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World Health Organization

Guidelines on second-and third-line medicines and type of insulin for *the control of blood glucose levels* in non-pregnant adults with diabetes mellitus

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Contents

Abbreviations

CDC	Centers for Disease Control and Prevention
CI	confidence interval
CrI	credibility interval
COI	conflict of interest
CVD	cardiovascular disease
DOI	declaration of interest
DPP-4 inhibitors	dipeptidyl peptidase-4 inhibitors
EMA	European Medicines Agency
EML	Essential Medicines List
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	glycated haemoglobin A1c
IDF	International Diabetes Federation
PICO	population – intervention – comparator – outcome
MET	metformin
MI	myocardial infarction
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NPH	neutral protamine hagedorn
OHA	oral hypoglycaemic agents
RCT	randomized controlled trial
RHI	regular human insulin
SIGN	Scottish Intercollegiate Guidelines Network
SGLT-2 inhibitor	sodium-glucose co-transporters type 2 inhibitors
SU	sulfonylureas
TZDs	thiazolidinediones (glitazones)
UHC	universal health coverage
WHO PEN	*WHO Package of Essential Non-Communicable Disease (NCD) Interventions* for primary care in low-resource settings

Glossary

Cardiovascular diseases (CVDs)
A group of disorders of the heart and blood vessels that include coronary heart disease and cerebrovascular disease.

Diabetic ketoacidosis and hyperosmolar hyperglycaemia
Life-threatening conditions characterized by fluid and electrolyte depletion, high blood glucose levels and metabolic acidosis (metabolic acidosis may be absent in hyperosmolar hyperglycaemia).

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors or gliptins)
Oral hypoglycaemic agents used in treating type 2 diabetes. They suppress the degradation of incretins by blocking the action of the enzyme dipeptidyl-peptidase 4. This stimulates insulin secretion and suppresses glucagon release.

HbA1c
Haemoglobin glycated by non-enzymatic attachment of glucose to haemoglobin. The concentration of HbA1c is the most commonly used measure of chronic glycaemia in clinical trials and diabetes management. It is considered to reflect the integrated mean glucose level over the previous 8–12 weeks.

Hypoglycaemia
Potentially life-threatening low concentration of blood glucose, most frequently a side-effect of pharmacological treatment. There is no universally agreed definition. In studies the definitions of hypoglycaemia are most frequently in the range <4 mmol/L to ≤ 2.8 mmol/L. Severe hypoglycaemia is most frequently defined as a symptomatic condition that requires the assistance of a third person for resuscitative actions.

Insulin analogues
Insulins different from any occurring in nature and derived from human insulin by modifying its structure to change the pharmacokinetic profile.

Metformin
A biguanide oral hypoglycemic agent used in treating type 2 diabetes. It decreases glucose production by the liver and increases the insulin sensitivity of body tissues.

Neutral Protamine Hagedorn (NPH or isophane) insulin
An intermediate-acting insulin preparation used in type 1 and type 2 diabetes. It is produced by crystallizing zinc-insulin-protamines at neutral pH. It is called neutral protamine Hagedorn for inventor Hans Christian Hagedorn.

Sodium-glucose co-transporters type 2 inhibitors (SGLT-2 inhibitors)
Oral hypoglycaemic agents used in treating type 2 diabetes. They lower blood glucose by causing the kidneys to remove glucose from the body through the urine.

Sulfonylureas
Oral hypoglycemic agents used in treating type 2 diabetes. They stimulate insulin secretion by the pancreas.

Thiazolidinediones (glitazones)
Oral hypoglycaemic agents used in treating type 2 diabetes. They work by lowering insulin resistance – a core physiologic defect in those with type 2 diabetes.

Type 1 diabetes
Diabetes caused by the destruction of pancreatic beta-cells, resulting in lack of insulin production by the pancreas and need for insulin injections for survival.

Type 2 diabetes
Diabetes characterized by various degrees of disorders of insulin action in the body and insulin secretion by the pancreas. Insulin injections are not needed for survival, but might be needed for controlling blood glucose levels.

Executive summary

Diabetes is a chronic, progressive disease characterized by elevated blood glucose levels. Diabetes can lead to complications such as cardiovascular disease, damage to eyes, kidneys and nerves, and premature death. Globally, more than 400 million adults live with diabetes, and diabetes directly caused 1.6 million deaths in 2015. Blood glucose management has an important role in preventing the development and progression of complications in both type 1 and type 2 diabetes.

The objective of the guidelines is to provide public health guidance on pharmacological agents for managing hyperglycaemia in type 1 and type 2 diabetes for use in primary health-care in low-resource settings. These guidelines update the *WHO Package of Essential NCD Interventions* (WHO PEN) for primary care in low-resources settings recommendations for managing hyperglycaemia, reviewing several newer oral agents: dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), sodium-glucose co-transporter 2 inhibitors (SGLT-2 inhibitors) and thiazolidinediones (TZDs). These agents have formerly been reviewed as first-line treatment options by the WHO Expert Committee on the Selection and Use of Essential Medicines and were not found to be superior to metformin and sulfonylurea. These guidelines consider their use as second- and third- line treatment for hyperglycaemia in type 2 diabetes. The guidelines also present new recommendations on the selection of type of insulin (analogue versus human insulin) for adults with type 1 diabetes and in adults with type 2 diabetes for whom insulin is indicated. WHO PEN recommendations on other aspects of diabetes treatment have not been updated because priority was given to the area where the majority of changes in evidence and practice have occurred since the publication of WHO PEN.

The guidelines were developed in accordance with the WHO Handbook for Guideline Development. In brief, the WHO Steering Group, in collaboration with the Guideline Development Group, developed key questions and rated outcomes to identify those critical for the guideline development. Systematic reviews of the evidence were used to build Summary of Findings tables according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology. The Guideline Development Group developed recommendations, considering the strength of the evidence; the balance between desirable and undesirable effects; resource requirements and cost-effectiveness; health equity; acceptability (including patient preferences); and feasibility.

Key recommendations of the guidelines are:

Hypoglycaemic agents for second and third-line treatment in type 2 diabetes
1. Give a sulfonylurea* to patients with type 2 diabetes who do not achieve glycaemic control** with metformin alone or who have contraindications to metformin (strong recommendation, moderate quality evidence). *Remarks* ** Glibenclamide should be avoided in patients aged 60 years and older. Sulfonylureas with a better safety record for hypoglycaemia (e.g. gliclazide) are preferred in patients for whom hypoglycaemia is a concern (people who are at risk of falls, people who have impaired awareness of hypoglycaemia, people who live alone, people who drive or operate machinery*

as part of their job).

*** The WHO PEN protocol recommends a target fasting blood glucose of <7 mmol/L (126 mg/dl). However, an individualized approach is encouraged in setting the patient's target level for glycaemic control, taking into account their comorbidities, risks from medication side-effects and their likely benefit from tight glycaemic control in view of life expectancy.*

2. Introduce human insulin treatment to patients with type 2 diabetes who do not achieve glycaemic control with metformin and/or sulfonylurea (strong recommendation, very low-quality evidence).

3. If insulin is unsuitable*, a DPP-4 inhibitor, SGLT-2 inhibitor or a TZD may be added (weak recommendation, very low-quality evidence).

Remark

** Insulin treatment could be unsuitable when circumstances make its use difficult (e.g. persons who live alone and are dependent on others to inject them with insulin).*

Insulin

4. Use human insulin to manage blood glucose in adults with type 1 diabetes, and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence**).

Remarks

** Recommendation 4 covers both short-acting (regular human insulin (RHI) and intermediate-acting human insulin (NPH insulin).*

***The recommendation is strong because evidence of better effectiveness of insulin analogues is lacking and human insulin has a better resource-use profile.*

5. Consider long-acting insulin analogues to manage blood glucose in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (weak recommendation,* moderate-quality evidence for severe hypoglycaemia).

Remark

**Recommendation 5 is a weak recommendation reflecting the lack of, or very low-quality evidence for, any of the long-term outcomes such as chronic diabetes complications and mortality, and the considerable higher costs for long-acting insulin analogues compared to intermediate-acting human insulin.*

1. Introduction

Diabetes mellitus (hereafter referred to as diabetes) is a chronic, progressive disease characterized by elevated blood glucose levels. Diabetes can lead to complications such as cardiovascular disease (CVD) and premature death, and can damage eyes, kidneys and nerves. Globally, more than 400 million adults live with diabetes – a disease that caused 1.6 million deaths in 2015 *(1, 2).* People with diabetes who have higher blood glucose levels are more likely to develop complications than those with lower blood glucose levels. Blood glucose management has an important role in preventing the development and progression of complications in both type 1 and type 2 diabetes.

