proposal

No new information was identified at any surveillance review.

This section of the guideline should not be updated.

Editorial amendments

Anti-hypertensive drug treatment

NG28 recommends

- (1.4.8) The first line anti-hypertensive drug treatment for a person of African or Caribbean family origin should be an ACE inhibitor plus either a diuretic or a generic calcium channel blocker
- (1.4.10) For a person with continuing intolerance to an ACE inhibitor (other than renal deterioration or hyperkalaemia), substitute an angiotensin-II-receptor antagonist for the ACE inhibitor.

However NICE's guideline on hypertension in adults, published 2011, recommends (1.6.15) considering an angiotensin II-receptor blocker, in combination with a calcium channel blocker, in preference to an ACE inhibitor in all African or Caribbean people because of the low risk of angioedema.

It is proposed that the NICE NG28 recommendations in question be reviewed by the committee and aligned appropriately with NICE's guideline on hypertension in adults. A cross

referral from NICE NG28 section 1.4 to NICE CG127 section 1.6 should be considered following the update of NICE CG127.

1.5 Antiplatelet therapy

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

Aspirin

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

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

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

New evidence is unlikely to change guideline recommendations.

1.6 Blood glucose management

Surveillance proposal

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

Editorial amendments

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

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

Self-monitoring of blood glucose

We identified 11 studies covering self-monitoring of blood glucose (SMBG) (Table 4)

SMBG specific studies

An RCT(21) (n=120) found that SMBG was not effective in reducing HbA1c compared to no SMBG over 8 months.

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

Continuous glucose monitoring

An RCT(22) (n=158) found that continuous glucose monitoring in T2D patients taking multiple daily insulin injections was more effective than usual care in reducing HbA1c over a 6 month period.

Flash glucose monitoring

An RCT(23) (n=224) assessed the impact of Flash glucose-sensing technology (FreeStyle Libre™ Flash Glucose Monitoring System) as a replacement for SMBG over a 12-month period in people with T2D who were on intensive insulin therapy. Flash glucose-sensing system significantly reduced hypoglycaemia without resulting in any serious adverse events.

Remote monitoring

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

- SMBG with enhanced patient feedback including automatic tailored messages did not confer any advantage over once daily SMBG or no SMBG for change in HbA1c or health related quality of life over 52 weeks(24) (n=450).
- Use of a wireless glucose meter (OneTouch Verio Flex glucose meter) alone or in combination with a diabetes app (OneTouch Reveal) resulted in significant improvements in HbA1c after 12 and 24 weeks(25) (n=137).
- Video conferences preceded by uploads of measurements as add-on to clinic-based care led to a significant reduction of HbA1c compared to that in standard care, but this effect was not maintained at 6 month follow-up(26) (n=165).
- A supported telemonitoring intervention, involving self-measurement and transmission of glucose data to a secure website for clinician review, was effective in reducing HbA1c and systolic and diastolic blood pressure at 9 month follow-up(27) (n=285).
- Remote lifestyle coaching plus a connected glucose meter with certified diabetes educator support improved HbA1c levels and weight loss compared with either no glucose meter or no lifestyle coaching over 12 weeks(28) (n=330).
- A telemedical lifestyle programme (TeLiPro) comprising coaching, medical-mental motivation, a formula diet, and SMBG improved HbA1c levels, 10 year CVD risk and quality of life when compared to standard care, with results maintained at 52 week follow-up(29) (n=202).
- Telemonitoring and health counselling did not improve HbA1c and quality of life relative to usual care only, over 19 months(30) (n=166).
- Structured SMBG improved HbA1c in T2D over 12 months. No additional benefit was observed with the addition of once-monthly TeleCare support(31) (n=446).

Intelligence gathering

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

Flash glucose monitoring

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

One of the trials(23) identified in this surveillance review has already been considered in the NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110). It is important to note that whilst NICE MIB110 emphasises the great potential of this innovative device, they also warn of the lack of available clinical data and economic analysis.

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

In January 2019, the MHRA issued a medical device alert warning that some users of the FreeStyle Libre device were experiencing skin reactions to the adhesive provided. This led to them applying barrier creams and sprays before attaching the sensor which may have affected the performance of the device. The manufacturer has confirmed that from April 2019, the formulation of the adhesive will be revised.

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

Impact statement

Self-monitoring of blood glucose

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

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

Continuous glucose monitoring

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

Remote monitoring and telemedicine

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

Flash glucose monitoring

The NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110) emphasises that all evidence to date is limited to people with well-controlled diabetes and that the resource impact is unclear due to uncertainty around staff training and support requirements that may be needed. Long-term impact on patient outcomes is also uncertain, with the longest follow-up being 6 months. We are monitoring the progress of 2 ongoing trials in this area (ISRCTN87654534 and ISRCTN12543702) which may clarify the long-term effectiveness of FreeStyle Libre in patients with T2D. We will review these results and assess impact on the guideline as soon as they are published.

New evidence is unlikely to change guideline recommendations.

Drug treatment

2019 surveillance summary

Class level comparisons

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

Initial therapy

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

Initial therapy: Metformin

An RCT(32) (n=571) evaluated the glycaemic effects and safety of metformin delayed-release (DR) compared to metformin immediate release (IR) and placebo in adults with T2D and with either normal renal function or mild renal impairment (defined as eGFR ≥60 mL/min/1.73 m^2) who were not taking metformin for 2 or more months. Metformin DR 1200 and 1500 mg significantly reduced HbA1c and fasting plasma glucose compare to placebo. Metformin IR had a significantly greater reduction in HbA1c than metformin DR and placebo, but with a 3-fold greater plasma metformin exposure.

Initial therapy: SGLT-2 inhibitors

We identified a health technology assessment(33) covering canagliflozin, dapagliflozin and empagliflozin monotherapies. However, these interventions are covered as monotherapies by the TA guideline):

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

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

We identified 7 RCTs covering ertugliflozin (34–40). However, this intervention is covered by the NICE TAs:

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

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

Initial therapy: DPP-4 inhibitors

RCT results showed that:

- Evogliptin monotherapy was superior to placebo in reducing HbA1c in T2D(41) (n=160).
- Initial combination therapy with gemigliptin and metformin was superior to monotherapy with either drug in reducing HbA1c, without severe side effects(42) (n=433).
- Initial combination therapy with linagliptin and metformin was superior to linagliptin monotherapy in reducing HbA1c(43) (n=316).

Initial therapy: Sulfonylureas

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

First intensification

We identified a total of 39 studies covering first intensification of drug treatment for T2D in adults (table 6)

First intensification: Class level comparisons

A systematic review and network meta-analysis(44) (NMA) (9 studies, n=87,162) compared the CV outcomes of new classes of antidiabetic medications (DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors) in patients with T2DM. The primary outcomes were:

- the composite endpoint of CV death, nonfatal myocardial infarction (MI), and nonfatal stroke
- death from CV causes
- nonfatal MI
- nonfatal stroke
- death from any cause.

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

A systematic review(45) (3 studies, n=34,322) examined the effectiveness of SGLT-2 inhibitors, compared to placebo, on primary and secondary prevention of CV and renal outcomes in T2D. SGLT2 inhibitors reduced major adverse CV events with benefit only seen in patients with atherosclerotic CVD and not in those without. SGLT2 inhibitors reduced the risk of CV death or hospitalisation for heart failure, with a similar benefit in patients with and without atherosclerotic CVD, and with and without a history of heart failure. SGLT2 inhibitors reduced the risk of progression of renal disease in all patients, but with a lesser effect for those with more severe kidney disease at baseline.

A Cochrane review (46) (44 studies, n=13,036) examined the efficacy and safety of insulin and other pharmacological interventions for lowering glucose levels in people with diabetes and chronic kidney disease (CKD). Studies were identified examining SGLT2 inhibitors, DPP-4 inhibitors, GLP-1 agonists and glitazones. Results indicated that compared to placebo, SGLT-2 inhibitors may significantly reduce HbA1c, fasting blood glucose, systolic blood pressure, systolic blood pressure, and weight. However, there was no significant effect on risk of CV death, hypoglycaemia and acute kidney injury. Compared to placebo, DPP-4 inhibitors may significantly reduce HbA1c but there was little or no effect on fasting blood glucose, risk of CV death and weight. Compared to placebo, GLP-1 agonists may significantly reduce HbA1c. The evidence on glitazones was uncertain. Additionally, SGLT2 inhibitors were found to increase genital infections, and slightly increase creatinine. The safety profile for GLP-1 agonists was found to be uncertain.

First intensification: SGLT-2 inhibitors

We identified 19 studies covering individual SGLT-2 inhibitors canagliflozin(47–53), dapagliflozin(54–62) and empagliflozin(63–65) and one cost effectiveness study of different drugs in this class(66). However, these interventions are covered by the published technology appraisals:

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

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

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

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

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

We identified 2 RCTs covering ertugliflozin in a triple therapy regimen with other drug treatments(36,39). However, this intervention is the subject of an ongoing technology appraisal:

[ID1160] Ertugliflozin in a triple therapy regimen for treating type 2 diabetes

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

An RCT (67) (n=165) found that Ipragliflozin added to metformin significantly reduced HbA1c and body weight after 12 weeks and showed a safety profile comparable to placebo.

First intensification: GLP-1 analogues

Semaglutide

We identified 10 RCTs covering semaglutide intensification treatment for T2D(68–77). However, this intervention is the subject of an ongoing technology appraisal:

[ID1450] Semaglutide for treating type 2 diabetes

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

Albiglutide

The Harmony Outcomes RCT(78) (n=9463) assessed the safety and efficacy of albiglutide in preventing death from CVD, MI, or stroke. It found that albiglutide was superior to placebo with respect to major adverse CVD events in patients with T2D and established CVD, with no significant differences in other serious adverse effects. Established CVD was defined as MI, at least 50% stenosis in 1 or more coronary arteries, previous coronary revascularisation, ischemic stroke, at least 50% carotid artery stenosis, a previous carotid vascular procedure, intermittent claudication and an ankle to brachial index below 0.9, nontraumatic amputation, or a previous peripheral vascular procedure. However, albiglutide was withdrawn from the market for commercial reasons and is no longer available in the UK.

Dulaglutide

We identified 4 RCTs and a cost effectiveness study covering dulaglutide intensification treatment for T2D (77,79–82). However, this intervention is the subject of an ongoing technology appraisal:

[ID1451] Dulaglutide for treating type 2 diabetes

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

Exenatide

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

- Exenatide once-weekly autoinjection was associated with a significantly greater reduction in HbA1c, similar weight loss and a favourable gastrointestinal adverse effect (AE) profile compared with exenatide twice daily, sitagliptin once daily or oral placebo(83,84) (n=375, n=365).
- Exenetide once-weekly extended release injection was non-inferior to placebo but not superior with regard to CV safety(85) (n=14,752).
- Exenatide 2 mg once-weekly was cost-effective over a lifetime horizon compared to once daily liraglutide 1.2 mg, liraglutide 1.8 mg, and lixisenatide 20 mg(82).
- Exenetide was non-inferior to insulin and superior to pioglitazone in lowering HbA1c in the early stage of T2D(86) (n=416).

Liraglutide

We identified 3 studies covering liraglutide for T2D (see also insulin-based treatment for insulin combinations)(87–89). The findings indicated that for T2D:

- Liraglutide was cost-effective compared to exenatide and lixisenatide, based on improved quality-adjusted life expectancy, and reduced cost. Cost savings were gained from the avoidance of complications to offset increased acquisition costs(87).
- Liraglutide resulted in lower rates of the development and progression of diabetic kidney disease than placebo, over a median follow-up of 3.84 years(88) (n=9,340).
- Insulin glargine and liraglutide both reduced HbA1c to target levels of 7% but glargine had significantly greater reductions in HbA1c and fasting plasma glucose. Glargine was significantly worse for weight change over 24 weeks(89) (n=489).

First intensification: DPP-4 inhibitors

Sitagliptin

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

- For reduction in HbA1c sitagliptin was superior to:
  - placebo when added to either metformin, metformin plus sulfonylurea, or acarbose monotherapy(90,91) (n=427, n=381).

  - glimepiride when added to metformin, with additional improvements in hypoglycaemia(92) (n=292).
  - placebo during up-titration of metformin from 1000 mg/day to 2000 mg/day with similar safety and tolerability(93) (n=458).
- For reduction in HbA1c sitagliptin was non-inferior to:
  - glimepiride in all adults and specifically elderly patients, with a significantly lower risk of hypoglycaemia and lower increase in body weight and lower fasting plasma glucose (92,94) (n=388, n= 292).
  - pioglitazone in lowering HbA1c and superior in change in body weight when added to metformin over 12 weeks (95) (n=160).
- Over a 3 year follow-up in the TECOS study (n=14,671), sitagliptin was non-inferior to placebo for the risk of:
  - acute pancreatitis and pancreatic cancer(96)
  - fractures(97)
  - the composite of CV death, nonfatal myocardial infarction, nonfatal stroke(98)
  - hospitalisation for heart failure or unstable angina(98).
- Sitagliptin was not superior to either evogliptin or anagliptin for glycaemic control, when added to metformin, with comparable adverse events (99,100) (n=222, n=180).

Saxagliptin

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

- saxagliptin was non-inferior to
  - glimepiride for reduction in HbA1c, change in body weight and hypoglycaemia in all adults (101) (n=388)
  - glimepiride for reducing HbA1c specifically in elderly and very elderly patients (102) (n=720).
  - placebo or acarbose for reduction in HbA1c across all age groups(103,104) (n=462, n=288)
  - placebo for composite of CV mortality, myocardial infarction, or ischemic stroke in older patients (105) (n=16,492).
- Across all age groups, saxagliptin treatment was associated with an increased risk or hospitalisation for heart failure (106) (n=16,492).