In 2013 the World Health Organization (WHO) published the *WHO Package of Essential Non-Communicable Diseases Interventions* (WHO PEN) for primary care in low-resource settings. These guidelines are based on a public health approach, which means focusing primarily on the health needs of a population rather than managing individual cases. This approach ensures the widest possible access to services and medicines at population level; supports a simplified and standardized approach; and balances implementing the best-proven standard of care with what is feasible on a large-scale in resource-limited settings. With respect to managing diabetes, the main elements of a public health approach include: integrating services at the primary care level; task sharing; using simplified drug formularies; providing care and drugs free of charge; and introducing simple clinical monitoring.

The WHO–PEN recommendations for control of glycaemia in people with type 2 diabetes include diet, physical activity and metformin as first-line treatment; sulfonylurea as second-line treatment (or first-line treatment if metformin is contraindicated); and insulin as third line treatment. In the past decade new classes of oral hypoglycaemic agents have become available, including dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors); sodium-glucose co-transporter type 2 inhibitors (SGLT-2 inhibitors); and thiazolidinediones (TZDs). These agents work through different pathways to those of sulfonylureas and metformin. WHO Member States frequently seek guidance on the use of newly marketed oral hypoglycaemic agents, particularly because of their high price. Clinicians and policy-makers also frequently seek guidance on the place of insulin analogues which are intensively marketed by manufacturers. Indeed, some countries have documented expenditures on insulin analogues which surpassed the total budget for insulin, leading to shortages of insulin for part of the diabetic population that needed it *(3, 4)*. A study of 35 developing countries found that people with diabetes had a substantially higher risk of incurring catastrophic personal medical expenditures than their peers without diabetes *(5).* In guidelines of high-income countries the newer oral medicines and insulin analogues are deemed equally suitable and interchangeable with sulfonylurea and human insulin for treatment intensification *(6, 7)*. For poorer health systems or where the majority of the population pays out of pocket, price is a more important consideration when available evidence shows similar effectiveness.

1.1 Scope and aim of guidelines

These guidelines aim to provide public health guidance on pharmacological agents for managing glycaemia in type 1 and type 2 diabetes for use in primary health-care in low-resource settings. The recommendations target the general adult, non-pregnant diabetes population.

These guidelines update WHO PEN recommendations on the choice of second- and third-line treatment for type 2 diabetes based on a review of the evidence regarding the three new oral hypoglycaemic agents: dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors); sodium-glucose co-transporter type 2 inhibitors (SGLT-2 inhibitors); thiazolidinediones (TZDs); and insulin analogues. The new oral medicines have not been shown to lower glycaemia more effectively than metformin and sulfonylurea as first-line treatment and have thus not been included in the WHO Model List of Essential Medicines when reviewed by the WHO Expert Committee on the Selection and Use of Essential Medicines, nor are they recommended as first-line treatment options in evidence-based guidelines of high-income countries *(8, 9, 10*). However, they might be suitable to intensify treatment in cases where metformin and/or sulfonylurea treatment fail to control glycaemia. Before the development of newer oral agents, treatment options for these patients were limited to insulin.

These guidelines also present new recommendations on selecting the type of insulin (human insulin versus insulin analogues) as insulin is used in primary health care in some low- and middle-income countries. The long-acting insulin analogues considered are detemir and glargine, and the short-acting insulins aspart, lispro and glulisine. These guidelines do not consider the newer 100U and 200U insulin degludec nor 300U insulin glargine because of lack of direct comparisons with NPH insulin.

The guidelines provide the basis for selecting medicines for blood glucose control in countries' own national guidelines for diabetes management. They are not an update of all WHO PEN recommendations for management of diabetes. The scope has been limited to agents for glycaemic control because that field is a dynamic one and has seen more change in evidence and practice in recent years than have other aspects of diabetes management (for example, blood pressure and blood lipids control, or screening for and management of complications).

The objectives of these guidelines are:

- To consider the use of DPP-4 inhibitors, SGLT-2 inhibitors, and TZDs as second- and third-line treatment after metformin and sulfonylurea for controlling hyperglycaemia in type 2 diabetes in non-pregnant adults, including whether these oral agents are preferable to insulin.
- To provide guidance regarding the use of insulin analogues for type 1 and type 2 diabetes.

Evidence-based protocols for managing diabetes in primary health care, including managing CVD risk and screening for complications, are available in the WHO PEN 2013 and are not repeated in this guideline.

1.2 Target audience

This guideline targets policy-makers, national diabetes programme managers, procurement officers , clinicians and health care professionals responsible for developing local protocols for treating diabetes that will be used in primary care units in low-resource settings. The recommendations in the guideline would be also relevant for decisions at secondary and tertiary health care levels, and where national recommendations and protocols do not exist. Other potential users include institutions for education of health care workers, as well as nongovernmental organizations (NGOs) and relief agencies, to guide resource allocation.

2. Methods for developing the guidelines

2.1 Guideline contributors

WHO established three groups to develop these guidelines:

1. An internal WHO Guideline Steering Group to coordinate the guideline development process.
2. A Guidelines Development Group (hereafter referred to as the Guideline Group) composed of diabetes physicians and endocrinologists, researchers and academics, programme managers and representatives of patients' groups to review the evidence and develop recommendations. WHO selected members of the Guideline Group based on relevant expertise but also considered appropriate representation by region and sex.
3. An External Peer Review Group composed of technical experts, representatives of diabetes patient groups, and ministries of health from low-resource countries to provide peer review of the guidelines.

Appendix 1 lists the contributors in each group. Appendix 2 describes the process for declaring and managing conflicts of interest.

2.2 Outcome rating

Members of the WHO Steering Group, in consultation with the Guideline Group, developed two initial lists of treatment outcomes for type 1 and type 2 diabetes. The Guideline Group then indicated whether it considered each outcome critical (rated 7–9), important (rated 4–6) or not important (rated 1–3) for formulating the recommendations. The average of the scores was then used to identify the outcomes critical to decision-making (Appendix 3).

2.3 Reviews of evidence

The WHO Steering Group, with the participation of the Guideline Group, determined the scope of the guidelines and identified three questions in population, intervention, comparison, and outcomes (PICO) format to guide the systematic reviews (Appendix 3). A systematic search was carried out in PubMed to identify existing systematic reviews answering the PICO questions. Suitable systematic reviews were then evaluated using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool and if they were recent and of good quality they were used to inform the guidelines (Appendix 4).

Four systematic reviews informed the guideline development process *(6, 11, 12, 13*). In addition, preliminary results of a Cochrane Systematic Review update were presented at the Guideline Group meeting. Primary studies were searched for potential updating of the Tricco et al review *(11)* of long-acting analogues. Only two relevant trials in adults were identified. The review was not updated with these new studies because it already had sufficient power to detect a clinically significant difference in short-term outcomes (moderate quality evidence) and the new study results were consistent with the review meta-analysis results. The new studies provided no additional evidence on the long-term critical outcomes, as they were not designed for that purpose. The other systematic reviews were considered to be acceptably recent.

Three the systematic reviews *(6, 11, 12)* used network meta-analysis. This method allows comparison of the relative effectiveness of treatments even if no studies compare them directly *(14)* and can also improve the precision of the direct estimates *(15)*. However, severe imbalance in terms of the amount of evidence for each intervention may affect the power and reliability of the overall analysis. Network meta-analysis requires the same assumptions as pairwise methods (similarity of studies in terms of effect modifiers; no relevant heterogeneity between trial results) and an additional assumption that there must not be any relevant discrepancy and inconsistency between direct and indirect evidence *(16).* Because the method is more complex than pairwise meta-analysis, the interpretation of results and evaluation of whether assumptions have been met is more difficult. Although the use of network meta-analysis for WHO guideline development is recent, the method is well established within national health technology assessment agencies. The method has also recently been adopted by Cochrane and it is gaining importance for the optimal evaluation of competing interventions *(17).*

The health economist provided supporting evidence with two narrative reviews of publications on cost-effectiveness of the newer medications as intensification treatment (Appendix 7). Two narrative reviews of publications on patient preferences also informed the decision making (Appendix 8). One review examined whether patients with type 1 diabetes preferred insulin analogues to human insulin. The other review examined whether patients preferred oral agents to insulin when intensification of treatment was necessary for controlling blood glucose levels. This review also examined which treatment attributes were valued by patients.

2.4 Quality of evidence and strength of recommendations

The Guideline Group examined the quality of evidence and formulated the recommendations using the GRADE methodology *(18)*. In the GRADE process, the quality of a body of evidence is defined as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence are close to the actual effects of interest. The strength of the recommendations reflects the degree of confidence of the Guideline Group that the desirable effects (e.g. beneficial health outcomes) of the recommendations outweigh the undesirable effects (e.g. adverse effects). Systematic review authors or members of the Steering Group with the help of the methodologist developed Summary of findings tables. For standard meta-analyses, the quality of the evidence was captured in Summary of findings tables. For network meta-analysis, the evidence was summarized in treatment matrices that allow comparison of all evaluated treatments *(19)*. With

the help of the methodologist, the quality of the evidence derived from network meta-analysis was evaluated using approaches described in two existing papers *(20, 21)*.

The following levels of assessment of the evidence were used in the GRADE profiles:

Evidence level	Rationale
High ⊕⊕⊕⊕	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate ⊕⊕⊕O	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low ⊕⊕OO	Further research is very likely to have an impact on the estimate of effect and is likely to change the estimate.
Very low ⊕OOO	Any estimate of effect is very uncertain.

The recommendations in these guidelines were graded into two categories:

- **A strong recommendation** is one for which the Guideline Group was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects.

- **A weak** or **conditional recommendation** is one for which the Guideline Group concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects, but the Guideline Group was not confident about these trade-offs.

2.5 Deciding upon recommendations

The Guideline Group met in Geneva in March 2017. Systematic reviews and GRADE tables were presented at the meeting. Formulation of recommendations and their relative strength were facilitated by the chair and supported by the methodologist, with the aim of achieving unanimous consensus. Full consensus was reached on all recommendations. Had there been disagreement, the planned procedure was for the Guideline Group to vote and accept the recommendation on a simple majority vote, with reporting of any objections. The Guideline Group used evidence-to-decision tables to guide it through the process of developing recommendations and to consider the quality of evidence, the balance between desirable and undesirable effects, values, resource use and cost-effectiveness, equity, acceptability and feasibility. The considerations are addressed in the body of the text of the document while Summary of judgments tables are included in the different Appendices following the Summary of findings tables. The WHO Steering Group noted remarks made by members of the Expert Peer Review Group and considered incorporating these into the final guidelines. One reviewer perceived the evidence on risk-benefit for newer medication to be insufficient and the price too high to mention them in any recommendation. Another reviewer was in favour of including DPP-4 inhibitors and TZDs along with human insulin for type 2 patients, in anticipation of patient expiry and the possibility of cheaper generic versions becoming available. The Guideline Group's opinion was that there was considerable uncertainty over whether and when significantly cheaper versions would become widely available.

2.6 Funding

The development of these guidelines was financially supported by the US Centers for Disease Control and Prevention and the World Health Organization.

3. Recommendations

The Guideline Group developed recommendations for oral hypoglycaemic agents for second- and third-line treatment in type 2 diabetes, for insulin in patients with type 2 diabetes for whom insulin is indicated, and for insulin for treating patients with type 1 diabetes.

3.1 Hypoglycaemic agents for second-line treatment in type 2 diabetes

1. Give a sulfonylurea to patients with type 2 diabetes who do not achieve glycaemic control with metformin alone or who have contraindications to metformin (strong recommendation, moderate quality evidence).

Remarks

Glibenclamide should be avoided in patients aged 60 years and older. Sulfonylureas with a better safety record for hypoglycaemia (e.g. gliclazide) are preferred in patients for whom hypoglycaemia is a concern (people who are at risk of falls, people who have impaired awareness of hypoglycaemia, people who live alone, people who drive or operate machinery as part of their job).

The WHO PEN protocol recommends a target fasting blood glucose of <7 mmol/L (126 mg/dl). However, an individualized approach is encouraged in setting the patient's target level for glycaemic control, taking into account their comorbidities, risks from medication side-effects and their likely benefit from tight glycaemic control in view of life expectancy.

3.1.1 Summary of the evidence

The evidence summary for second-line treatment intensification (adding medicines to metformin) was obtained from the systematic review and network meta-analysis carried out by the Methods and Applications Group for Indirect Treatment Comparisons (MAGIC) for the Canadian Agency for Drugs and Technologies in Health (CADTH) *(6)*. The systematic review included 166 Randomized Controlled Trials (RCTs) that reported at least one of the outcomes of interest. The network meta-analysis included sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, TZDs and basal insulins, as well as bolus insulins, biphasic insulins, meglitinides, alpha-glucosidase inhibitors, and glucagon-like peptide-1 (GLP-1) agonists (which were not of interest to the guidelines).

All evaluated hypoglycaemic agents added to metformin performed similarly in lowering HbA1c compared to placebo. DPP-4 inhibitors performed less well compared to sulfonylurea (mean difference 0.12%, 95% CI: 0.01, 0.24) and TZD (mean difference 0.19%, 95% CI: 0.05, 0.33). There was lower risk of severe hypoglycaemia with DPP-4 inhibitors (OR 0.14, 95% CI: 0.07, 0.26) and SGLT-2 inhibitors (OR 0.09, 95% CI: 0.02, 0.44) compared to sulfonylurea. DPP-4 inhibitors and SGLT-2 inhibitors were associated with weight loss, while TZDs and basal insulin were associated with

weight gain. Evidence on quality of life and microvascular complications was not available. There were no significant differences for CVD incidence (myocardial infarction (MI) or stroke) or CVD mortality, but the network meta-analysis (NMA) model was not robust (very few events and a large number of trials with no events). In a separate analysis of patients at high risk of CVD, there was no significant difference in CVD mortality. Treatment matrices including the comparisons of all treatments with each other, and GRADE quality assessment, are reported in Appendix 5.

3.1.2 Rationale for the recommendation

Balance between desirable and undesirable effects

While sulfonylureas showed a similar effect in lowering HbA1c compared to newer medicines, they also showed a higher odds of severe hypoglycaemia compared to DPP-4 inhibitors and SGLT-2 inhibitors. The Guideline Group noted the absence of estimates of absolute risk for severe hypoglycaemia in these trial reports but recognized that observational studies have shown that the risk of hypoglycaemia of varying severity in patients without renal impairment treated with sulfonylureas to be in the range from 0.2 to 1.8 events per 100 person-years *(22, 23)*, which the Guideline Group considered not to be very high. The Guideline Group also recognized that there was large heterogeneity between the studies in how severe hypoglycaemia was defined.

The Guideline Group acknowledged that SGLT-2 inhibitors look particularly promising, particularly for survival, but acknowledged this evidence derived from placebo-controlled studies. SGLT-2 inhibitors led to the greatest weight loss of all classes of medicines included in the NMA. Furthermore, empagliflozin, when compared to placebo, had a protective effect on a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in one study in people at high CVD risk *(24)*. More evidence is needed to determine whether this is a class effect and whether there is a cardioprotective effect in the general population of people with type 2 diabetes. Because SGLT-2 inhibitors are a relatively new class of drugs, more safety data is likely to emerge from ongoing trials and from their use outside trial populations. The Guideline Group also noted the lack of RCTs on how each new drug class compares with all the others (particularly new agents vs. old ones) and concluded that the evidence reviewed did not convincingly show the superiority or inferiority of any one class.

Resource requirements

The Guideline Group remarked that no substantial differences in health care staff capacity or mode of delivery are to be expected between the different oral hypoglycaemic agents. Differences in price between the oral agents are the main reason for difference in resources required, in addition to the resources required to address the drug side effects (which differ between the various agents). The use of insulin requires additional resources such as needles, blood-glucose self-monitoring and management at a higher level of care.

Medicine prices were compared for a number of countries, selected on the basis of online public availability of official information on medicines prices (see Appendix 6). Sulfonylureas are invariably sold at substantially lower prices than DPP-4 inhibitors, SGLT-2 inhibitors and TZD. Reliable data on the prices of these medicines in low-income countries are not available, but it is unlikely that the new medicines have a more favourable price ratio to sulfonylurea in low- and middle-income countries than in high-income countries. Resources were unavailable for a multi-country study.

However, abundant anecdotal evidence supports the claim that these newer medicines are globally substantially higher priced than metformin and sulfonylurea.

The Guideline Group recognized that some patents for DPP-4 inhibitors will soon expire and cheaper generics could appear on the market soon *(25)* because this has consistently happened with hypoglycaemic agents in the past. However, the Guideline Group concluded that the new oral hypoglycaemic agents are currently substantially more expensive compared to sulfonylureas, and that the modest clinical benefit (fewer events of severe hypoglycaemia and weight loss with DPP-4 inhibitors and SGLT-2 inhibitors) does not sufficiently outweigh the current price difference in the context of a public health approach.