Other DPP-4 inhibitors

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

- Linagliptin:
  - for T2D and early stages of diabetic kidney disease, improved HbA1c but did not lower albuminuria (107) (n=360). This study covered both first and second intensification, since patients were treatment-naive or receiving 2 or less oral glucose-lowering drugs (metformin, sulfonylureas, meglitinides or alpha-glucosidase inhibitors) or insulin.
  - with low dose metformin combination was non-inferior to high dose metformin for reducing HbA1c (108) (n=689)
  - among adults with type 2 diabetes and high CV and renal risk, linagliptin added to usual care compared with placebo added to usual care resulted in a non-inferior risk of a composite CV outcome, with similar renal outcomes (109) (n=6,979).
- Alogliptin:
  - was cost-effective as add-on therapy to metformin compared to sufonylurea, in terms of improved long-term patient outcomes, QALY gains, and ICERs (110) (n=2,639)
  - improved the mean change in carotid intima-media thickness (IMT) among patients without apparent CVD, in comparison with conventional treatment (111) (n=341)
  - was non-inferior to placebo for CV mortality over a median follow-up of 18 months (112) (n=5,380).
- Vildagliptin as an add-on therapy to sulfonylurea:
  - significantly reduced HbA1c and fasting plasma glucose when combined with metformin, compared to metformin plus dose increasing sulfonylurea (113) (n=344)
  - was comparable to Neutral Protamine Hagedorn (NPH) insulin in achieving a composite endpoint of achieving HbA1c <7.0%, without any hypoglycaemic episodes or weight gain of 3% or more (114) (n=162).

Second intensification

We identified 16 studies on second intensification (table 7)

Second intensification: SGLT-2 inhibitors

A cost effectiveness study (115) found that an intensification strategy of SGLT-2 inhibitors compared with immediate NPH insulin intensification in patients with T2D who were not at goal on metformin and sitagliptin was cost-neutral (no interpretable incremental cost effectiveness ratio) or cost-effective, based on different scenario analyses. Additional drug costs were offset by diabetes-related complication decreases, leading to slightly lower direct medical costs.

Second intensification: GLP-1 analogues

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

- Exenetide plus insulin glargine and metformin:

  - when compared to placebo, improved HbA1c, body weight and postprandial glucose, with similar rates of hypoglycaemia (116) (n=464).
  - when compared to insulin lispro plus insulin glargine and metformin, was non-inferior in improving HbA1c (117) (n=627).

- Lixisenatide in a titratable fixed-ratio combination with insulin glargine (100 units) was superior to its individual components alone for reducing HbA1c and change in body weight with similar rates of hypoglycaemia (118–120) (n=736, n=1,170, n=323).
- Liraglutide in combination with basal insulin, including degludec:
  - as a once daily injection with degludec was non-inferior to insulin degludec alone, and superior to liraglutide alone or insulin glargine alone in reducing HbA1c (121–123) (n=1663, n=557, n= 346)
  - improved glycaemic control, compared to placebo, reduced body weight, blood pressure and enabled patients to lower their insulin doses (124,125) (n=451, n=124). This was also observed as add-on treatment to sulfonylurea with or without metformin (126) (n=435).
  - as a once-weekly dose based on 2 plasma glucose (PG) readings was non-inferior to a twice weekly dose titration based on 3 PG readings, in terms of HbA1c reduction (127) (n=420).
  - caused more incidences of hypoglycaemia, particularly when added to sulfonylurea treatment (n=435, n=451).

Second intensification: DPP-4 inhibitors

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

- In combination with sitagliptin, twice daily biphasic insulin aspart 30 had superior glycaemic control over a once daily dose, but the once daily dose had a lower rate of hypoglycaemia and resulted in lower weight gain (128) (n=582).
- When initiating insulin glargine therapy, continuation of sitagliptin, compared with discontinuation, resulted in a significantly greater reduction in HbA1c without an increase in hypoglycaemia, and reduced the insulin dose requirement (129,130) (n=743, n=660).
- When added to metformin and sulfonylurea, alogliptin significantly reduced HbA1c, hypoglycaemia, CV death and all-cause mortality compared to placebo. The risk of CV death was higher in patients with a recent acute coronary syndrome, but remained similar between alogliptin and placebo(131) (n=1,398).

Insulin based treatments

We identified 31 studies (table 8) covering different types and dosages of insulin. These included 3 Cochrane reviews and 28 RCTs.

Short acting insulin analogues

A Cochrane review (132) (10 studies, n=2,751) assessed the effects of short acting insulin analogues compared to regular human insulin in adult, non-pregnant people with T2D. Overall, the incidence of severe hypoglycaemic events was low, and none of the trials showed a clear difference between the 2 intervention arms. The review found no clear benefits of short acting insulin analogues over regular human insulin.

An RCT (133) (n=412) found that metformin in combination with insulin analogues did not reduce carotid IMT despite a significant reduction in HbA1c, less weight gain, and smaller insulin dose compared with placebo plus insulin.

Insulin aspart

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

- Fast-acting insulin aspart was non-inferior to conventional insulin aspart for change in HbA1c and overall rates of hypoglycaemia, although worse for post meal hypoglycaemia (134) (n=689).
- When added to basal insulin, fast-acting insulin aspart improved glycaemic control but was worse for hypoglycaemia and change in body weight (135) (n=236).
- Stepwise intensification with biphasic insulin aspart from 1 to 3 times daily:
  - was superior to basal-bolus treatment for change in HbA1c and nocturnal severe or blood glucose confirmed hypoglycaemia (136) (n=335).
  - was superior to insulin aspart 3 times daily in combination with insulin detemir once daily, and insulin detemir alone once daily, but no different for change in carotid IMT and worse for weight gain (136,137) (n=335, n=412).
- Twice daily insulin degludec combined with insulin aspart was non-inferior to biphasic insulin aspart 30 for change in HbAlc and superior for reductions in fasting plasma glucose and incidence of overall and nocturnal confirmed hypoglycaemia (138) (n=394).
- A basal plus regimen of insulin glargine and glulisine was non-inferior to biphasic insulin aspart for change in HbA1c with a similar overall rate, but higher nocturnal rate, of hypoglycaemia (139) (n=335).

Long acting insulin analogues

A study based on the SWITCH 1 and 2 trials (140) assessed the cost effectiveness of degludec compared to glargine U100. Cost effectiveness was analysed over a 1-year time horizon based on the different rates of hypoglycaemia and actual doses of insulin used, rather than glycaemic control due to the treat-to-target trial design. It was estimated that quality of life was improved (0.0065 QALYs gain) with degludec compared with glargine U100 at an increased annual cost of £117 (incremental cost effectiveness ratio, £17,939), indicating that degludec would be cost effective relative to glargine U100.

A further 5 studies on degludec indicated that:

- Degludec was non-inferior to glargine for change in HbA1c and major CV events and superior for hypoglycaemia(141–143) (n=7,637, n=833, n=721).
- Insulin glargine 300 Units/mL was non-inferior to insulin degludec 100 Units/mL for change in HbA1c. Hypoglycaemia incidence and rates were comparable with both insulins during the full 24 week study period (144) (n=929).
- Insulin degludec and insulin aspart administered either as a twice daily co-formulation or as a basal-bolus regimen in multiple separate injections were both effective in improving HbA1c. The co-formulation resulted in a significantly lower total daily insulin dose, a smaller change in body weight, and similar rates of confirmed hypoglycaemia (145) (n=274).

Glargine dosage

The EDITION 1, 2 and 3 studies compared glargine 300 U/ml (Gla-300) versus glargine 100 U/ml (Gla-100) in patients using basal plus meal-time insulin for 12 months. In EDITION 1 (146) (n=807) the higher dose was superior in terms of HbA1c levels and the rate of daytime or nocturnal confirmed severe hypoglycaemia. However, overall hypoglycaemia was similar.

In the EDITION 2 trial (147) (n=629), Gla-300 and Gla-100 were similar in terms of HbA1c levels for people with T2D using basal insulin and oral antihyperglycaemic drugs, but Gla-300 was superior for weight change and nocturnal or severe hypoglycaemia.

In the EDITION 3 trial (148) (n=878) Gla-300 was as effective as Gla-100 in reducing HbA1c in insulin-naïve people with T2D, but with a lower overall risk of hypoglycaemia.

The SENIOR study (149) (n=1,014) found that Gla-300 was as effective as Gla-100 in older people (65 years or older) in terms of HbA1c reduction and risk of hypoglycaemia, with a lower risk of hypoglycaemia in people over 75 years.

Biosimilars

The SORELLA 2 RCT (150) (n=505) found that the in-development biosimilar SAR342434 was non-inferior to Gla-100 in reducing HbA1c, with no differences in adverse events.

The INSTRIDE RCT (151) (n=560) found that MYL-1501D insulin biosimilar plus oral antidiabetic drugs (OAD) was non-inferior to insulin glargine plus OADs, with similar rates of hypoglycaemia.

NICE Evidence summary 64 on insulin glargine biosimilar Abasaglar has been published. This includes a review of the ELEMENT 2 trial (152) in people with T2D (n=756), where once-daily Abasaglar was non-inferior to once-daily insulin glargine Lantus (primary end point) in reducing HbA1c, demonstrating equivalent efficacy of both medicines. The safety profile of Abasaglar is comparable to that of Lantus.

Insulin analogues compared to human insulin

An RCT (153) (n=701) found that insulin glargine was not superior to NPH insulin in improving HbA1c, or in limiting nocturnal hypoglycaemia using a using a protocol designed to limit pre-breakfast and nocturnal hypoglycaemia.

Insulin strategies for hospitalised patients

A Cochrane review (154) (8 studies, n=1048) examined the effects of sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus. The main comparison was between sliding scale insulin and basal-bolus insulin therapy. Results indicated that basal-bolus insulin therapy may be associated with an increased risk of severe hypoglycaemic episodes (defined as blood glucose levels below 40 mg/dL). Sliding scale insulin was associated with higher blood glucose levels compared to basal-bolus insulin therapy. There were no significant differences in mean length of hospital stay and post-operative infections. The review was inconclusive as to which insulin strategy (Sliding scale or basal-bolus insulin) is best. A basal-bolus insulin strategy in these patients might result in better short-term glycaemic control but could increase the risk for severe hypoglycaemic episodes.

Insulin monotherapy compared with the addition of OADs

A Cochrane review (155) (37 studies, n=3227) assessed the effects of insulin monotherapy compared with the addition of oral glucose-lowering agents (sulfonylureas, pioglitazone, alpha-glucosidase inhibitors, DPP-4 inhibitors, and metformin plus glimepiride) to insulin monotherapy for people with T2D already on insulin therapy and inadequate glycaemic control. The review found that the addition of all oral glucose-lowering agents in people with T2D and inadequate glycaemic control who are on insulin therapy had positive effects on glycaemic control and insulin requirements. The addition of sulfonylureas resulted in more hypoglycaemic events. Additional weight gain was only avoided by adding metformin to insulin.

Intelligence gathering

Drug treatment

SGLT-2 inhibitors and GLP-1 analogues

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

is being synchronised with the surveillance review of NICE NG28 to align publication. Relevant evidence identified in the surveillance review has been passed to the NICE TA team for consideration in these topics.

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

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

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

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

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

Newer insulins

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

Ongoing studies

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

Costs and health economics

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

Impact statement

Initial therapy

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

New evidence is unlikely to change guideline recommendations.

First intensification

Clinical characteristics

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

- The presence of established atherosclerotic CVD, for which there is now evidence to support the use of SGLT2 inhibitors and GLP1 agonist classes. However, some studies of individual drugs within these classes have demonstrated superiority over placebo (Harmony Outcomes [albiglutide], LEADER [liraglutide]) whereas others do not (ELIXA [lixisenatide] and EXSCEL [exenatide]) suggesting that this may not be a class effect.
- Other comorbidities, such as heart failure or CKD.
- Risk of specific adverse medicine effects, particularly hypoglycaemia and weight gain.
- Safety and tolerability.

Patient adherence

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

Cost effectiveness

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

The committee therefore agreed it was appropriate that a larger scale update of the antidiabetic drug pathway in NICE NG28 be undertaken, and that this should be timed to also take in to account the evidence from several large trials, which were ongoing at the time, so all the relevant drugs from these classes can be considered:

These key CVD outcome trials, have now published:

DECLARE-TIMI 58 (dapagliflozin), HARMONY Outcomes (albiglutide),

EXSCEL (exenatide)

REWIND (dulaglutide – preliminary results).

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

- Consideration of the concurrent review of related TAs and development of new TAs for SGLT-2 inhibitors and GLP-1 analogues. These will consider new evidence for canagliflozin, dapagliflozin, empagliflozin and ertugliflozin in the SGLT-2 class, and semaglutide and dulaglutide in the GLP-1 class. Both dual and triple (second intensification) therapy are covered within the scope of these TAs.
- Clinical characteristics detailed above and the potential need to adopt a risk stratification approach to sequencing of treatment.
- Safety and tolerability, taking into account the latest MHRA safety warning for SGLT-2 inhibitors.
- Patient adherence, taking into account frequency of monitoring and route of administration.
- Acquisition costs of individual drugs and cost effectiveness of drug combinations from different classes. The 2017 review committee noted that SGLT2 inhibitors had the same price per dose in 2017. No cost studies were identified on this class, but new evidence for GLP-1 analogues is conflicting on the comparative cost effectiveness of liraglutide and exenatide. A review of the health economic model is proposed.