The health economist presented findings of a narrative literature review of cost-effectiveness studies of second-line treatment for type 2 diabetes (Appendix 7). The Guideline Group noted that the cost-effectiveness studies were not easily comparable because there was large heterogeneity between the different studies, e.g. in choice of model (e.g. Center for Outcomes Research (CORE) Diabetes Model, DiDACT, UKPDS); comprehensiveness of model; inclusion of indirect costs and level of cost detail related to diabetes complications; perspective (e.g. public health payer, single private hospital, etc); clinical practice and treatment regimens examined (e.g. treatment dosages, timing of treatment relative to meals); country-specific prices; and difference in country-specific utility tariffs. The Guideline Group further noted that all cost-effectiveness studies were carried out in high-income countries. Because cost-effectiveness studies are setting-specific, with cost-effectiveness thresholds higher in high-income than in middle- and low-income countries, it was difficult for the Guideline Group to translate these findings to low-resource settings. The Guideline Group also noted that that industry-funded cost-effectiveness studies tended to report that new treatments were cost-effective *(26–31)*, while the only independent study favoured sulfonylurea *(32).*

Health equity

The Guideline Group noted that in 2013 the 18th WHO Expert Committee on the Selection and Use of Essential Medicines replaced glibenclamide in the core list with gliclazide, and added that glibenclamide should not be used in patients aged 60 years and older because of concerns about hypoglycaemia in this group (9). The Guideline Group agreed with this assessment and adopted this into the recommendation.

Because sulfonylurea is currently more affordable than new oral hypoglycaemic agents (OHAs) for people who pay out of pocket, it is likely to be more accessible, thus contributing to greater equity.

Acceptability (patient preferences)

A literature review (Appendix 8) found the treatment characteristics patients valued most when choosing between treatment regimens were avoidance of side-effects, particularly hypoglycaemia. While the newer agents generally had a neutral or slightly better profile for hypoglycaemia compared to sulfonylurea as measured by relative risk, there was insufficient evidence about the magnitude of the absolute risk. The Guideline Group therefore concluded that the putative benefit of newer agents did not justify the large difference in price.

Feasibility

Sulfonylurea was recommended as second-line treatment in WHO PEN 2013 and has been shown to be acceptable and feasible *(1)*. Sulfonylureas have been in use for 60 years and remain in use globally.

3.2 Hypoglycaemic agents for third-line treatment in type 2 diabetes

2. Introduce human insulin treatment to patients with type 2 diabetes who do not achieve glycaemic control with metformin and/or sulfonylurea (strong recommendation, very low-quality evidence).

3. If insulin is unsuitable, a DPP-4 inhibitor, SGLT-2 inhibitor or a TZD may be added (weak recommendation, very low-quality evidence).

Remark

Insulin treatment could be unsuitable when circumstances make its use difficult (e.g. persons who live alone and are dependent on others to inject them with insulin).

3.2.1 Summary of evidence

The evidence summary for third line treatment (medicines added to metformin and sulfonylurea) was obtained from a systematic review and network meta-analysis that was published in 2016 *(12).* Five trials evaluated triple therapy. The network meta-analysis included DPP-4 inhibitors, SGLT-2 inhibitors, TZDs, basal insulin (medicines of interest to this guideline) as well as meglitinides, alpha-glucosidase inhibitors, GLP-1 agonists, and basal-bolus insulin (medicines not of interest for these guidelines).

All drug classes lowered HbA1c to a similar extent. TZDs (mean difference: -0.86%, 95% CI: -0.25, -1.48) and basal insulin (mean difference: -0.86%, 95% CI: -0.18, -1.55) were the only two medicines that performed significantly better than placebo in lowering HbA1c. DPP-4 inhibitors (mean difference: -0.23kg, 95% CI: -0.46, 0.00) and SGLT-2 inhibitors (mean difference: -0.33kg, 95% CI: -0.59, -0.07) were associated with a lower body weight compared to TZDs. There were very few events of CVD mortality and no significant differences between treatments. Insufficient observations were available to generate evidence networks for CVD incidence. There were no data for the critical outcomes severe hypoglycaemia and quality of life. Treatment matrices, including the comparisons of all treatments with each other and GRADE quality assessment, are reported in Appendix 9.

3.2.2 Rationale for the recommendation

Balance between desirable and undesirable effects

The Guideline Group considered insulin to be comparable to DPP-4 inhibitors, SGLT 2-inhibitors or TZDs when weighing desirable and undesirable effects. Insulin and TZDs performed best for lowering HbA1c while DPP-4 inhibitors and SGLT-2 inhibitors performed better than TZDs in lowering body weight. Basal insulin did not lead to statistically significant increase in body weight compared to the

oral drugs when added to metformin and sulfonylurea. All drug classes were associated with an increased risk of hypoglycaemia compared to placebo, but there were no statistically significant differences between the drug classes.

The long-term benefits and harms of triple therapy with three oral agents are unclear. The Guideline Group discussed the clinical trial observation that type 2 diabetes is a progressive disease with increasing beta cell dysfunction and that many patients will eventually require insulin *(33, 34)*.

Resource requirements

Human insulin is available at lower prices than the three newer, oral medicines in most countries listed in Appendix 6. However, the Guideline Group recognized that insulin treatment has further associated resource implications such as needles and blood glucose self-monitoring. Furthermore, in low-resource settings, introducing insulin and follow-up is typically done by medically qualified health care staff at higher levels of care. How much this additional need for resources when using insulin affects the cost difference between insulin and newer oral agents has not been estimated, but they certainly reduce the advantage due to the lower cost of insulin.

Health equity

Because human insulin is currently more affordable than new OHAs for people who pay out of pocket, it is likely to be more accessible to people, thus contributing to greater equity. On the other hand, in low-resource settings, people on insulin are usually managed at higher levels of care which are often more difficult to access than primary care facilities. How these differences impact outcomes is unclear.

Acceptability (patient preferences)

A literature review of treatment preferences of patients with type 2 diabetes (Appendix 8) identified three RCTs comparing treatment intensification with oral agents to treatment intensification with insulin *(35, 36, 37, 38)*. Two of the three studies found a greater treatment satisfaction with the addition of insulin compared to the addition of an oral agent, while one study found high levels of satisfaction in both groups. The Guideline Group had some reservations about the results of the RCTs because of potential bias (all three RCTs were sponsored by insulin manufacturers).

The literature review also identified three discrete choice experiments describing preferences and treatment attributes that contribute to treatment satisfaction *(39, 40 41)*. The treatment characteristics that patients valued most when choosing between treatment regimens were route of administration, avoiding or reducing the number of injections, side effects, avoidance of nausea, glycaemic control, avoiding hypoglycaemia, avoiding weight gain, reducing CVD risk, and reducing frequency of blood glucose monitoring. The Guideline Group interpreted these preferred treatment characteristics to indicate that most patients prefer oral agents to insulin if glycaemic control were comparable. However, patient preference for newer oral agents was not deemed a sufficiently strong reason to recommend them in the context of a public health approach because the price of newer oral medicines is currently higher than that of human insulin.

Feasibility

Metformin for first-line treatment, sulfonylurea for second-line treatment, and insulin for third-line treatment was recommended in WHO PEN 2013. It has been shown that it can be implemented in primary health care with referrals to higher levels of health care for insulin introduction and periodic

specialist assessment. The Guideline Group emphasized that patients should receive support for insulin initiation and they point out that the use of insulin requires more monitoring and more patient visits. Nonetheless, this is a simple approach, using well-known medicines that are widely available and are currently more affordable than new treatments of similar effectiveness.

3.3 Insulin

4. Use human insulin to control blood glucose levels in adults with type 1 diabetes, and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence).

Remarks

Recommendation 4 covers both short-acting (regular human insulin – RHI) and intermediate-acting human insulin (NPH insulin). The recommendation is strong because evidence of better effectiveness of insulin analogues is lacking and human insulin has a better resource-use profile.

5. Consider long-acting insulin analogues to control blood glucose levels in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (weak recommendation, moderate-quality evidence for severe hypoglycaemia).

Remarks

Recommendation 5 is a weak recommendation reflecting the lack of, or very low-quality, evidence for any of the long-term outcomes such as chronic diabetes complications and mortality, and the considerable higher costs for long-acting insulin analogues compared to intermediate-acting human insulin.

3.3.1 Summary of the evidence

Two recent, high-quality systematic reviews and preliminary results from a Cochrane Review update were used to answer the questions. The first systematic review compared long-acting insulin analogues to intermediate-acting human insulin for type 1 diabetes *(11)* and the second systematic review compared a short-acting insulin analogue to a short-acting human insulin for type 1 diabetes *(13)*. The third systematic review evaluated long-acting insulin analogues versus NPH insulin for type 2 diabetes *(42).*

Long-acting insulin analogues in type 1 diabetes

The population in the review consisted of non-pregnant adults with type 1 diabetes. The systematic review included a network meta-analysis comparing different treatment regimens (e.g. insulin detemir, insulin glargine, NPH) and in different administration frequencies (e.g. once daily, twice daily, four times daily) (11). For the purpose of the guideline development, NPH administered twice daily was considered to be usual care (that is, the reference standard). Glargine once a day and detemir once or twice a day were the relevant interventions. Because direct pair-wise meta-analyses

were available for the comparisons of interest, and there was consistency between direct and combined-direct and indirect estimates, direct results were used.

Neither detemir once or twice daily (mean difference -0.04, 95% CI: -0.12, 0.03) nor glargine once daily (mean difference -0.08, 95% CI: -0.19, 0.02) significantly reduced HbA1c compared to NPH once or twice daily. Detemir once or twice daily was superior to NPH once or twice daily for reducing the number of severe hypoglycaemia incidents (OR 0.68, 95% CI: 0.52, 0.89). Although glargine appeared to reduce the risk of severe hypoglycaemia compared to NPH, the difference was not statistically significant. There was no significant difference between analogues and NPH in all-cause mortality, with one death reported in the treatment and control arms. Two studies reported on CVD mortality, with both reporting one CVD death in the control group; in neither study was there a significant difference between the two groups. There were no data for the other critical outcomes – progression of nephropathy, end-stage renal disease, lower-limb amputation or ketoacidosis. The only RCT reporting on quality of life did not find a difference between glargine once daily and NPH twice daily. GRADE Summary of findings tables are reported in Appendix 10.

Short-acting insulin analogues in type 1 diabetes

The systematic review included nine trials and 2693 participants (13). The population consisted of non-pregnant adults with type 1 diabetes. Short-acting insulin analogues significantly reduced HbA1c compared to short-acting human insulin (mean difference -0.15%, 95% CI: -0.20, -0.10). Mortality was not a primary outcome in any of the included trials, but in six trials that reported deaths as adverse events there was one death in the treatment arm. There was no significant reduction in severe hypoglycaemic episodes when using short-acting insulin analogues compared to RHI (OR 0.89, 95% CI: 0.71% , 1.12%). Health-related quality of life was assessed in subpopulations of three trials but no details were reported. Overall, there was no clear evidence for a substantial effect of short-acting insulin analogues on this outcome. Outcomes were not reported for critical outcomes of CVD mortality, progression of nephropathy, visual impairment, end-stage renal disease, lower limb amputation or ketoacidosis. The GRADE Summary of findings table is reported in Appendix 11.

Long-acting analogues in type 2 diabetes

Preliminary results of an update of the Cochrane Reviews on long-acting insulin analogues versus NPH insulin for type 2 diabetes (42) were presented to the Guideline Group. The preliminary results of the meta-analyses showed no significant difference in HbA1c between NPH insulin and glargine (mean difference 0%, 95%CI: -0.09, 0.08) or detemir (mean difference 0.18%, 95%CI: -0.01, 0.38). The evidence on HbA1c difference was of very low (glargine) and low quality (detemir). There were fewer severe hypoglycaemic events with glargine (OR 0.65, 95%CI: 0.49, 0.88) or detemir (OR 0.37, 95%CI: 0.16, 0.92)compared to NPH (moderate quality evidence); and lower body weight (mean difference: -1.26kg, 95%CI: -1.78, - 0.73) with detemir compared to NPH (high quality evidence). The findings were interpreted with caution because analyses had not been completed (e.g. potential impact of various therapeutic schemes, context-specific interpretations missing, sensitivity or subgroup analyses not yet done, high heterogeneity of study results not yet explored, predictive intervals not yet calculated). A review of the evidence on short-acting insulins for type 2 diabetes was not considered to be a priority.

3.3.2 Rationale for the recommendations

Balance between desirable and undesirable effects

Human insulin and insulin analogues are equally effective at lowering blood glucose levels. Although short-acting insulin analogues statistically significantly reduced HbA1c compared to short-acting human insulin, the Guideline Group did not consider this to be a clinically meaningful reduction according to criteria widely used in clinical guidelines and recommendations of medicines licensing bodies (10, 43). Long-acting insulin analogues are associated with a moderate reduction in risk of severe hypoglycaemia and small reduction in body weight compared with NPH insulin. The Guideline Group noted the absence of data on nocturnal hypoglycaemia and the lack of evidence on long-term critical outcomes such as complications and mortality.

Resource requirements

Resource requirements were a leading concern for the Guideline Group. Long-acting insulin analogues have marginal benefits in preventing severe hypoglycaemia but both long-acting insulin analogues and short-acting insulin analogues are considerably more expensive than human insulins. The Guideline Group considered the resources needed for the different methods for insulin delivery, concluding that both human insulin and insulin analogues are packaged in vials for use with needles and syringes, in cartridges for use with pen-injectors and pre-filled pen-injectors. Cold chain requirements and patient monitoring of blood glucose are also the same for both types of insulin and would not lead to different resource requirements. Thus, the price is the main difference between human insulin and insulin analogues when it comes to resource requirements.
Buying human insulin instead of insulin analogues would have significant impact on country budgets in settings where governments aim to achieve universal health coverage *(4, 44).* In the absence of universal health coverage, insulin analogues are far more expensive for patients paying out-of-pocket *(4, 44).* Considering that patients with type 1 diabetes cannot survive without insulin, ensuring access to affordable insulin for all patients with type 1 diabetes is a priority.

The Guideline Group noted that most cost-effectiveness studies showed that insulin analogues were cost-effective compared to human insulin, but all these studies were funded by the manufacturers of these insulins (Appendix 6). Independent cost-effectiveness studies generally showed that human insulin was more cost-effective. Taking into account that cost-effectiveness is context-specific and that there was only one study from a middle-income country *(45)* and no studies from low-income countries, the Guideline Group put more weight on the affordability findings of the Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS) study. Thus, considering the consistently and substantially higher prices for insulin analogues and the potential negative consequences for access, the Guideline Group strongly preferred human insulin.

Health equity

The guidelines are based on a public health approach. By addressing the health needs of a population, the recommendations are aimed at ensuring the widest possible access to services and medicines at population level. The Guideline Group reiterated that such an approach is most likely to optimize equity with respect to access to affordable medicines (46).

Acceptability (patient preferences)

The findings of a narrative review of preferences related to type of insulin for treatment of type 1 diabetes were presented to the Guideline Group (Appendix 7). Four studies comparing long-acting analogue and intermediate-acting human insulin found significantly higher satisfaction with analogue insulin. Of eight studies comparing short-acting analogue insulin and short-acting human insulin, two studies, including the single study that was blinded, found no difference in satisfaction scores between groups, while six studies found significantly higher satisfaction scores with short-acting analogue insulin. Of the studies comparing biphasic insulin or basal-bolus regimens, one study found patients preferred the analogue insulin and one study found no difference between groups. The following treatment characteristics were reported to influence treatment satisfaction: treatment or dietary flexibility, convenience, reducing perceived hyperglycaemia or hypoglycaemia, improving stability of blood glucose levels, and reducing fatigue. The Guideline Group recognized that almost all included studies were at high risk of bias, and in the single blinded study patients could not distinguish which type of insulin they were receiving. It was therefore difficult to take into account patient preferences and acceptability of different types of insulin.

Feasibility

The Guideline Group expressed some concern about the transferability of findings from clinical trial settings in predominantly high-income countries to routine health care practice in middle- and low income settings, especially considering the rapidly increasing prevalence of diabetes in these settings. The Guideline Group concluded by basing its recommendations on the available evidence and addressed their concerns in the section on research gaps later in the guideline document.

4. Research gaps

During the review of evidence and the development of recommendations, several research gaps were identified. Addressing these will help inform revision of these guidelines.

Operational research studies evaluating the effectiveness of treatment under routine conditions in health care practice in low-income countries, as opposed to the highly controlled environment of trials, are required. In addition there should be studies exploring barriers to access to care and studies evaluating context-specific interventions to enhance patient adherence.

4.1. Oral hypoglycaemic agents

Trials of new oral hypoglycemic agents should include metformin and sulfonylurea as comparators, rather than placebo only. This is most important for long-term, hard outcomes for which there are very little data in samples that representative of the general diabetic population.

There are questions remaining regarding treatment options and combination of medicines for type 2 diabetes, including whether adding a third oral agent postpones the need for introducing insulin and if so, by how long; and role for combining new oral agents with insulin.

For newer medicines there is the need for continuous surveillance of side effects.

4.2 Insulin

Epidemiological research into the burden of diabetes (particularly type 1 diabetes) in low-income countries is needed. Estimates of the number of children and adults with type 1 diabetes in many countries are likely inaccurate, leading to difficulties in procurement because of uncertainties about the number of people who are in need of insulin.

5. Publication, implementation and evaluation

5.1 Publication

The guideline will be available to download from the WHO website. Systematic reviews and evidence used for the development of the guideline are published in peer-reviewed journals or available online.

5.2 Implementation and dissemination

WHO regional and country offices, through their contacts with ministries of health, will encourage implementation at country level. WHO will provide technical assistance if substantial country adaptation is needed.

The updated recommendations will be part of the technical package of the recently launched WHO Global Hearts Initiative, built on the WHO PEN – an initiative to improve prevention of CVD in primary health care.

5.3 Evaluation

WHO will monitor uptake and implementation of the guidelines in national policies and programmes by reviewing the number of countries that have adapted or endorsed the guidelines nationally.