New evidence identified that may change current recommendations.

Second intensification

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

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

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

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

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

- The evidence indicating that SGLT-2 inhibitors as a class are cost-neutral or cost effective, with additional drug costs offset by diabetes-related complication decreases, leading to slightly lower direct medical costs. The weight loss benefits are an important consideration for patients for whom this is a priority outcome.
- Evidence supporting the use of liraglutide for T2D in combination with insulin, particularly for improving glucose control, CV outcomes and weight loss.

New evidence identified that may change current recommendations.

Insulin based treatments

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

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

The price reduction of Tresiba (degludec) and evidence indicating its cost effectiveness, in addition to the emergence of cheaper biosimilars, following expiry of the patent for insulin glargine, have implications for the health economics of insulin-based treatments. Further

biosimilars are also in development. The choice between these longer-acting basal insulins may be determined by factors such as access and cost, alongside clinical considerations.

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

New evidence identified that may change current recommendations.

Insulin monotherapy compared with the addition of oral antidiabetic drugs

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

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

New evidence identified that may change current recommendations.

Insulin strategies for hospitalised patients

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

New evidence is unlikely to change guideline recommendations.

1.7 Managing complications

Surveillance proposal

This section of the guideline should be updated.

2019 surveillance summary

We identified 7 Studies on managing complications (Table 9).

Eye disease

We identified 2 Cochrane reviews and 3 RCTs on interventions to manage eye disease in T2D. Two Cochrane reviews (156,157) and 5 RCTs (158–162) focused on the use of anti-vascular endothelial growth factor (anti-VEGF) for diabetic macular oedema which is covered by the NICE technology appraisal guidance on Ranibizumab for treating diabetic macular oedema (TA274). These studies have been passed to the NICE TA team for consideration in reviewing this guidance.

Treatment of proliferative diabetic retinopathy

A Cochrane review (163) (18 studies n=1005) examined the effectiveness and safety of anti-VEGF for proliferative diabetic retinopathy. The comparator in this case was panretinal photocoagulation (PRP) which is usual care. Results indicated that anti-VEGFs (bevacizumab, pegaptanib, ranibizumab) significantly improved visual acuity compared to no anti-VEGF treatment. Any anti-VEGF treatment was also associated with significantly reduced risk of vitreous or pre-retinal haemorrhage and risk of losing 3 or more lines of visual acuity. Authors noted that the evidence was of very low quality and further trials are needed to inform treatment decisions.

One RCT (164) (n not reported in the abstract, 22 ophthalmic centres) found that intravitreous injection of aflibercept was more effective than standard care with photocoagulation at improving visual acuity. A related NICE TA covering aflibercept for treating diabetic macular oedema is available, but the scope does not cover diabetic retinopathy.

Treatment of diabetic macular oedema

A Cochrane review (165) of 24 studies (n= 4422 eyes) examined the efficacy and safety of laser photocoagulation as monotherapy in the treatment of diabetic macular oedema. Results indicated that compared to no intervention, those receiving laser treatment were significantly less likely to lose best-corrected visual acuity (BCVA) at one year. There was some indication that the less invasive laser techniques (e.g. subthreshold technique) may be as effective as standard laser therapy, however authors note that further evidence is required.

An RCT (166) (n=125) found that compared to placebo, there was no effect of topical nepafenac on change in optical coherence tomography retinal volume.

Diabetes-related distress

A Cochrane review (167) (30 studies, n=9177) assessed the effects of psychological interventions for diabetes-related distress (DRD) in adults with T2D. The trials included a wide spectrum of interventions and were both individual- and group-based. Low-quality evidence showed that none of the psychological interventions would improve DRD more

than usual care. Low-quality evidence showed improved self-efficacy and HbA1c after psychological interventions at 6 to 12 month follow-up.

Cognitive impairment and dementia

A Cochrane review (168) (7 studies, n=16,044) assessed the effects of different strategies for managing T2D on cognitive function and the incidence of dementia. The review found no good evidence that any specific treatment or treatment strategy for T2D can prevent or delay cognitive impairment. An intensive treatment strategy was more likely than standard treatment to cause hypoglycaemia, but there were no differences in death rates. The quality of the evidence for all outcomes to be low or moderate due to risk of bias in the included studies, small sample sizes, and imprecise estimates of the effects.

Intelligence gathering

No topic expert feedback was relevant to this section.

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

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

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.

New evidence identified that may change current recommendations.

Treatment of diabetic macular oedema

We identified new evidence on the treatment of diabetic macular oedema. A Cochrane review supports the use of laser therapy compared to no intervention and suggested that less invasive techniques may be just as effective as the standard laser, however these results

were highly uncertain. A further study found no effect of nepafenac on change in optical coherence tomography retinal volume. As mentioned above, the guideline currently only has recommendations on screening for diabetic retinopathy and referral criteria. There are no recommendations on diabetic macular oedema and the original guideline committee did not consider surgical evidence in this area. Given the growing evidence base in this area and the related NICE technology appraisal guidance on treatments for diabetic macular oedema, there may be a need for new recommendations to be developed.

New evidence identified that may change current recommendations.

Diabetes-related distress

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

New evidence is unlikely to change guideline recommendations.

Cognitive impairment and dementia

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

New evidence is unlikely to change guideline recommendations.

Research recommendations

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

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

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

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

Data summary tables

Table 1 Individualised care

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

Table 2 Patient education

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

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

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

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

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

Table 3 Dietary advice

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Low carbohydrate diet								
Carter, Sharayah; et al. 2018 (17)	RCT	137	Adults (age not specified)	Intermittent energy restriction (500-600 cal/day) (2 non-consecutive days per week, with usual diet 5 days per week)	Continuous energy restriction (1200-1500 cal/day) for 7 days per week	Change in HbA1c	12 months	Intervention non-inferior
						Change in body weight	12 months	No effect of intervention
						Hypoglycaemia	2 weeks	No effect of intervention
Huntriss, R.; et al. 2018 (11)	SR	18 RCTs (n=2204) included in total. 7 RCTs in meta-analysis of 1 year data	Adults (age not specified)	LCD	Usual care	CVD outcomes	1 year	Improved with intervention
Korsmo-Haugen, Henny-Kristine; et al. 2019 (12)	SR	23 studies (n=2178)	Adult (age not specified)	LCD	Higher carbohydrate diets	Change in HbA1c	NR	Improved with intervention
						Change in body weight	NR	No effect of intervention
						Blood pressure	NR	No effect of intervention
Lean, M.E.J; et al. 2019 (14, 15) DIRECT	RCT	298	Adult (20-65 years)	Integrated structured weight-management programme (withdrawal of anti-diabetes and anti-hypertensive drugs, total diet replacement, stepped food reintroduction plus structured support for maintenance)	Best practice care in accordance with guidelines	Change in body weight (weight loss of 15 kg or more)	24 months	Improved with intervention
						Diabetes remission (HbA1c below 6.5% after withdrawal of anti-diabetes medications)	24 months	Improved with intervention
						Change in body weight	24 months	Improved with intervention
						Change in HbA1c	24 months	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Liu, Kai; et al. 2018 (15)	RCT	122	Adult (age not specified)	LCHP diet combined with omega-3 polyunsaturated fatty acid [PFU] (LHCP+omega-3)	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Change in HbA1c	12 weeks	No effect of intervention
				LCHP plus corn oil placebo	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Fasting glucose	12 weeks	No effect of intervention
				LCHP plus corn oil placebo	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Change in HbA1c	12 weeks	No effect of intervention
				Omega-3	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Change in HbA1c	12 weeks	No effect of intervention
				LCHP+omega-3	LCHP plus corn oil placebo	Change in HbA1c	12 weeks	Improved with intervention
				LCHP+omega-3	omega-3	Change in HbA1c	12 weeks	Improved with intervention
				LCHP+omega-3	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Fasting glucose at 4 weeks	4 weeks	Improved with intervention
				LCHP+omega-3	LCHP plus corn oil placebo	Fasting glucose at 12 weeks	12 weeks	Improved with intervention
				LCHP+omega-3	omega-3	Fasting glucose at 12 weeks	12 weeks	Improved with intervention
				LCHP diet combined with omega-3 polyunsaturated fatty acid [PFU] (LHCP+omega-3)	HCLP diet with low omega-3 PUFAs (corn oil placebo)	Change in HbA1c	12 weeks	No effect of intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Meng, Y.; et al (11)	SR	9 studies (n=734)	Adult (age not specified)	LCD	Normal or High carbohydrate diet	Change in HbA1c	NR	Improved with intervention
						Short term weight loss	NR	Improved with intervention
Shakil-Ur-Rehman, Syed; et al. 2017 (18)	RCT	102	Adult (age not specified)	Supervised structured aerobic exercise training programme plus routine medication and dietary plan	Routine medication and dietary plan	Fasting blood glucose	25 weeks	Improved with intervention
Tay, J.; et al. 2015 (16)	RCT	115	Adult (age not specified)	Very low carbohydrate, high unsaturated fat, low saturated fat diet, combined with supervised aerobic and resistance exercise	High carbohydrate, low-fat (energy-matched) diet, combined with supervised aerobic and resistance exercise	Change in HbA1c	Assessed at 24 and 52 weeks	No effect of intervention
						Fasting blood glucose	Assessed at 24 and 52 weeks	No effect of intervention
						Change in body weight	Assessed at 24 and 52 weeks	No effect of intervention
						Blood pressure	Assessed at 24 and 52 weeks	No effect of intervention
Vitamin D supplementation								
Krul-Poel, Y. H. M.; et al. 2015 (19) SUNNY	RCT	275	Adult (age not specified)	Vitamin D supplementation (50,000 IU/month) for 6 months	Placebo for 6 months	Change in HbA1c	6 months	No effect of intervention
Angellotti, E.; et al. 2018 (20)	RCT	127	Adults (mean age 60 years)	4000 units of vitamin D (cholecalciferol) daily for 48 weeks	Placebo daily for 48 weeks	Change in HbA1c	24 weeks	Improved with intervention
						Insulin secretion rate	24 weeks	No effect of intervention
						Change in HbA1c	Measured at 16, 24, 36, and 48 weeks	No effect of intervention
						Mean 25(OH)D levels	24 weeks	Direction of change not reported

Abbreviations: RCT – Randomised controlled trial; SR – systematic review; LCHP – low carbohydrate high protein; HCLP – high carbohydrate low protein

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

Table 4 Self-monitoring of blood glucose

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
SMBG specific studies								
Sodipo, O. O.; et al. (21)	RCT	120	Adult (age not specified)	SMBG	No SMBG	Change in HbA1c	8 months	No effect of intervention
Continuous glucose monitoring								
Beck, R. W.; et al. (22)	RCT	158	Adult (mean age 60 years)	Continuous Glucose Monitoring	Usual care	Change in HbA1c	6 months	Improved with intervention
Flash glucose monitoring								
Haak, Thomas; et al. (23)	RCT	224	Adult (age not specified)	Flash glucose-sensing technology (FreeStyle Libre TM Flash Glucose Monitoring System)	Self-monitoring of blood glucose (FreeStyle Lite TM)	Hypoglycaemia	12 months (6 months treatment, 6 months open access)	Improved with intervention
Remote monitoring								
Young, L. A.; et al. (24)	RCT	450	Adult (30 years and older)	SMBG	No SMBG	Change in HbA1c	52 weeks	No effect of intervention
Grady, Mike; et al. (25)	RCT	128	Adult (age not specified)	Blood glucose meter plus mobile app	Blood glucose meter only	Change in HbA1c	12 weeks	No effect of intervention
Hansen, C. R.; et al. (26)	RCT	165	Adult (age not specified)	Telemedicine intervention added to clinic-based care (8 month duration)	Clinic-based care	Change in HbA1c	At completion of 8 month intervention	Improved with intervention
						Change in HbA1c	6 month follow-up	No effect of intervention
Bollyky, J. B.; et al. (28)	RCT	330	Adult (age not specified)	Lifestyle coaching plus a connected glucose meter	Usual care	Change in HbA1c	12 weeks	Improved with intervention
Wild, S. H.; et al. (27)	RCT	285	Adult (age not specified)	Supported telemonitoring intervention (self-measurement and	Usual care (with at least annual review, more frequent review for those with	Systolic blood pressure	Assumed 9 months. Outcome: ambulatory systolic blood pressure	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
				transmission to secure website of twice weekly morning and evening glucose for clinician review)	poor glycaemic or blood pressure control)	Diastolic blood pressure	Assumed 9 months. Outcome: ambulatory diastolic blood pressure	Improved with intervention
						Change in HbA1c	9 months	Improved with intervention
Kempf, K.; et al. (29)	RCT	202	Adult (age not specified)	Telemedical Lifestyle intervention Program TeLiPro	Routine care	Change in HbA1c	12 weeks	Improved with intervention
						10-year CVD risk	12 weeks	Improved with intervention
						quality of life	12 weeks	Improved with intervention
Lindberg, Inger; et al. (30)	RCT	166	Adult (age not specified)	Telemonitoring and health counselling	Usual care	Change in HbA1c	19 months	No effect of intervention
						Quality of life	19 months	No effect of intervention
Parsons, S. N.; et al. (31)	RCT	446	Adult (age not specified)	Structured SMBG	Usual care	Change in HbA1c	12 months	Improved with intervention
Abbreviations: RCT – Randomised controlled trial; CVD – cardiovascular disease; SMBG – self-monitoring of blood glucose Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated								