The Global HEARTS technical package that is currently being developed will include clinical and process indicators for diabetes. Indicators will use routinely collected data on service delivery using client screening forms, registers and monthly summary forms. The toolkit will be piloted in Barbados, Colombia, Ethiopia, Nepal, the Philippines, Tajikistan and Uganda.

5.4 Future updating of the guideline

The guidelines are expected to be valid for a period of 5 years. This period reflects the fact that new research findings are likely to become available in the meantime but also represents a feasible time frame considering the costs, time and other resources that are needed to update such guidelines. If the evidence base or user needs change before the 5-year mark, consideration will be given to producing updates sooner. Of particular relevance for an update would be clinical trials that compare sulfonylurea and metformin with newer agents in their effect on the incidence of CVD, mortality, and hard outcomes of kidney and eye complications. Such trials require more time than those for surrogate outcomes such as glycaemic control and – particularly those that are independent from industry funding – are rare. The existing body of evidence on glycaemic control and hypoglycaemia is relatively robust and unlikely to change by adding new trial data.

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Appendix 1. Acknowledgements

The World Health Organization (WHO) would like to thank the members of the Guideline Group, the scientists that provided systematic reviews and the external peer reviewers for their contributions to the development of these recommendations. Professor Edwin Gale chaired the meeting.

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Overall coordination and writing of the guideline

The guideline process was coordinated by the Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention. The first draft was written by Saskia Den Boon. Drafts were reviewed by the Guideline Development Group and external peer reviewers, and subsequently revised by Gojka Roglic and Saskia Den Boon.

[1] MAGIC: Methods and Applications Group for Indirect Treatment Comparisons, Ottawa, Canada. Sponsored by the Canadian Institutes for Health Research, Drug Safety and Effectiveness Program (CIHR-DSEN).

Appendix 2. Managing declarations of interest and conflicts of interest

Members of the Guideline Group, the external review group and the systematic review teams completed the WHO Declaration of Interest (DOI) form. Members of the WHO steering group, supported by the Office of Compliance, Risk Management and Ethics (CRE), assessed the declarations of interest to determine the presence of a conflict of interest (COI) which warranted partial or total exclusion of participation in the guideline development process. Declared interests were shared with all participants at the meeting of the Guideline Group so that the group was aware of any existing interests among the members.

In accordance with WHO DOI policy for experts, a brief biography of all members of the Guideline Group was posted on the WHO website for a period of 15 days with a description of the objective of the Guideline Group's meeting. No public comments or objections were received concerning the group's membership. The WHO Secretariat reviewed the curriculum vitae of each potential participant and conducted Internet searches (PubMed, Open Payments Data, Google Scholar) for information on potential financial and academic conflicts of interest related to the subject of the meeting. All declarations of interest are on file at the WHO Department for Management of Noncommunicable Diseases, Disability, Violence and Injury Prevention.

These members of the Guideline Group declared an interest related to diabetes:

Edwin Gale declared having given a talk entitled "Diabetes in a changing world" at the Steno symposium in Denmark in May 2015. The meeting was sponsored by Novo-Nordisk and Edwin Gale received a speaker's fee.

Molly Lepeska is employed by Health Action International on a study that researches barriers to affordable insulin. She is co-founder of the 100 Campaign that advocates for affordable global access to insulin.

Naomi Levitt's unit received 150 000 ZAR (approximately US$ 11,600) in 2014 and 2015 from Roche Diagnostics and Lilly Laboratories as a partial payment of a salary for a diabetes patient educator.

Pamela Donggo gave a lecture on diabetes management in 2013 as part of the Buddy Doctor Initiative of Novo Nordisk. She did not receive remuneration for the lecture, but received USD 2000 for subsequent mentoring of a group of health care workers. In 2014 her attendance at the Second African Diabetes Congress was sponsored by Sanofi Africa.

Tint Swe Latt's institution received a grant of €137 000 from the World Diabetes Foundation to conduct a study of diabetes prevalence in Myanmar. In 2015 and 2016 his attendance at three diabetes conferences was sponsored by Getz Pharma, Denk Pharma and Pfizer.

The other members or the Guideline Group and the Peer Review Group did not declare any interest. The completed DOI forms were reviewed by the WHO Guideline Steering Group. None of the declared interests was judged sufficient enough to affect the expert's objective judgment on the guideline development process or recommendations, or therefore to preclude their full participation in the guideline development.

Appendix 3: PICO questions and ranked outcomes

1. How do outcomes in people with type 2 diabetes treated with DPP-4 inhibitors, SGLT-2 inhibitors, or glitazones added to metformin, sulfonylurea, or metformin + sulfonylurea compare to those of people treated with metformin, sulfonylurea, or metformin + sulfonylurea only?

P	People with type 2 diabetes for whom first-line treatment with metformin and/or sulfonylurea has failed to achieve the set target of glycaemic control (measured by HbA1c values). • Diagnosed with type 2 diabetes according to WHO criteria (fasting plasma glucose ≥ 7.0 mmol/L or 2-h plasma glucose of ≥ 11.1 mmol/L or HbA1c >=6.5%) • Adults ≥18 years
I	MET + DPP-4 inhibitor MET + SGLT-2 inhibitor MET + TZD SU + DPP-4 inhibitor SU + SGLT-2 inhibitor SU + TZD MET + SU + DPP-4 inhibitor MET + SU + SGLT-2 inhibitor MET + SU + TZD MET + TZD + DDP-4 inhibitor
C	MET MET + PLACEBO SU SU + PLACEBO MET + SU MET + SU + PLACEBO
O	See list of critical, important and not-important outcomes for type 2 diabetes (Table 1 in Appendix 3)

2. How do outcomes in people with type 2 diabetes treated with DPP-4 inhibitor / SGLT-2 inhibitor/glitazones compare to those of people treated with insulin when introduced as intensification of metformin/sulfonylurea/metformin + sulfonylurea?

P	People with type 2 diabetes for whom first-line treatment with metformin and/or sulfonylurea has failed to achieve the set target of glycaemic control (measured by HbA1c values). • Diagnosed with type 2 diabetes according to WHO criteria (fasting plasma glucose ≥ 7.0 mmol/L or 2-h plasma glucose of ≥ 11.1 mmol/L or HbA1c >=6.5%) • Adults ≥18 years
I	MET + DPP-4 inhibitor MET + SGLT-2 inhibitor MET + TZD SU + DPP-4 inhibitor SU + SGLT-2 inhibitor SU + TZD

	MET + SU + DPP-4 inhibitor MET + SU + SGLT-2 inhibitor MET + SU + TZD MET + TZD + DDP-4 inhibitor
C	MET + insulins SU + insulins MET + SU + insulins
O	See list of critical, important and not-important outcomes for type 2 diabetes (Table 1 in Appendix 3)

3. How do outcomes in people with type 1 diabetes treated with short-acting analogue insulins compare to those of people treated with short-acting human insulins?

P	People with type 1 diabetes
I	Short-acting analogue insulins
C	Short-acting human insulins
O	See list of critical, important and not-important outcomes for type 1 diabetes (Table 2 in Appendix 3)

4. How do outcomes in people with type 1 diabetes treated with long-acting analogue insulins compare to those of people treated with intermediate-acting human insulins?

P	People with type 1 diabetes
I	Long-acting analogue insulins
C	Intermediate-acting human insulins
O	See list of critical, important and not-important outcomes for type 1 diabetes (Table 2 in Appendix 3)

5. How do outcomes in people with type 2 diabetes mellitus treated with short-acting analogue insulins compare to those of people treated with short-acting human insulins?

P	People with type 2 diabetes
I	Short-acting analogue insulins
C	Short-acting human insulins
O	See list of critical, important and not-important outcomes for type 2 diabetes (Table 1 in Appendix 3)

6. How do outcomes in people with type 2 diabetes treated with long-acting analogue insulins compare to those of people treated with intermediate-acting human insulins?