Table 5 Drug treatment: Initial therapy

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Henry, Robert R.; et al. (32)	RCT	571	Adults and CKD	Metformin delayed-release	Placebo	Change in HbA1c	16 weeks	Improved with intervention
				Metformin immediate release	Placebo or metformin delayed-release	Change in HbA1c	16 weeks	Improved with intervention
Park, J.; et al. (41)	RCT	160	Adult (age not specified)	Evogliptin	Placebo	Change in HbA1c	24 weeks	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Lim, S.; et al. (42) INICOM	RCT	433	Adult (age not specified)	Initial combination therapy with gemigliptin and metformin	Gemigliptin or metformin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
Ross, S. A.; et al. (43)	RCT	316	Adult (age not specified)	Linagliptin 5 mg once daily and metformin twice daily	Linagliptin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
Abbreviations: RCT – Randomised controlled trial; CKD - Chronic kidney disease Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated								

Table 6 Drug treatment: First intensification

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Class level comparisons								
Alfayez, Osamah M.;et al. 2019 (44)	SR	9 studies (n=87,162)	Adult (age not specified)	DPP4-inhibitors	Placebo	CVD outcomes	NR	No effect of intervention
				GLP-1 agonists	Placebo	CVD outcomes	NR	Improved with intervention
				GLP-1 agonists	Placebo	CV or all-cause death	NR	Improved with intervention
				SGLT-2 inhibitors	Placebo	Hospitalisation for heart failure	NR	Improved with intervention
Zelniker, T. A.; et al. (45)	SR	34,322	Adult (age not specified)	SGLT2 inhibitors	Placebo	CVD outcomes	NR	Improved with intervention
						Renal outcomes	NR	Improved with intervention
						Hospitalisation for heart failure	NR	Improved with intervention
Lo, C.; et al. 2018 (46)	Cochrane	7 studies n=1092	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Change in HbA1c	NR	Improved with intervention
		5 studies n=855	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Fasting blood glucose	NR	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
		7 studies n=1198	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Systolic blood pressure	NR	Improved with intervention
		7 studies n=3086	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Genital infections	NR	Worse with intervention
		5 studies n=1029	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Weight	NR	Improved with intervention
		9 studies n=Not reported	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Risk of cardiovascular death	NR	No effect of intervention
		9 studies n=Not reported	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Hypoglycaemia	NR	No effect of intervention
		9 studies n=Not reported	Adult (age not specified) and CKD	SGLT-2 inhibitors	Placebo	Acute kidney injury	NR	No effect of intervention
		2 studies n=5897	Adult (age not specified) and CKD	DPP-4 inhibitors	Placebo	Cardiovascular death	NR	No effect of intervention
		2 studies n=210	Adult (age not specified) and CKD	DPP-4 inhibitors	Placebo	Weight	NR	No effect of intervention
		7 studies n=867	Adult (age not specified) and CKD	GLP-1 agonists	Placebo	Change in HbA1c	NR	Improved with intervention
		2 studies n=551	Adult (age not specified) and CKD	Sitagliptin	Glipizide	Hypoglcaemia	NR	Improved with intervention
SGLT-2 inhibitors								
Shestakova, M. V.; et al. 2018 (67)	RCT	165	Adult (age not specified)	Ipragliflozin	Placebo	Change in HbA1c	12 weeks	Improved with intervention
						Change in body weight	12 weeks	Improved with intervention
GLP-1 analogues								

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Hernandez, A. F.; et al. 2018 (78) Harmony Outcomes	RCT	9,463	Adult (over 40 years)	Albiglutide	Placebo	CVD outcomes	1.6 years	Improved with intervention
Chuang, L. H.; et al. 2016 (82)	Cost study		Adult (age not specified)	Exenetide 2mg twice weekly	liraglutide 1.2 mg and 1.8 mg once daily	Cost effectiveness		Intervention cost-effective
					lixisenatide 20 µg	Cost effectiveness		Intervention cost-effective
Wysham, C. H.; et al. 2018 (83)	RCT	375	Adult (age not specified)	Exenetide once-weekly (autoinjected)	Exenetide twice daily	Change in HbA1c	28 weeks	Improved with intervention
						Change in body weight	28 weeks	Intervention non-inferior
Gadde, K. M.; et al. 2017 (84)	RCT	365	Adult (age not specified)	Exenetide once-weekly	Sitagliptin	Change in HbA1c	28 weeks	Improved with intervention
					Placebo	Change in HbA1c	28 weeks	Improved with intervention
Holman, R. R.; et al. 2017 (85)	RCT	14,752	Adult (age not specified)	Exenatide	Placebo	CVD outcomes	Median 3.2 years	Intervention non-inferior
Xu, W.; et al. 2015 (86)	RCT	416	Adult (age not specified)	Exenatide	Insulin	Change in HbA1c	48 weeks	Intervention non-inferior
					Pioglitazone	Change in HbA1c	48 weeks	Improved with intervention
Hunt, Barnaby; et al. 2017 (87)	Cost		Adults (age unspecified)	Liraglutide	Exenatide, lixisenatide	Cost effectiveness	NR	Intervention cost effective
Mann, J. F. E.; et al. 2017 (88)	RCT	9,340	Adults (age unspecified)	Liraglutide	Placebo	Renal outcomes	Median 3.84 years	Improved with intervention
D'Alessio, D.; et al. 2015 (89)	RCT	489	Adult (age not specified)	Insulin glargine	Liraglutide	Change in body weight	24 weeks	Worse with intervention
						Adverse events	24 weeks	Improved with intervention
						Hypoglycaemia	24 weeks	Worse with intervention
DPP-4 inhibitors								

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Moses, R. G.; et al. 2016 (90)	RCT	427	Adult (age not specified)	Sitagliptin and metformin fixed-dose combination	Placebo	Change in HbA1c	NR	Improved with intervention
Wang, W.; et al. 2017 (91)	RCT	381	Adult (age not specified)	Sitagliptin	Placebo	Change in HbA1c	24 weeks	Improved with intervention
Kim, S. S.; et al. 2017 (92)	RCT	292	Adult (18 years and over)	Sitagliptin and metformin fixed-dose combination	Glimepiride	Change in HbA1c	30 weeks	Improved with intervention
						Hypoglycaemia	30 weeks	Improved with intervention
						Fasting plasma glucose	30 weeks	Improved with intervention
						Change in body weight	30 weeks	Improved with intervention
Frias, Juan Pablo; et al. 2019 (93) CompoSIT-M	RCT	458	Adult (age not specified)	Sitagliptin plus metformin up-titration	Metformin up-titration alone	Change in HbA1c	20 weeks	Improved with intervention
Hartley, P.; et al. 2015 (94)	RCT	388	Elderly	Sitagliptin	Glimepiride	Change in HbA1c	30 weeks	Intervention non-inferior
						Hypoglycaemia	30 weeks	Intervention non-inferior
Jameshorani, M.; et al. 2017 (95)	RCT	160	Adult (age not specified)	Sitagliptin	Pioglitazone	Change in HbA1c	12 weeks	No effect of intervention
						Change in body weight	12 weeks	Improved with intervention
Buse, J. B.; et al. 2017 (96) TECOS	RCT	14,671	Adults and CVD	Sitagliptin	Placebo	Acute pancreatitis and pancreatic cancer	3 years	Intervention non-inferior
Josse, R. G.; et al. 2017 (97) TECOS	RCT	14,671	Adults (mean age 65.5 years)	Sitagliptin	Placebo	Fracture incidence	3 years	Intervention non-inferior
Green, J. B.; et al. 2015 (98) TECOS	RCT	14,671	Adult (age not specified)	Sitagliptin	Placebo	CVD outcomes	Median 3 years	Intervention non-inferior
Hong, S. M.; et al. 2017 (99)	RCT	222	Adult (age not specified)	Evogliptin	Sitagliptin	Change in HbA1c	24 weeks	Intervention non-inferior

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Jin, S. M.; et al. 2015 (100)	RCT	180	Adult (age not specified)	Anagliptin	Sitagliptin	Change in HbA1c	24 weeks	Intervention non-inferior
Gu, Tianwei; et al. 2018 (101) SPECIFY	RCT	388	Adult (age not specified)	Saxagliptin	Glimepiride	Change in HbA1c	48 weeks	Improved with intervention
						Change in body weight	48 weeks	Improved with intervention
						Hypoglycaemia	48 weeks	Improved with intervention
Schernthaner, G.; et al. 2015 (102) GENERATION	RCT	720	Adult (65 years and older)	Saxagliptin	Glimepiride	Change in HbA1c	NR	Intervention non-inferior
Chen, Y.; et al. 2018 (103) SUPER	RCT	462	Adult (age not specified)	saxagliptin	Placebo	Change in HbA1c	NR	Improved with intervention
Du, J.; et al. 2017 (104) SMART	RCT	488	Adult (age not specified)	Saxagliptin	Acarbose	Change in HbA1c	24 weeks	Intervention non-inferior
Leiter, L. A.; et al. 2015 (105) SAVOR-TIMI 53	RCT	16,492	Adult (65 years and older)	Saxagliptin	Placebo	CVD outcomes	Median 2.1 years	Intervention non-inferior
Scirica, B. M.; et al. 2014 (106) SAVOR-TIMI 53	RCT	16,492	Adult (age not specified)	saxagliptin	Placebo	Heart failure	NR	Worse with intervention
Groop, P. H.; et al. 2017 (107) MARLINA-T2D	RCT	360	Adults and CKD	Linagliptin	Placebo	Change in HbA1c	NR	Improved with intervention
						urinary albumin-to-creatinine ratio	NR	No effect of intervention
Ji, L.; et al. 2015 (108)	RCT	689	Adult (age not specified)	Linagliptin plus low dose metformin	High dose metformin	Change in HbA1c	14 weeks	Intervention non-inferior
Rosenstock, Julio; et al. 2018 (109) CARMELINA	RCT	6,979	Elderly	Linagliptin	Placebo	CVD outcomes	Median 2.2 years	Intervention non-inferior
Gordon, Jason; et al. 2016 (110)	RCT	2,639	Adult (age not specified)	Alogliptin	Sulfonylurea	Cost effectiveness	2 years	Intervention cost effective

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Mita, T.; et al. 2016 (111) SPEAD-A	RCT	341	Adult (age not specified)	Alogliptin	Placebo	Mean change in carotid IMT	24 months	Improved with intervention
White, W. B.; et al. 2016 (112) EXAMINE	RCT	5,380	Adults and recent acute coronary syndrome	Alogliptin	Placebo	CV mortality	Median 18 months	Intervention non-inferior
Hong, A. R.; et al. 2015 (113) VISUAL	RCT	344	Adult (age not specified)	Vidalgiptin	Sulfonylurea dose increasing	Change in HbA1c	24 weeks	Improved with intervention
Forst, T.; et al. 2015 (114)	RCT	162	Adult (age not specified)	Vildagliptin	NPH insulin	Change in HbA1c	24 weeks	Intervention non-inferior

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

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

Table 7 – Drug treatment: Second intensification

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
SGLT-2 inhibitors								
Pawaskar, Manjiri; et al. 2018 (115)	Cost	NR	Adult (age not specified)	SGLT-2 inhibitors	NPH insulin	Cost effectiveness		Cost-neutral or cost-effective
GLP-1 analogues								
Guja, C.; et al. 2018 (116) DURATION-7	RCT	464	Adult (age not specified)	Exenetide plus insulin glargine	Placebo	Change in HbA1c	28 weeks	Improved with intervention
						Change in body weight	28 weeks	Improved with intervention
						postprandial glucose	28 weeks	Improved with intervention
Diamant, M.; et al. 2014 (117)	RCT	627	Adult (age not specified)	Exenetide plus insulin glargine	Insulin lispro plus insulin glargine	Change in HbA1c	30 weeks	Intervention non-inferior
	RCT	736	Adult (age not specified)	Insulin glargine plus lixisenatide	Insulin glargine	Change in HbA1c	30 weeks	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Aroda, V. R.; et al. 2016 (118)						Change in body weight	30 weeks	Improved with intervention
Rosenstock, J.; et al. 2016 (119) LixiLan-O	RCT	1,170	Adult (age not specified)	Insulin glargine plus lixisenatide	Insulin glargine or lixisenatide	Change in HbA1c	30 weeks	Improved with intervention
						Change in body weight	30 weeks	Improved with intervention
Rosenstock, J.; et al. 2016 (120)	RCT	323	Adult (age not specified)	Lixisenatide and Insulin glargine	Insulin glargine	Change in HbA1c	24 weeks	Intervention non-inferior
Gough, S. C.; et al. 2014 (121)	RCT	1663	Adult (age not specified)	Insulin degludec plus liraglutide	Insuline degludec or liraglutide alone	Change in HbA1c	26 weeks	Intervention non-inferior
Lingvay, I.; et al. 2016 (122) DUAL V	RCT	557	Adult (age not specified)	Insulin degludec plus liraglutide	Insulin glargine	Change in HbA1c	26 weeks	Improved with intervention
						Change in body weight	26 weeks	Improved with intervention
						Hypoglycaemia	26 weeks	Improved with intervention
Aroda, V. R.; et al. 2016 (123) BEGIN: ADD TO GLP-1	RCT	346	Adult (age not specified)	Insulin degludec plus liraglutide	Placebo plus liraglutide	Change in HbA1c	26 weeks	Improved with intervention
						Hypoglycaemia	26 weeks	Worse with intervention
Ahmann, A.; et al. 2015 (124)	RCT	451	Adult (age not specified)	Basal insulin plus liraglutide	Basal insulin plus placebo	Change in HbA1c	26 weeks	Improved with intervention
Lind, M.; et al. 2015 (125)	RCT	124	Adult (age not specified)	Liraglutide	Placebo	Change in HbA1c	24 weeks	Improved with intervention
						Change in body weight	24 weeks	Improved with intervention
						Hypoglycaemia	24 weeks	Intervention non-inferior
Rodbard, H. W.; et al. 2017 (126)	RCT	435	Adult (age not specified)	Insulin degludec plus liraglutide	Placebo	Change in HbA1c	26 weeks	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Harris, S. B.; et al. 2017 (127) DUAL VI	RCT	420	Adult (age not specified)	Insulin degludec plus liraglutide once-weekly titration	Insulin degludec plus liraglutide twice weekly titration	Change in HbA1c	32 weeks	Intervention non-inferior
DPP-4 inhibitors								
Linjawi, S.; et al. 2015 (128) Sit2Mix	RCT	582	Adult (age not specified)	Once- and twice daily biphasic insulin aspart 30 with sitagliptin	Twice daily biphasic insulin aspart 30 without sitagliptin	Change in HbA1c	24 weeks	Improved with intervention
Roussel, Ronan; et al. 2018 (129) CompoSIT-I	RCT	743	Adult (age not specified)	Sitagliptin plus insulin glargine	Insulin glargine alone	Change in HbA1c	30 weeks	Improved with intervention
Mathieu, Chantal; et al. 2015 (130)	RCT	660	Adult (age not specified)	Sitagliptin	Placebo	Change in HbA1c	24 weeks	Improved with intervention
						Hypoglycaemia	24 weeks	Improved with intervention
White, W. B.; et al. 2018 (131) EXAMINE	RCT	1,398	Adults and recent acute coronary syndrome	Alogliptin plus baseline metformin and sulfonylurea	Placebo	Change in HbA1c	Up to 40 months (median 18 months)	Improved with intervention
						CVD outcomes	Up to 40 months (median 18 months)	Improved with intervention
Abbreviations: RCT – Randomised controlled trial; SR – systematic review; NR – not reported Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated								

Table 8 Drug treatment: Insulin-based treatments

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Short acting insulin analogues								
	SR	10 studies n=2751	Adult (age not specified)		Human insulin	Change in HbA1c	Not reported	Intervention non-inferior

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Fullerton, Birgit; et al. 2018 (132)				Short acting insulin analogues		Hypoglycaemia	Not reported	Intervention non-inferior
						All-cause mortality	Not reported	Intervention non-inferior
Lundby-Christensen, L.; et al. 2016 (133) (137)	RCT	412	Adult (age not specified)	Metformin in combination with insulin	Placebo	Change in HbA1c	18 months	Improved with intervention
				Metformin in combination with insulin	Placebo	Mean carotid IMT	18 months	No effect of intervention
				Metformin in combination with insulin	Placebo	Change in body weight	18 months	Improved with intervention
				Metformin in combination with insulin	Placebo	Hypoglycaemia	18 months	Improved with intervention
				biphasic insulin aspart	Insulin aspart 3 times daily in combination with insulin detemir	Mean carotid IMT	18 months	No effect of intervention
				biphasic insulin aspart	Insulin aspart 3 times daily in combination with insulin detemir, or insulin detemir alone	Change in HbA1c	18 months	Improved with intervention
Bowering, K.; et al. 2017 (134)	RCT	689	Adult (age not specified)	Fast-acting insulin aspart	Insulin aspart	Change in HbA1c	26 weeks	Intervention non-inferior
						Hypoglycaemia	26 weeks	Worse with intervention
Rodbard, H. W.; et al. 2017 (135)	RCT	236	Adult (age not specified)	Fast-acting insulin aspart plus basal insulin	Basal only insulin	Change in HbA1c	18 weeks	Improved with intervention
						Change in body weight	18 weeks	Worse with intervention
Linjawi, Sultan; et al. 2018 (136)	RCT	335	Adult (age not specified)	Biphasic insulin aspart	Basal-bolus insulin	Change in HbA1c	32 weeks	Improved with intervention
						Hypoglycaemia	32 weeks	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Franek, E.; et al. 2016 (138)	RCT	394	Adult (age not specified)	Insulin degludec plus insulin aspart	Biphasic insulin aspart	Change in HbA1c	26 weeks	Intervention non-inferior
						Fasting plasma glucose	26 weeks	Intervention non-inferior
Vora, J.; et al. 2015 (139)	RCT	335	Adult (age not specified)	Insulin glargine plus insulin glulisine	Insulin aspart plus aspart protamine	Change in HbA1c	24 weeks	Intervention non-inferior
Long acting insulin analogues								
Evans, M.; et al. 2018 (140)	Cost	Not applicable	Age and type not specified	Degludec	Glargine U100	Cost effectiveness based on rates of hypoglycaemia	NR	Intervention cost effective
Marso, S. P.; et al. 2017 (141)	RCT	7,637	Adult (age not specified)	Degludec	Glargine U100	CVD outcomes	NR	Intervention non-inferior
Pan, C.; et al. 2016 (142)	RCT	833	Adult (age not specified)	Insulin degludec	Insulin glargine	Change in HbA1c	26 weeks	Intervention non-inferior
Wysham, C.; et al. 2017 (143) SWITCH 2	RCT	721	Adult (age not specified)	Insulin degludec	Insulin glargine	Hypoglycaemia	32 weeks	Improved with intervention
Rosenstock, J.; et al. 2018 (144) BRIGHT	RCT	929	Adult (age not specified)	Insulin glargine 300 units/mL	Insulin degludec	Change in HbA1c	24 weeks	Intervention non-inferior
Rodbard, H. W.; et al. 2017 (145)	RCT	274	Adult (age not specified)	Insulin degludec plus insulin aspart	Insulin degludec	Change in HbA1c	26 weeks	No effect of intervention
Glargine dosage								
Riddle, M. C.; et al. 2015 (146) EDITION 1	RCT	807	Adult (age not specified)	Insulin glargine 300 units/mL	Insulin glargine 100 units/mL	Change in HbA1c	12 months	Improved with intervention
						Hypoglycaemia	12 months	Improved with intervention
Yki-Jarvinen, H.; et al. 2014 (147)	RCT	811	Adult (age not specified)	Insulin glargine 300 units/mL	Insulin glargine 100 units/mL	Change in HbA1c	12 months plus 6 month safety extension	Intervention non-inferior

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
EDITION 2						Hypoglycaemia	12 months plus 6 month safety extension	Improved with intervention
						Change in body weight	12 months plus 6 month safety extension	Improved with intervention
Bolli, G. B.; et al. 2017 (148) EDITION 3	RCT	878	Adult (age not specified)	Insulin glargine 300 units/mL	Insulin glargine 100 units/mL	Change in HbA1c	12 months	Intervention non-inferior
						Hypoglycaemia	12 months	Improved with intervention
Ritzel, R.; et al. 2018 (149) SENIOR	RCT	1,014	Adult (65 years and older)	Insulin glargine 300 units/mL	Insulin glargine 100 units/mL	Change in HbA1c	26 weeks	Intervention non-inferior
Biosimilars								
Derwahl, K. M.; et al. 2018 (150) SORELLA 2	RCT	505	Adult (age not specified)	SAR342434 insulin lispro biosimilar	Insulin lispro	Change in HbA1c	26 weeks	Intervention non-inferior
Blevins, T.; et al. 2018 (151) INSTRIDE 2	RCT	560	Adult (age not specified)	MYL-1501D insulin biosimilar plus oral antidiabetic drugs	Insulin glargine plus oral antidiabetic drugs	Change in HbA1c	24 weeks	Intervention non-inferior
Rosenstock, J.; et al. 2015 (152) ELEMENT 2	RCT	756	Adult (age not specified)	LY2963016 insulin glargine	Insulin glargine	Change in HbA1c	24 weeks	Intervention non-inferior
						Fasting plasma glucose	24 weeks	Intervention non-inferior
Insulin analogues compared to human insulin								
Home, P. D.; et al. 2015 (153)	RCT	701	Adult (mean age of 57 years)	Insulin glargine	Neutral protamine Hagedorn insulin	Change in HbA1c	36 weeks	Intervention non-inferior
Insulin strategies for hospitalised patients								
Colunga-Lozano, L. E.; et al. 2018 (154)	Cochrane	8 studies n=1048	Adult (age not specified)	Sliding scale insulin	Basal insulin, basal-bolus insulin, correction dose insulin	All-cause mortality	NR	No effect of intervention
						Hypoglycaemia	NR	No effect of intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Insulin monotherapy compared with the addition of OADs								
Vos, R. C.; et al. 2016 (155)	Cochrane	9 studies n=316	Adult (age not specified)	Insulin-sulfonylurea combination	Insulin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
		9 studies n=698	Adult (age not specified)	Insulin metformin	Insulin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
		3 studies n=448	Adult (age not specified)	Insulin plus alpha-glucosidase inhibitors	Insulin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
		2 studies n=265	Adult (age not specified)	Insulin plus DPP-4 inhibitors	Insulin monotherapy	Change in HbA1c	24 weeks	Improved with intervention
		7 studies n=220	Adult (age not specified)	Insulin-sulfonylurea combination	Insulin monotherapy	Hypoglycaemia	24 weeks	Worse with intervention
		7 studies n=615	Adult (age not specified)	Insulin metformin	Insulin monotherapy	Change in body weight	24 weeks	Improved with intervention
		2 studies n=362	Adult (age not specified)	Insulin plus DPP-4 inhibitors	Insulin monotherapy	Change in body weight	24 weeks	Worse with intervention
Insulin glargine and liraglutide								
D'Alessio, D.; et al. 2015 (89)	RCT	489	Adult (age not specified)	Insulin glargine	Liraglutide	Change in HbA1c	24 weeks	No effect of intervention
Billings, L. K.; et al. 2018 (169)	RCT	695	Adult (age not specified)	Insulin degludec plus liraglutide	Basal insulin	Change in HbA1c	Not reported	Intervention non-inferior
						Change in body weight	Not reported	Improved with intervention
						Hypoglycaemia	Not reported	Improved with intervention
Buse, J. B.; et al. 2014 (170)	RCT	413	Adult (age not specified)	Insulin degludec and liraglutide	Insulin degludec	Change in HbA1c	26 week	Improved with intervention
						Change in body weight	26 week	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Abbreviations: RCT – Randomised controlled trial; SR – systematic review; NR – not reported in abstract Unless otherwise stated, patient populations are all type 2 diabetes, with age and comorbidities as stated								

Table 9 Managing complications

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Treatment of proliferative diabetic retinopathy								
Martinez-Zapata, M. J. 2014 (163)	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 (164) CLARITY	RCT	22 ophthalmic centres (n not reported in the abstract)	Adults with proliferative diabetic retinopathy	Intravitreous injection of aflibercept (2mg/0.05ml)	Photocoagulation	Change in BCVA	1 year	Improved with intervention
Treatment of diabetic macular oedema								
Jorge, E. C.; et al. 2018 (165)	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

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
		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 (166)	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
Diabetes-related distress								
Chew, B. H.; et al. 2017 (167)	Cochrane	5 RCTs (N=1932)	Adult (18 and over)	Psychological intervention	Usual care	Health-related quality of life	Median 12 months (range 0 to 12 months)	No effect of intervention
		3 RCTs (N=1376)	Adult (18 and over)	Psychological intervention	Usual care	All-cause mortality	Median 12 months (range 0 to 12 months)	No effect of intervention
		3 RCTs (N=438)	Adult (18 and over)	Psychological intervention	Usual care	Adverse events	Median 12 months (range 0 to 12 months)	No effect of intervention
		6 RCTs (N=2675)	Adult (18 and over)	Psychological intervention	Usual care	Self-efficacy	6-12 months	Improved with intervention
		11 RCTs (N=3165)	Adult ((18 and over)	Psychological intervention	Usual care	Change in HbA1c	6-12 months	Improved with intervention
		12 RCTs (N=3315)	Adult (18 and over)	Psychological intervention	Usual care	Diabetes-related distress	Median 12 months (range 0 to 12 months)	No effect of intervention
Cognitive impairment and dementia								

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Areosa Sastre, A.; et al. 2017 (168)	SR	1 RCT, n=11,140	Adult (age not specified)	Intensive glycaemic control	Standard glycaemic control	Incidence of dementia	NR	No effect of intervention
		1 RCT, n=2794	Adult (age not specified)	Intensive glycaemic control	Standard glycaemic control	MMSE score	40 months	No effect of intervention
		2RCTs, n=12,827	T2D Age unspecified	Intensive glycaemic control	Standard glycaemic control	Hypoglycaemia	NR	Worse with intervention
		3 RCTs, 15,888	Adult (age not specified)	Intensive glycaemic control	Standard glycaemic control	All-cause mortality	NR	No effect of intervention
		1 RCT, n=156	Adult (age not specified)	Glibenclamide (glyburide)	Repaglinide	MMSE score	12 months	Improved with intervention
		1 RCT, n=11,140	Adult (age not specified)	Intensive glycaemic control	Standard glycaemic control	Decline by 3 points or more on Mini Mental State Examination (1 study)	NR	No effect of intervention

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

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

References

1. Kulzer B, Daenschel W, Daenschel I, Schramm W, Messinger D, Weissmann J, et al. (2018) Integrated personalized diabetes management improves glycemic control in patients with insulin-treated type 2 diabetes: Results of the PDM-ProValue study program. Diabetes Research & Clinical Practice 144:200–12

2. Murray E, Ross J, Pal K, Li J, Dack C, Stevenson F, et al. A web-based self-management programme for people with type 2 diabetes: the HeLP-Diabetes research programme including RCT.