P	People with type 2 diabetes
I	Long-acting analogue insulins
C	Intermediate-acting human insulins
O	See list of critical, important and not-important outcomes for type 2 diabetes (Table 1 in Appendix 3)

Table 1: Critical, important and not-important outcomes for type 2 diabetes

Outcome	Importance
Glycaemic control (HbA1c)	Critical
CVD mortality	Critical
CVD incidence	Critical
Severe hypoglycaemia	Critical
Body weight	Critical
Quality of life	Critical
Cost-effectiveness	Critical
All-cause mortality	Important
Mild hypoglycaemia	Important
End-stage renal disease	Important
Lower limb amputation	Important
Ketoacidosis	Important
Hyperosmolar hyperglycaemia	Important
Progression of nephropathy	Important
Visual impairment	Important
Foot ulcer	Important
Cancer	Important
Infections	Important
Pancreatitis	Important
Fractures	Not important

Table 2: Critical, important and not-important outcomes for type 1 diabetes

Outcome	Importance
Glycaemic control (HbA1c)	Critical
All-cause mortality	Critical
CVD mortality	Critical
Severe hypoglycaemia	Critical
Progression of nephropathy	Critical
Visual impairment	Critical
End-stage renal disease	Critical
Lower limb amputation	Critical
Ketoacidosis	Critical
Quality of life	Critical
Cost-effectiveness	Critical
CVD incidence	Important
Mild hypoglycaemia	Important
Foot ulcer	Important
Cancer	Important
Infections	Important
Body weight	Not important

Appendix 4. Methods for identification of recent high-quality systematic reviews

Search strategies

Questions 1 and 2

Population:

"Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 2"[Mesh] OR “type 2 diabetes mellitus”[Text Word] OR “T2DM”[Text Word]

Intervention (AND):

antihyperglycaemic [Text Word] OR “anti hyperglycaemic”[Text Word] OR anti-hyperglycaemic[Text Word] antihyperglycemic[Text Word] OR “anti hyperglycemic”[Text Word] OR anti-hyperglycemic[Text Word] OR (oral[Text Word] AND hyperglycemic[Text Word]) OR (oral[Text Word] AND hypoglycaemic[Text Word]) OR(glucose-lowering[Text Word] AND drug*[Text Word]) OR “Dipeptidyl-Peptidase IV Inhibitors”[MeSH] OR dpp-4[Text Word] OR dpp-iv[Text Word] OR sitagliptin*[All Fields] OR saxagliptin*[All Fields] OR linagliptin*[All Fields] OR alogliptin*[All Fields] OR vildagliptin*[All Fields] OR gliptin[All Fields] OR gliptins[All Fields] OR “sodium-glucose cotransporter 2 inhibitors”[Text Word] OR “sodium-glucose cotransporter 2 inhibitor”[Text Word] OR “sodium-glucose co-transporter 2 inhibitors”[Text Word] OR “sodium-glucose co-transporter 2 inhibitor”[Text Word] OR SGLT-2[Text Word] OR SGLT2[Text Word] OR canagliflozin[All Fields] OR dapagliflozin[All Fields] OR empagliflozin[All Fields] OR “thiazolidinediones”[MeSH] OR thiazolidinedione*[Text Word] OR pioglitazone[All Fields] OR rosiglitazone[All Fields] OR glitazone[All Fields] OR pioglitazones[All Fields] OR glitazones[All Fields]

Comparator (AND):

“metformin”[MeSH] OR metformin[Text Word] OR biguanide[All Fields] OR sulfonylurea[Text Word] OR sulphonylurea[Text Word] OR sulfonylureas[Text Word] OR sulphonylureas[Text Word] OR glibenclamide[All Fields] OR gliclazide[All Fields] OR glibenclamides[All Fields] OR "Insulin"[Mesh] OR "Insulin, Regular, Human"[Mesh]

Article Type (AND):

systematic[SB]

Limit to: yr 2006 – current

Question 3

Population:

"Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 1"[Mesh] OR “type 1 diabetes mellitus”[Text Word] OR “T1DM”[Text Word] OR "Diabetes Mellitus, Type 2"[Mesh] OR “type 2 diabetes mellitus”[Text Word] OR “T2DM”[Text Word]

Intervention (AND):

"Insulin"[Mesh] OR "Insulin, Long-Acting"[Mesh] OR "Insulin Aspart"[Mesh] OR "Insulin Lispro"[Mesh] OR (insulin[Text Word] AND analog*[Text Word]) OR "insulin glulisine"[Text Word]

OR (insulin[Text Word] AND short-acting[Text Word]) OR (insulin[Text Word] AND “short acting”[Text Word]) OR (insulin[Text Word] AND shortacting[Text Word]) OR (insulin[Text Word] AND fast-acting[Text Word]) OR (insulin[Text Word] AND “fast acting”[Text Word])

OR (insulin[Text Word] AND rapid-acting[Text Word]) OR (insulin[Text Word] AND “rapid acting”[Text Word]) OR (insulin[Text Word] AND derivative*[Text Word]) OR (insulin[Text Word] AND long-acting[Text Word]) OR (insulin[Text Word] AND “long acting”[Text Word]) OR (analog*[Text Word] AND long-acting[Text Word]) OR (analog*[Text Word] AND “long acting”[Text Word])

Comparator (AND):

"Insulin"[Mesh] OR "Insulin, Regular, Human"[Mesh] OR "Insulin, Short-Acting"[Mesh] OR "Insulin, Isophane"[Mesh] OR "Isophane Insulin, Human"[Mesh] OR "Insulin, Lente"[Mesh] OR (insulin[Text Word] AND short-acting[Text Word]) OR (insulin[Text Word] AND “short acting”[Text Word]) OR (insulin[Text Word] AND shortacting[Text Word]) OR “human insulin”[Text Word] OR (insulin[Text Word] AND intermediate-acting[Text Word]) OR (insulin[Text Word] AND “intermediate acting”[Text Word])

Article Type (AND):

systematic[SB]

Assessing the Methodological Quality of Systematic Reviews (AMSTAR) quality assessment

Study	1	2	3	4	5	6	7	8	9	10	11	Sum	
Tricco (2014)	1	1	1	1	0	1	1	1	1	1	1	10	
Fullerton (2016)	0	1	1	1	1	1	1	1	1	1	1	10	Not explicitly stated that there was a protocol
Palmer (2016)	1	1	0	0	0	1	1	1	1	1	1	8	Not explicitly stated that a supplementary and grey literature search was carried out.

The CADTH review and the Horvath review were not prospectively assessed for quality because the systematic reviews were still underway and results were only available shortly before the Guideline Group meeting.

AMSTAR criteria

1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest included?

Appendix 5. Hypoglycaemic agents for second-line treatment in type 2 diabetes

Treatment matrices were developed using data from the systematic review and network meta-analysis carried out by the Methods and Applications Group for Indirect Treatment Comparisons (MAGIC) for the Canadian Agency for Drugs and Technologies in Health (CADTH) *(6).*

The comparisons between medicines should be read from right to left and the estimate is in the cell in common between the column-defined treatment and the row-defined treatment. For binary outcome data (hypoglycaemic events, mortality), an odds ratio < 1 favours the column-defined treatment and an odds ratio >1 favors the row-defined treatment. A mean difference (HbA1c, body weight) < 0 indicates that that the column-defined treatment is associated with a lower HbA1c level or body weight than the row-defined treatment. A mean difference > 0 indicates that the column-defined treatment is associated with a higher HbA1c level or body weight than the row-defined treatment.

For example, reading Table 1 on HbA1c from right to left, DPP-4 inhibitors added to metformin were associated with higher HbA1c compared to sulfonylurea added to metformin (0.12, 95% CrI: 0.01, 0.24). And when reading Table 2 from right to left, DPP-4 inhibitors added to metformin was associated with an odds ratio of severe hypoglycaemia of 0.14 (95% CrI: 0.07, 0.26) compared to sulfonylurea added to metformin.

The treatment matrices also contain the quality of evidence assessed by the GRADE methodology.

Abbreviations: CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; SGLT-2 = sodium-glucose co-transporters type 2 inhibitor; SU = sulfonylurea; TZD = thiazolidinedione.

Table 1: HbA1c (mean difference in change from baseline with 95% credible interval)

SU	-0.07 ⊕⊕OO[1,2] (-0.20,0.07)	**0.12** ⊕⊕⊕O[1] **(0.01,0.24)**	0.04 ⊕⊕⊕O[2] (-0.16,0.24)	-0.15 (-0.45,0.17)	**0.70 (0.58,0.83)**
	TZD	**0.19 (0.05,0.33)**	0.11 (-0.11,0.32)	-0.08 ⊕⊕⊕O[2] (-0.40,0.25)	**0.77 (0.63,0.92)**
		DPP-4 inhibitor	-0.09 ⊕⊕OO[1,2] (-0.28,0.10)	-0.27 ⊕⊕⊕O[2] (-0.57,0.04)	**0.58** ⊕⊕⊕O[1] **(0.48,0.68)**
			SGLT-2 inhibitor	-0.18 ⊕⊕⊕O[2] (-0.53,0.18)	**0.67** ⊕⊕⊕⊕ **(0.49,0.84)**
				Basal insulin	**0.85 (0.53,1.16)**
					Placebo

[1] Study limitations /risk of bias

[2] Imprecision

Table 2: Severe hypoglycaemia (odds ratio with 95% credible interval)