3. Bajaj HS, Venn K, Ye C, Aronson R (2016) Randomized Trial of Long-Acting Insulin Glargine Titration Web Tool (LTHome) Versus Enhanced Usual Therapy of Glargine Titration (INNOVATE Trial). Diabetes Technology & Therapeutics 18(10):610–5

4. Attridge M, Creamer J, Ramsden M, Cannings?John R, Hawthorne K (2014) Culturally appropriate health education for people in ethnic minority groups with type 2 diabetes mellitus. Cochrane Database of Systematic Reviews (9)

5. Dallosso HM, Bodicoat DH, Campbell M, Carey ME, Davies MJ, Eborall HC, et al. (2015) Self-monitoring of blood glucose versus self-monitoring of urine glucose in adults with newly diagnosed Type 2 diabetes receiving structured education: a cluster randomized controlled trial. Diabetic Medicine 32(3):414–22

6. Hermanns N, Ehrmann D, Schall S, Maier B, Haak T, Kulzer B (2017) The effect of an education programme (MEDIAS 2 BSC) of non-intensive insulin treatment regimens for people with Type 2 diabetes: a randomized, multi-centre trial. Diabetic Medicine 34(8):1084–91

7. Guo XH, Ji LN, Lu JM, Liu J, Lou QQ, Liu J, et al. (2014) Efficacy of structured education in patients with type 2 diabetes mellitus receiving insulin treatment. Journal Of Diabetes 6(4):290–7

8. Bowen ME, Cavanaugh KL, Wolff K, Davis D, Gregory RP, Shintani A, et al. (2016) The diabetes nutrition education study randomized controlled trial: A comparative effectiveness study of approaches to nutrition in diabetes self-management education. Patient Education & Counseling 99(8):1368–76

9. Cheng L, Sit JWH, Choi KC, Chair SY, Li X, Wu Y, et al. (2018) Effectiveness of a patient-centred, empowerment-based intervention programme among patients with poorly controlled type 2 diabetes: A randomised controlled trial. International Journal of Nursing Studies 79:43–51

10. Meng Y, Bai H, Wang S, Li Z, Wang Q, Chen L (2017) Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: A systematic review and meta-analysis of randomized controlled trials. Diabetes research and clinical practice 131:124–31

11. Huntriss R, Campbell M, Bedwell C (2018) The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. European Journal of Clinical Nutrition 72(3):311–25

12. Korsmo-Haugen H-K, Brurberg KG, Mann J, Aas A-M (2019) Carbohydrate quantity in the dietary management of type 2 diabetes: A systematic review and meta-analysis. Diabetes, Obesity & Metabolism 21(1):15–27

13. ME L, WS L, AC B, Brosnahan N, Thom G, McCombie L, et al. (2018) Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet (London, England) 391(10120):541–51

14. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. (2019) Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. The lancet. Diabetes & endocrinology

15. Liu K, Wang B, Zhou R, Lang H-D, Ran L, Wang J, et al. (2018) Effect of combined use of a low-carbohydrate, high-protein diet with omega-3 polyunsaturated fatty acid supplementation on glycemic control in newly diagnosed type 2 diabetes: a randomized, double-blind, parallel-controlled trial. American Journal of Clinical Nutrition 108(2):256–65

16. Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA, et al. (2015) Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. American Journal of Clinical Nutrition 102(4):780–90

17. Carter S, Clifton PM, Keogh JB (2018) Effect of Intermittent Compared With Continuous Energy Restricted Diet on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Noninferiority Trial. JAMA Network Open 1(3):e180756

18. Shakil-Ur-Rehman S, Karimi H, Gillani SA (2017) Effects of supervised structured aerobic exercise training program on fasting blood glucose level, plasma insulin level, glycemic control, and insulin resistance in type 2 diabetes mellitus. Pakistan Journal of Medical Sciences 33(3):576–80

19. Krul-Poel YHM, Westra S, Boekel ET, Wee MMT, Van SNM, Van WH, et al. (2015) Effect of Vitamin D supplementation on glycemic control in patients with type 2 diabetes (SUNNY Trial): A randomized placebo-controlled trial. Diabetes Care 38(8):1420–6

20. Angellotti E, D'Alessio D, Dawson-Hughes B, Nelson J, Cohen RM, Gastaldelli A, et al. (2018) Vitamin D supplementation in patients with type 2 diabetes: The vitamin D for established type 2 diabetes (DDM2) study. Journal of the Endocrine Society 2(4):310–21

21. Sodipo OO, Adedokun A, Olusola AA (2017) Effect of self-monitoring of blood glucose on glycaemic outcome among type 2 diabetic patients. South african family practice 59(6):208–13

22. Beck RW, Riddlesworth TD, Ruedy K, Ahmann A, Haller S, Kruger D, et al. (2017) Continuous Glucose Monitoring Versus Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections: A Randomized Trial. Annals of Internal Medicine 167(6):365–74

23. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline J-P, Rayman G (2017) Use of Flash Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring in Insulin-treated Type 2 Diabetes. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 8(3):573–86

24. Young LA, Buse JB, Weaver MA, Vu MB, Mitchell CM, Blakeney T, et al. (2017) Glucose Self-monitoring in Non-Insulin-Treated Patients With Type 2 Diabetes in Primary Care Settings: A Randomized Trial. JAMA Internal Medicine 177(7):920–9

25. Grady M, Katz LB, Cameron H, Levy BL (2017) Diabetes App-Related Text Messages

From Health Care Professionals in Conjunction With a New Wireless Glucose Meter With a Color Range Indicator Improves Glycemic Control in Patients With Type 1 and Type 2 Diabetes: Randomized Controlled Trial. JMIR Diabetes 2(2):e19

26. Hansen CR, Perrild H, Koefoed BG, Zander M (2017) Video consultations as add-on to standard care among patients with type 2 diabetes not responding to standard regimens: a randomized controlled trial. European Journal of Endocrinology 176(6):727–36

27. Wild SH, Hanley J, Lewis SC, McKnight JA, McCloughan LB, Padfield PL, et al. (2016) Supported Telemonitoring and Glycemic Control in People with Type 2 Diabetes: The Telescot Diabetes Pragmatic Multicenter Randomized Controlled Trial. PLoS Medicine / Public Library of Science 13(7):e1002098

28. Bollyky JB, Bravata D, Yang J, Williamson M, Schneider J (2018) Remote Lifestyle Coaching Plus a Connected Glucose Meter with Certified Diabetes Educator Support Improves Glucose and Weight Loss for People with Type 2 Diabetes. Journal of Diabetes Research 2018:3961730

29. Kempf K, Altpeter B, Berger J, Reus O, Fuchs M, Schneider M, et al. (2017) Efficacy of the Telemedical Lifestyle intervention Program TeLiPro in Advanced Stages of Type 2 Diabetes: A Randomized Controlled Trial. Diabetes Care 40(7):863–71

30. Lindberg I, Torbjornsen A, Soderberg S, Ribu L (2017) Telemonitoring and Health Counseling for Self-Management Support of Patients With Type 2 Diabetes: A Randomized Controlled Trial. JMIR Diabetes 2(1):e10

31. Parsons SN, Luzio SD, Harvey JN, Bain SC, Cheung WY, Watkins A, et al. (2019) Effect of structured self-monitoring of blood glucose, with and without additional TeleCare support, on overall glycaemic control in non-insulin treated Type 2 diabetes: the SMBG Study, a 12-month randomized controlled trial. Diabetic Medicine 17:17

32. Henry RR, Frias JP, Walsh B, Skare S, Hemming J, Burns C, et al. (2018) Improved glycemic control with minimal systemic metformin exposure: Effects of Metformin Delayed-Release (Metformin DR) targeting the lower bowel over 16 weeks in a randomized trial in subjects with type 2 diabetes. PLoS ONE [Electronic Resource] 13(9):e0203946

33. Johnston R, Uthman O, Cummins E, Clar C, Royle P, Colquitt J, et al. (2017) Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. Health Technology Assessment (Winchester, England) 21(2):1–218

34. Miller S, Krumins T, Zhou H, Huyck S, Johnson J, Golm G, et al. (2018) Ertugliflozin and Sitagliptin Co-initiation in Patients with Type 2 Diabetes: The VERTIS SITA Randomized Study. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 9(1):253–68

35. Aronson R, Frias J, Goldman A, Darekar A, Lauring B, Terra SG (2018) Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. Diabetes, Obesity & Metabolism 20(6):1453–60

36. Pratley RE, Eldor R, Raji A, Golm G, Huyck SB, Qiu Y, et al. (2018) Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: The VERTIS FACTORIAL randomized trial. Diabetes, Obesity & Metabolism 20(5):1111–20

37. Grunberger G, Camp S, Johnson J, Huyck S, Terra SG, Mancuso JP, et al. (2018) Ertugliflozin in Patients with Stage 3 Chronic Kidney Disease and Type 2 Diabetes Mellitus: The VERTIS RENAL Randomized Study. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 9(1):49–66

38. Rosenstock J, Frias J, Pall D, Charbonnel B, Pascu R, Saur D, et al. (2018) Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). Diabetes, Obesity and Metabolism 20(3):520–9

39. Dagogo-Jack S, Liu J, Eldor R, Amorin G, Johnson J, Hille D, et al. (2018) Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: The VERTIS SITA2 placebo-controlled randomized study. Diabetes, Obesity & Metabolism 20(3):530–40

40. Hollander P, Liu J, Hill J, Johnson J, Jiang ZW, Golm G, et al. (2018) Ertugliflozin Compared with Glimepiride in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin: The VERTIS SU Randomized Study. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 9(1):193–207

41. Park J, Park SW, Yoon KH, Kim SR, Ahn KJ, Lee JH, et al. (2017) Efficacy and safety of evogliptin monotherapy in patients with type 2 diabetes and moderately elevated glycated haemoglobin levels after diet and exercise. Diabetes, Obesity & Metabolism 19(12):1681–7

42. Lim S, Han KA, Yu J, Chamnan P, Kim ES, Yoon KH, et al. (2017) Efficacy and safety of initial combination therapy with gemigliptin and metformin compared with monotherapy with either drug in patients with type 2 diabetes: A double-blind randomized controlled trial (INICOM study). Diabetes, Obesity & Metabolism 19(1):87–97

43. Ross SA, Caballero AE, Del PS, Gallwitz B, Lewis-D'Agostino D, Bailes Z, et al. (2015) Initial combination of linagliptin and metformin compared with linagliptin monotherapy in patients with newly diagnosed type 2 diabetes and marked hyperglycaemia: a randomized, double-blind, active-controlled, parallel group, multinational clinical trial. Diabetes, Obesity & Metabolism 17(2):136–44

44. Alfayez OM, Al YMS, Alshibani M, Fallatah SB, Al KNM, Alsheikh R, et al. (2019) Network meta-analysis of nine large cardiovascular outcome trials of new antidiabetic drugs. Primary care diabetes 31:31

45. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. (2019) SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 393(10166):31–9

46. 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)

47. Perkovic V, de ZD, Mahaffey KW, Fulcher G, Erondu N, Shaw W, et al. (2018) Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. The Lancet Diabetes & Endocrinology 6(9):691–704

48. Fan G, Han R, Zhang Y, Zhang Z, Liu Y, Wang D, et al. (2016) Safety assessment of canagliflozin for type 2 diabetes mellitus. International Journal of Clinical and Experimental Medicine 9(2):2595–612

49. Radholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de ZD, et al. (2018) Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus. Circulation 138(5):458–68

50. Mahaffey KW, Neal B, Perkovic V, de ZD, Fulcher G, Erondu N, et al. (2018) Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). Circulation 137(4):323–34

51. Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, et al. (2016) Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus. Journal of Clinical Endocrinology & Metabolism 101(1):157–66

52. Neuen BL, Ohkuma T, Neal B, Matthews DR, de ZD, Mahaffey KW, et al. (2018) Cardiovascular and Renal Outcomes With Canagliflozin According to Baseline Kidney Function. Circulation 138(15):1537–50

53. Cusi K, Bril F, Barb D, Polidori D, Sha S, Ghosh A, et al. (2018) Effect of canagliflozin treatment on hepatic triglyceride content and glucose metabolism in patients with type 2 diabetes. Diabetes, Obesity & Metabolism 16:16

54. Handelsman Y, Mathieu C, Del PS, Johnsson E, Kurlyandskaya R, Iqbal N, et al. (2018) Sustained 52-week efficacy and safety of triple therapy with dapagliflozin plus saxagliptin versus dual therapy with sitagliptin added to metformin in patients with uncontrolled type 2 diabetes. Diabetes, Obesity & Metabolism 30:30

55. Charokopou M, McEwan P, Lister S, Callan L, Bergenheim K, Tolley K, et al. (2015) The cost-effectiveness of dapagliflozin versus sulfonylurea as an add-on to metformin in the treatment of Type 2 diabetes mellitus. Diabetic Medicine 32(7):890–8

56. Charokopou M, McEwan P, Lister S, Callan L, Bergenheim K, Tolley K, et al. (2015) Cost-effectiveness of dapagliflozin versus DPP-4 inhibitors as an add-on to Metformin in the Treatment of Type 2 Diabetes Mellitus from a UK Healthcare System Perspective. BMC Health Services Research 15:496

57. Muller-Wieland D, Kellerer M, Cypryk K, Skripova D, Rohwedder K, Johnsson E, et al. (2018) Efficacy and safety of dapagliflozin or dapagliflozin plus saxagliptin versus glimepiride as add-on to metformin in patients with type 2 diabetes. Diabetes, Obesity & Metabolism 20(11):2598–607

58. Fioretto P, Del PS, Buse JB, Goldenberg R, Giorgino F, Reyner D, et al. (2018) Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): The DERIVE Study. Diabetes, Obesity & Metabolism 20(11):2532–40

59. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. (2019) Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine 380(4):347–57

60. Jabbour SA, Frias JP, Hardy E, Ahmed A, Wang H, Ohman P, et al. (2018) Safety and Efficacy of Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients With Type 2 Diabetes Inadequately Controlled With Metformin Monotherapy: 52-Week Results of the DURATION-8 Randomized Contro... Diabetes Care 41(10):2136–46

61. Scott R, Morgan J, Zimmer Z, Lam RLH, O'Neill EA, Kaufman KD, et al. (2018) A randomized clinical trial of the efficacy and safety of sitagliptin compared with dapagliflozin in patients with type 2 diabetes mellitus and mild renal insufficiency: The

CompoSIT-R study. Diabetes, Obesity & Metabolism 20(12):2876–84

62. Vega-Hernandez G, Wojcik R, Schlueter M (2017) Cost-Effectiveness of Liraglutide Versus Dapagliflozin for the Treatment of Patients with Type 2 Diabetes Mellitus in the UK. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 8(3):513–30

63. Merker L, Haring HU, Christiansen A V., Roux F, Salsali A, Kim G, et al. (2015) Empagliflozin as add-on to metformin in people with Type 2 diabetes. Diabetic Medicine 32(12):1555–67

64. Ridderstrale M, Rosenstock J, Andersen KR, Woerle HJ, Salsali A, investigators E-RHHS trial (2018) Empagliflozin compared with glimepiride in metformin-treated patients with type 2 diabetes: 208-week data from a masked randomized controlled trial. Diabetes, Obesity & Metabolism 20(12):2768–77

65. Cherney D, Lund SS, Perkins BA, Groop PH, Cooper ME, Kaspers S, et al. (2016) The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes. Diabetologia 59(9):1860–70

66. Evans M, Achha S, Neslusan C (2017) Cost of Glycemic Target Achievement with Sodium Glucose Co-transporter 2 Inhibitors in Patients with Type 2 Diabetes in the UK. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 8(5):1175–85

67. Shestakova M V., Wilding JPH, Wilpshaar W, Tretter R, Orlova VL, Verbovoy AF (2018) A phase 3 randomized placebo-controlled trial to assess the efficacy and safety of ipragliflozin as an add-on therapy to metformin in Russian patients with inadequately controlled type 2 diabetes mellitus. Diabetes Research & Clinical Practice 146:240–50

68. Aroda VR, Bain SC, Cariou B, Piletic M, Rose L, Axelsen M, et al. (2017) Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre,... The Lancet Diabetes & Endocrinology 5(5):355–66

69. Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, et al. (2018) Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial. Diabetes Care 41(2):258–66

70. Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, Rosenstock J (2017) Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. JAMA 318(15):1460–70

71. Lingvay I, Desouza C V., Lalic KS, Rose L, Hansen T, Zacho J, et al. (2018) A 26-Week Randomized Controlled Trial of Semaglutide Once Daily Versus Liraglutide and Placebo in Patients With Type 2 Diabetes Suboptimally Controlled on Diet and Exercise With or Without Metformin. Diabetes Care 41(9):1926–37

72. Rodbard HW, Lingvay I, Reed J, de la RR, Rose L, Sugimoto D, et al. (2018) Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): A Randomized, Controlled Trial. Journal of Clinical Endocrinology & Metabolism 103(6):2291–301

73. Nauck MA, Petrie JR, Sesti G, Mannucci E, Courreges JP, Lindegaard ML, et al. (2016) A Phase 2, Randomized, Dose-Finding Study of the Novel Once-Weekly Human GLP-1 Analog, Semaglutide, Compared With Placebo and Open-Label Liraglutide in Patients With Type 2 Diabetes. Diabetes Care 39(2):231–41

74. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. (2016) Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. New England Journal of Medicine 375(19):1834–44

75. Ahren B, Masmiquel L, Kumar H, Sargin M, Karsbol JD, Jacobsen SH, et al. (2017) Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. The Lancet Diabetes & Endocrinology 5(5):341–54

76. Sorli C, Harashima SI, Tsoukas GM, Unger J, Karsbol JD, Hansen T, et al. (2017) Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. The Lancet Diabetes & Endocrinology 5(4):251–60

77. Pratley RE, Aroda VR, Lingvay I, Ludemann J, Andreassen C, Navarria A, et al. (2018) Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. The Lancet Diabetes & Endocrinology 6(4):275–86

78. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB. S, Granger CB, Jones NP, et al. (2018) Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet 392(10157):1519–29

79. Tuttle KR, Lakshmanan MC, Rayner B, Busch RS, Zimmermann AG, Woodward DB, et al. (2018) Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. The Lancet Diabetes & Endocrinology 6(8):605–17

80. Ludvik B, Frias JP, Tinahones FJ, Wainstein J, Jiang H, Robertson KE, et al. (2018) Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. The Lancet Diabetes & Endocrinology 6(5):370–81

81. Pozzilli P, Norwood P, Jodar E, Davies MJ, Ivanyi T, Jiang H, et al. (2017) Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). Diabetes, Obesity & Metabolism 19(7):1024–31

82. Chuang LH, Verheggen BG, Charokopou M, Gibson D, Grandy S, Kartman B (2016) Cost-effectiveness analysis of exenatide once-weekly versus dulaglutide, liraglutide, and lixisenatide for the treatment of type 2 diabetes mellitus: an analysis from the UK NHS perspective. Journal of Medical Economics 19(12):1127–34

83. Wysham CH, Rosenstock J, Vetter ML, Dong F, Ohman P, Iqbal N (2018) Efficacy and tolerability of the new autoinjected suspension of exenatide once weekly versus exenatide twice daily in patients with type 2 diabetes. Diabetes, obesity & metabolism 20(1):165–72

84. Gadde KM, Vetter ML, Iqbal N, Hardy E, Ohman P, investigators D-N (2017) Efficacy

and safety of autoinjected exenatide once-weekly suspension versus sitagliptin or placebo with metformin in patients with type 2 diabetes: The DURATION-NEO-2 randomized clinical study. Diabetes, Obesity & Metabolism 19(7):979–88

85. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. (2017) Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine 377(13):1228–39

86. Xu W, Bi Y, Sun Z, Li J, Guo L, Yang T, et al. (2015) Comparison of the effects on glycaemic control and beta-cell function in newly diagnosed type 2 diabetes patients of treatment with exenatide, insulin or pioglitazone: a multicentre randomized parallel-group trial (the CONFIDENCE study). Journal of Internal Medicine 277(1):137–50

87. Hunt B, Ye Q, Valentine WJ, Ashley D (2017) Evaluating the Long-Term Cost-Effectiveness of Daily Administered GLP-1 Receptor Agonists for the Treatment of Type 2 Diabetes in the United Kingdom. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 8(1):129–47

88. Mann JFE, Orsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, et al. (2017) Liraglutide and Renal Outcomes in Type 2 Diabetes. New England Journal of Medicine 377(9):839–48

89. D'Alessio D, Haring HU, Charbonnel B, de P-VP, Candelas C, Dain MP, et al. (2015) Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. Diabetes, Obesity & Metabolism 17(2):170–8

90. Moses RG, Round E, Shentu Y, Golm GT, O'Neill EA, Gantz I, et al. (2016) A randomized clinical trial evaluating the safety and efficacy of sitagliptin added to the combination of sulfonylurea and metformin in patients with type 2 diabetes mellitus and inadequate glycemic control. Journal of Diabetes.

91. Wang W, Ning G, Ma J, Liu X, Zheng S, Wu F, et al. (2017) A randomized clinical trial of the safety and efficacy of sitagliptin in patients with type 2 diabetes mellitus inadequately controlled by acarbose alone. Current Medical Research & Opinion 33(4):693–9

92. Kim SS, Kim IJ, Lee KJ, Park JH, Kim YI, Lee YS, et al. (2017) Efficacy and safety of sitagliptin/metformin fixed-dose combination compared with glimepiride in patients with type 2 diabetes: A multicenter randomized double-blind study. Journal Of Diabetes 9(4):412–22

93. Frias JP, Zimmer Z, Lam RLH, Lic GA, Ntabadde C, Iredale C, et al. (2019) Double-blind, randomized clinical trial assessing the efficacy and safety of early initiation of sitagliptin during metformin up-titration in treatment of patients with type 2 diabetes: the CompoSIT-M Study. Diabetes, Obesity & Metabolism 04:04

94. Hartley P, Shentu Y, Betz-Schiff P, Golm GT, Sisk CM, Engel SS, et al. (2015) Efficacy and Tolerability of Sitagliptin Compared with Glimepiride in Elderly Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control: A Randomized, Double-Blind, Non-Inferiority Trial. Drugs & Aging 32(6):469–76

95. Jameshorani M, Sayari S, Kiahashemi N, Motamed N (2017) Comparative study on adding pioglitazone or sitagliptin to patients with type 2 diabetes mellitus insufficiently controlled with metformin. Open access macedonian journal of medical sciences 5(7):955–62

96. Buse JB, Bethel MA, Green JB, Stevens SR, Lokhnygina Y, Aschner P, et al. (2017)

Pancreatic Safety of Sitagliptin in the TECOS Study. Diabetes Care 40(2):164–70

97. Josse RG, Majumdar SR, Zheng Y, Adler A, Bethel MA, Buse JB, et al. (2017) Sitagliptin and risk of fractures in type 2 diabetes: Results from the TECOS trial. Diabetes, Obesity & Metabolism 19(1):78–86

98. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. (2015) Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine 373(3):232–42

99. Hong SM, Park CY, Hwang DM, Han KA, Lee CB, Chung CH, et al. (2017) Efficacy and safety of adding evogliptin versus sitagliptin for metformin-treated patients with type 2 diabetes: A 24-week randomized, controlled trial with open label extension. Diabetes, Obesity & Metabolism 19(5):654–63

100. Jin SM, Park SW, Yoon KH, Min KW, Song KH, Park KS, et al. (2015) Anagliptin and sitagliptin as add-ons to metformin for patients with type 2 diabetes: a 24-week, multicentre, randomized, double-blind, active-controlled, phase III clinical trial with a 28-week extension. Diabetes, obesity & metabolism 17(5):511–5

101. Gu T, Ma J, Zhang Q, Zhu L, Zhang H, Xu L, et al. (2018) Comparative effect of saxagliptin and glimepiride with a composite endpoint of adequate glycaemic control without hypoglycaemia and without weight gain in patients uncontrolled with metformin therapy: Results from the SPECIFY study, a 48-week, multi-c... Diabetes, Obesity & Metabolism 05:05

102. Schernthaner G, Duran-Garcia S, Hanefeld M, Langslet G, Niskanen L, Ostgren CJ, et al. (2015) Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). Diabetes, Obesity & Metabolism 17(7):630–8

103. Chen Y, Liu X, Li Q, Ma J, Lv X, Guo L, et al. (2018) Saxagliptin add-on therapy in Chinese patients with type 2 diabetes inadequately controlled by insulin with or without metformin: Results from the SUPER study, a randomized, double-blind, placebo-controlled trial. Diabetes, Obesity & Metabolism 20(4):1044–9

104. Du J, Liang L, Fang H, Xu F, Li W, Shen L, et al. (2017) Efficacy and safety of saxagliptin compared with acarbose in Chinese patients with type 2 diabetes mellitus uncontrolled on metformin monotherapy: Results of a Phase IV open-label randomized controlled study (the SMART study). Diabetes, Obesity & Metabolism 19(11):1513–20

105. Leiter LA, Teoh H, Braunwald E, Mosenzon O, Cahn A, Kumar KM, et al. (2015) Efficacy and safety of saxagliptin in older participants in the SAVOR-TIMI 53 trial. Diabetes Care 38(6):1145–53

106. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al. (2014) Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 130(18):1579–88

107. Groop PH, Cooper ME, Perkovic V, Hocher B, Kanasaki K, Haneda M, et al. (2017) Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial. Diabetes, Obesity & Metabolism 19(11):1610–9

108. Ji L, Zinman B, Patel S, Ji J, Bailes Z, Thiemann S, et al. (2015) Efficacy and safety of linagliptin co-administered with low-dose metformin once daily versus high-dose metformin twice daily in treatment-naive patients with type 2 diabetes: a double-blind

randomized trial. Advances in Therapy 32(3):201–15

109. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, et al. (2018) Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. Jama 09:09

110. Gordon J, McEwan P, Hurst M, Puelles J (2016) The Cost-Effectiveness of Alogliptin Versus Sulfonylurea as Add-on Therapy to Metformin in Patients with Uncontrolled Type 2 Diabetes Mellitus. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 7(4):825–45

111. Mita T, Katakami N, Yoshii H, Onuma T, Kaneto H, Osonoi T, et al. (2016) Alogliptin, a Dipeptidyl Peptidase 4 Inhibitor, Prevents the Progression of Carotid Atherosclerosis in Patients With Type 2 Diabetes: The Study of Preventive Effects of Alogliptin on Diabetic Atherosclerosis (SPEAD-A). Diabetes Care 39(1):139–48

112. White WB, Kupfer S, Zannad F, Mehta CR, Wilson CA, Lei L, et al. (2016) Cardiovascular Mortality in Patients With Type 2 Diabetes and Recent Acute Coronary Syndromes From the EXAMINE Trial. Diabetes Care 39(7):1267–73

113. Hong AR, Lee J, Ku EJ, Hwangbo Y, Kim KM, Moon JH, et al. (2015) Comparison of vildagliptin as an add-on therapy and sulfonylurea dose-increasing therapy in patients with inadequately controlled type 2 diabetes using metformin and sulfonylurea (VISUAL study): A randomized trial. Diabetes Research & Clinical Practice 109(1):141–8

114. Forst T, Koch C, Dworak M (2015) Vildagliptin versus insulin in patients with type 2 diabetes mellitus inadequately controlled with sulfonylurea: results from a randomized, 24 week study. Current Medical Research & Opinion 31(6):1079–84

115. Pawaskar M, Bilir SP, Kowal S, Gonzalez C, Rajpathak S, Davies G (2018) Cost-effectiveness of intensification with sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes on metformin and sitagliptin vs direct intensification with insulin in the United Kingdom. Diabetes, Obesity & Metabolism 18:18

116. Guja C, Frias JP, Somogyi A, Jabbour S, Wang H, Hardy E, et al. (2018) Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: The DURATION-7 randomized study. Diabetes, Obesity & Metabolism 20(7):1602–14

117. Diamant M, Nauck MA, Shaginian R, Malone JK, Cleall S, Reaney M, et al. (2014) Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care 37(10):2763–73

118. Aroda VR, Rosenstock J, Wysham C, Unger J, Bellido D, Gonzalez-Galvez G, et al. (2016) Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial. Diabetes Care 39(11):1972–80

119. Rosenstock J, Aronson R, Grunberger G, Hanefeld M, Piatti P, Serusclat P, et al. (2016) Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial. Diabetes Care 39(11):2026–35

120. Rosenstock J, Diamant M, Aroda VR, Silvestre L, Souhami E, Zhou T, et al. (2016)

Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Lixisenatide and Insulin Glargine, Versus Insulin Glargine in Type 2 Diabetes Inadequately Controlled on Metformin Monotherapy: The LixiLan Proof-of-Concept Randomized Trial. Diabetes Care 39(9):1579–86

121. Gough SC, Bode B, Woo V, Rodbard HW, Linjawi S, Poulsen P, et al. (2014) Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type... The Lancet Diabetes & Endocrinology 2(11):885–93

122. Lingvay I, Perez MF, Garcia-Hernandez P, Norwood P, Lehmann L, Tarp-Johansen MJ, et al. (2016) Effect of Insulin Glargine Up-titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes: The DUAL V Randomized Clinical Trial. JAMA 315(9):898–907

123. Aroda VR, Bailey TS, Cariou B, Kumar S, Leiter LA, Raskin P, et al. (2016) Effect of adding insulin degludec to treatment in patients with type 2 diabetes inadequately controlled with metformin and liraglutide: a double-blind randomized controlled trial (BEGIN: ADD TO GLP-1 Study). Diabetes, Obesity & Metabolism 18(7):663–70

124. Ahmann A, Rodbard HW, Rosenstock J, Lahtela JT, de LL, Tornoe K, et al. (2015) Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: a randomized, placebo-controlled trial. Diabetes, Obesity & Metabolism 17(11):1056–64

125. Lind M, Hirsch IB, Tuomilehto J, Dahlqvist S, Ahren B, Torffvit O, et al. (2015) Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). BMJ 351:h5364

126. Rodbard HW, Bode BW, Harris SB, Rose L, Lehmann L, Jarlov H, et al. (2017) Safety and efficacy of insulin degludec/liraglutide (IDegLira) added to sulphonylurea alone or to sulphonylurea and metformin in insulin-naive people with Type 2 diabetes: the DUAL IV trial. Diabetic Medicine 34(2):189–96

127. Harris SB, Kocsis G, Prager R, Ridge T, Chandarana K, Halladin N, et al. (2017) Safety and efficacy of IDegLira titrated once weekly versus twice weekly in patients with type 2 diabetes uncontrolled on oral antidiabetic drugs: DUAL VI randomized clinical trial. Diabetes, Obesity & Metabolism 19(6):858–65

128. Linjawi S, Sothiratnam R, Sari R, Andersen H, Hiort LC, Rao P (2015) The study of once- and twice-daily biphasic insulin aspart 30 (BIAsp 30) with sitagliptin, and twice-daily BIAsp 30 without sitagliptin, in patients with type 2 diabetes uncontrolled on sitagliptin and metformin-The Sit2Mix trial. Primary care diabetes 9(5):370–6

129. Roussel R, Duran-Garcia S, Zhang Y, Shah S, Darmiento C, Shankar RR, et al. (2018) Double-blind, randomized clinical trial comparing the efficacy and safety of continuing or discontinuing the dipeptidyl peptidase-4 inhibitor sitagliptin when initiating insulin glargine therapy in patients with type 2 diabetes: The CompoSIT-I Study. Diabetes, Obesity & Metabolism 04:04

130. Mathieu C, Shankar RR, Lorber D, Umpierrez G, Wu F, Xu L, et al. (2015) A Randomized Clinical Trial to Evaluate the Efficacy and Safety of Co-Administration of Sitagliptin with Intensively Titrated Insulin Glargine. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 6(2):127–42

131. White WB, Heller SR, Cannon CP, Howitt H, Khunti K, Bergenstal RM, et al. (2018)

Alogliptin in Patients with Type 2 Diabetes Receiving Metformin and Sulfonylurea Therapies in the EXAMINE Trial. American Journal of Medicine 131(7):813–819.e5

132. Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A, et al. (2018) Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 12:cd013228

133. Lundby-Christensen L, Tarnow L, Boesgaard TW, Lund SS, Wiinberg N, Perrild H, et al. (2016) Metformin versus placebo in combination with insulin analogues in patients with type 2 diabetes mellitus-the randomised, blinded Copenhagen Insulin and Metformin Therapy (CIMT) trial. BMJ Open 6(2):e008376

134. Bowering K, Case C, Harvey J, Reeves M, Sampson M, Strzinek R, et al. (2017) Faster Aspart Versus Insulin Aspart as Part of a Basal-Bolus Regimen in Inadequately Controlled Type 2 Diabetes: The onset 2 Trial. Diabetes Care 40(7):951–7

135. Rodbard HW, Tripathy D, Vidrio VM, Demissie M, Tamer SC, Piletic M (2017) Adding fast-acting insulin aspart to basal insulin significantly improved glycaemic control in patients with type 2 diabetes: A randomized, 18-week, open-label, phase 3 trial (onset 3). Diabetes, Obesity & Metabolism 19(10):1389–96

136. Linjawi S, Lee B-W, Tabak O, Lovdahl S, Werther S, Abusnana S (2018) A 32-Week Randomized Comparison of Stepwise Insulin Intensification of Biphasic Insulin Aspart (BIAsp 30) Versus Basal-Bolus Therapy in Insulin-Naive Patients with Type 2 Diabetes. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders 9(1):1–11

137. Lundby-Christensen L, Vaag A, Tarnow L, Almdal TP, Lund SS, Wetterslev J, et al. (2016) Effects of biphasic, basal-bolus or basal insulin analogue treatments on carotid intima-media thickness in patients with type 2 diabetes mellitus: the randomised Copenhagen Insulin and Metformin Therapy (CIMT) trial. BMJ Open 6(2):e008377

138. Franek E, Haluzik M, Canecki VS, Sargin M, Macura S, Zacho J, et al. (2016) Twice-daily insulin degludec/insulin aspart provides superior fasting plasma glucose control and a reduced rate of hypoglycaemia compared with biphasic insulin aspart 30 in insulin-naive adults with Type 2 diabetes. Diabetic Medicine 33(4):497–505

139. Vora J, Cohen N, Evans M, Hockey A, Speight J, Whately-Smith C (2015) Intensifying insulin regimen after basal insulin optimization in adults with type 2 diabetes: a 24-week, randomized, open-label trial comparing insulin glargine plus insulin glulisine with biphasic insulin aspart (LanScape). Diabetes, Obesity & Metabolism 17(12):1133–41

140. Evans M, Mehta R, Gundgaard J, Chubb B (2018) Cost-Effectiveness of Insulin Degludec vs. Insulin Glargine U100 in Type 1 and Type 2 Diabetes Mellitus in a UK Setting. Diabetes Therapy 9(5):1919–30

141. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, et al. (2017) Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. New England Journal of Medicine 377(8):723–32

142. Pan C, Gross JL, Yang W, Lv X, Sun L, Hansen CT, et al. (2016) A Multinational, Randomized, Open-label, Treat-to-Target Trial Comparing Insulin Degludec and Insulin Glargine in Insulin-Naive Patients with Type 2 Diabetes Mellitus. Drugs in R & D 16(2):239–49

143. Wysham C, Bhargava A, Chaykin L, de la RR, Handelsman Y, Troelsen LN, et al. (2017)

Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial. JAMA 318(1):45–56

144. Rosenstock J, Cheng A, Ritzel R, Bosnyak Z, Devisme C, Cali AMG, et al. (2018) More Similarities Than Differences Testing Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head BRIGHT Trial. Diabetes Care 41(10):2147–54

145. Rodbard HW, Cariou B, Pieber TR, Endahl LA, Zacho J, Cooper JG (2016) Treatment intensification with an insulin degludec (IDeg)/insulin aspart (IAsp) co-formulation twice daily compared with basal IDeg and prandial IAsp in type 2 diabetes: a randomized, controlled phase III trial. Diabetes, Obesity & Metabolism 18(3):274–80

146. Riddle MC, Yki-Jarvinen H, Bolli GB, Ziemen M, Muehlen-Bartmer I, Cissokho S, et al. (2015) One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. Diabetes, Obesity & Metabolism 17(9):835–42

147. Yki-Jarvinen H, Bergenstal RM, Bolli GB, Ziemen M, Wardecki M, Muehlen-Bartmer I, et al. (2015) Glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus insulin glargine 100 U/ml in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: the EDITION 2 randomized 12-month trial including 6-month ext... Diabetes, Obesity & Metabolism 17(12):1142–9

148. Bolli GB, Riddle MC, Bergenstal RM, Wardecki M, Goyeau H, Home PD, et al. (2017) Glycaemic control and hypoglycaemia with insulin glargine 300U/mL versus insulin glargine 100U/mL in insulin-naive people with type 2 diabetes: 12-month results from the EDITION 3 trial. Diabetes & Metabolism 43(4):351–8

149. Ritzel R, Harris SB, Baron H, Florez H, Roussel R, Espinasse M, et al. (2018) A Randomized Controlled Trial Comparing Efficacy and Safety of Insulin Glargine 300 Units/mL Versus 100 Units/mL in Older People With Type 2 Diabetes: Results From the SENIOR Study. Diabetes Care 41(8):1672–80

150. Derwahl KM, Bailey TS, Wernicke-Panten K, Ping L, Pierre S (2018) Efficacy and Safety of Biosimilar SAR342434 Insulin Lispro in Adults with Type 2 Diabetes, Also Using Insulin Glargine: SORELLA 2 Study. Diabetes Technology & Therapeutics 20(1):49–58

151. Blevins TC, Barve A, Sun B, Raiter Y, Aubonnet P, Muniz R, et al. (2018) Efficacy and safety of MYL-1501D versus insulin glargine in patients with type 2 diabetes after 24 weeks: results of the phase III INSTRIDE 2 study. Diabetes, obesity & metabolism (no pagination)

152. Rosenstock J, Hollander P, Bhargava A, Ilag LL, Pollom RK, Zielonka JS, et al. (2015) Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus) in patients with type 2 diabetes who were insulin-naive or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). Diabetes, Obesity & Metabolism 17(8):734–41

153. Home PD, Bolli GB, Mathieu C, Deerochanawong C, Landgraf W, Candelas C, et al. (2015) Modulation of insulin dose titration using a hypoglycaemia-sensitive algorithm: insulin glargine versus neutral protamine Hagedorn insulin in insulin-naive people with type 2 diabetes. Diabetes, Obesity & Metabolism 17(1):15–22

154. Colunga?Lozano LE, Gonzalez TFJ, 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)

155. Vos RC, van AMJP, Jansen H, Goudswaard AN, van den DM, Gorter K, et al. (2016) Insulin monotherapy compared with the addition of oral glucose?lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control. Cochrane Database of Systematic Reviews (9)

156. 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)

157. 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)

158. 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

159. 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

160. 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

161. 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

162. 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

163. 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)

164. 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

165. Jorge EC, Jorge EN, Botelho M, Farat JG, Virgili G, El Dib R Monotherapy laser photocoagulation for diabetic macular oedema. The Cochrane database of systematic reviews 10:CD010859

166. 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 (Philadelphia, Pa.) 35(5):944–56

167. Chew BH, Vos RC, Metzendorf MI, Scholten R, Rutten G (2017) Psychological interventions for diabetes?related distress in adults with type 2 diabetes mellitus. Cochrane Database of Systematic Reviews (9)

168. Areosa SA, Vernooij RWM, Gonz?lez?Cola?o HM, Mart?nez G (2017) Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia. Cochrane Database of Systematic Reviews (6)

169. Billings LK, Doshi A, Gouet D, Oviedo A, Rodbard HW, Tentolouris N, et al. (2018) Efficacy and Safety of IDegLira Versus Basal-Bolus Insulin Therapy in Patients With Type 2 Diabetes Uncontrolled on Metformin and Basal Insulin: The DUAL VII Randomized Clinical Trial. Diabetes Care 41(5):1009–16

170. Buse JB, Vilsboll T, Thurman J, Blevins TC, Langbakke IH, Bottcher SG, et al. (2014) Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). Diabetes Care 37(11):2926–33