SU	0.36 ⊕⊕⊕O[2] (0.04,2.65)	**0.14** ⊕⊕⊕O[1] **(0.07,0.26)**	**0.09** ⊕⊕⊕⊕ **(0.02,0.44)**	0.52 (0.10,2.83)	**0.16 (0.06,0.45)**
	TZD	0.39 (0.05,3.13)	0.26 (0.03,3.03)	1.37 ⊕⊕⊕O[2] (0.15,30.36)	0.43 (0.06,3.33)
		DPP-4 inhibitor	0.66 ⊕⊕OO[1,2] (0.15,2.98)	3.61 ⊕⊕⊕O[2] (0.74,20.31)	1.10 ⊕⊕OO[1,2] (0.41,2.94)
			SGLT-2 inhibitor	5.25 ⊕⊕⊕O[2] (0.73,56.37)	1.64 ⊕⊕⊕O[2] (0.42,7.69)
				Basal insulin	0.32 (0.04,1.54)
					Placebo

[1] Study limitations/risk of bias

[2] Imprecision

Table 3: Body weight in kg (mean difference in change from baseline with 95% credible interval)

SU	1.09 (0.48,1.70)	**-1.93 (-2.37,-1.49)**	**-4.32 (-5.00,-3.66)**	0.65 (-0.57,1.95)	**-2.11 (-2.63,-1.59)**
	TZD	**-3.02 (-3.61,-2.43)**	**-5.41 (-6.18,-4.63)**	-0.44 (-1.70,0.90)	**-3.20 (-3.82,-2.57)**
		DPP-4 inhibitor	**-2.39 (-2.98,-1.80)**	**2.59 (1.41,3.82)**	-0.18 (-0.58,0.22)
			SGLT-2 inhibitor	**4.98 (3.68,6.31)**	**2.21 (1.67,2.75)**
				Basal insulin	**-2.76 (-4.01,-1.56)**
					Placebo

Table 4: CVD mortality in patients with established CVD or at high risk for cardiovascular events (odds ratio with 95% credible interval)

SU	-	-	-	-	-
	TZD	1.16 (0.19,6.67)	0.70 (0.09,5.56)	-	1.20 (0.27,5.00)
		DPP-4 inhibitor	0.60 ⊕OOO[234] (0.10,3.72)	-	1.03 ⊕OOO[1234] (0.37,3.03)
			SGLT-2 inhibitor	-	1.72 ⊕OOO[234] (0.39,7.14)
				Basal insulin	-
					Placebo

[1] Study limitations/risk of bias

[2] Imprecision

[3] Indirectness

[4] Inconsistency

Summary of judgments

	Favours sulfonylurea	Probably favours sulfonylurea	Choose either sulfonylurea or DPP-4 inhibitor, SGLT-2 inhibitor, or glitazones	Probably favours DPP-4 inhibitor, SGLT-2 inhibitor, or glitazones	Favours DPP-4 inhibitor, SGLT-2 inhibitor, or glitazones
Problem	☐	☐	X	☐	☐
Desirable effects	☐	☐	X	☐	☐
Undesirable effects	☐	☐	☐	X	☐
Certainty of the evidence of effects	☐	☐	X	☐	☐
Values	☐	☐	X	☐	☐
Resource use	X	☐	☐	☐	☐
Cost-effectiveness	☐	X	☐	☐	☐
Equity	☐	X	☐	☐	☐
Acceptability	☐	☐	X	☐	☐
Feasibility	☐	☐	X	☐	☐
	We recommend sulfonylurea over DPP-4 inhibitor, SGLT-2 inhibitor, or glitazones	We suggest using sulfonylurea over DPP-4 inhibitor, SGLT-2 inhibitor, or glitazones	We suggest using either sulfonylurea or DPP-4 inhibitor, SGLT-2 inhibitor, or glitazones	We suggest using DPP-4 inhibitor, SGLT-2 inhibitor, or glitazones over sulfonylurea	We recommend DPP-4 inhibitor, SGLT-2 inhibitor, or glitazones over sulfonylurea
Type of recommendation	X	☐	☐	☐	☐

Appendix 6. Price of Defined Daily Dose* of blood glucose-lowering medicines, compared to sulfonylurea

	Sulfonylurea	DPP-4 inhibitors	SGLT-2 inhibitors	Pioglitazone (TZD)	Basal human insulin**
Australia	reference	4.5X	4.5X	3.1X	2.3X
Canada	reference	13X	13X	---	11.5X
Croatia	reference	7X	9 X	5X	5X
Denmark	reference	3.5X	11X	3.4X	1X
France	reference	18X	----	----	6.8X
The Netherlands	reference	30X	26 X	1.9X	4.5X
Switzerland	reference	8.6X	9.5X	5.8X	4X

*Source: WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health, Oslo, Norway (https://www.whocc.no/atc_ddd_index/ accessed 15 March 2017.

** Price of test strips for blood glucose self-monitoring not included

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Canada	New drugs for type 2 diabetes: second-line therapy – recommendations report. CADTH Therapeutic Review. 2017;4:1c).
Croatia	http://www.hzzo.hr/zdravstveni-sustav-rh/trazilica-za-lijekove-s-vazecih-lista/
Denmark	http://medicinpriser.dk/default.aspx?lng=2
France	http://www.ameli.fr/fileadmin/user_upload/documents/2016063_memo_antidiabetiqueCout_MetropoleMAJ_BD.pdf https://www.univadis.fr/references/drug-database
The Netherlands	https://www.medicijnkosten.nl
Switzerland	Compendium des Médicaments (https://compendium.ch/home/fr)

Appendix 7: Cost-effectiveness of medicines to treat Type 1 and Type 2 diabetes: a narrative review of the published literature

Comparing and aggregating data on the health economics of various diabetes treatments is difficult because of the range of research models used – for example, the Center for Outcomes Research (CORE) Diabetes Model, DiDACT, UKPDS Outcomes Model vary in their ability to capture cost-utility differences. A good illustration of this is the UKPDS Outcomes Model, which – while it may be well validated – does not include the direct effects of changes in body weight, severe hypoglycemic events, nor fear of severe hypoglycemic events *(1).* While these extra issues are presented separately in the results, they are not fully taken into account in the cost-effectiveness analysis measure.

Some studies compare whole disease progression strategies based on first-, second- and third-line treatments while others compare only single lines of treatment. Models also use different costs, for example, the inclusion of indirect costs varies (even the definition of an indirect cost can vary). Many of the costs related to diabetes concern the treatment of diabetes-related complications rather than the disease itself, and some studies look more thoroughly into these costs than others. Studies also vary in perspective (e.g. depending on provider, such as a public health body or a single private hospital), time horizon, and discount rate used. Reflecting the diversity in clinical practice, much can vary across the regimens examined – for example which therapy lines are considered, which treatment dosages, and the timing of treatment relative to meals. In many cases omission of detail itself precludes direct comparison with other studies. The studies described next used sufficiently similar methods to have their results described together, however, their diversity should be stressed.

Cost-effectiveness evidence comparing **insulins for type 1 diabetes** is not extensive, and the published base-case evidence is very briefly summarized here. The treatments most often compared are detemir and NPH, with comparisons mainly made by four authors in western European and Canadian settings. The bulk of the evidence, which is industry funded, suggests that detemir is cost-effective compared to NPH. However, the single, independently conducted study concluded that that the cost-utility ratio was well above the acceptable threshold, suggesting that detemir was not cost-effective compared to NPH *(2)*. For glargine versus NPH, three of the four studies concluded that glargine was cost-effective compared to NPH given the thresholds commonly used in the context in which it was considered (again western European or Canadian). Again, in contrast, the independent study *(2)* concluded that glargine was not cost-effective compared to NPH in the Canadian setting. For glargine versus detemir one US-focused, industry-sponsored study concluded that glargine was more expensive and less effective than detemir. For insulin aspart versus regular human insulin the Cameron study estimated insulin aspart to be dominant compared to regular human insulin (less expensive and more effective). For insulin lispro versus regular human insulin the same Canadian study suggested that insulin lispro had an incremental cost-utility that fell within the accepted threshold and therefore was considered cost-effective compared to human insulin. A UK-focussed, industry-funded study found insulin lispro to be dominant compared to regular human insulin even with varying assumptions.

The evidence base on cost-effectiveness of **insulins for type 2 diabetes** is relatively new (post-2002). To date, industry-funded studies in Canada, the USA and several western European countries have

found determir to be more cost-effective than NPH. However, in a largescale review conducted by NICE in 2010 *(1)* determir and glargine were not found to be cost-effective compared to NPH as first-line insulin. The Cameron study (2009) also found that detemir and glargine were not cost-effective compared to NPH. Industry studies based in Canada, Switzerland, the USA, and a three-country study of India, Indonesia and Saudi Arabia found glargine to be more cost-effective than NPH. A recent independent study from Thailand *(3)* found NPH to be more cost-effective than insulin glargine. For insulin aspart versus regular human insulin the Cameron (2009) study found insulin aspart to be cost-effective compared to regular human insulin, but for insulin lispro versus regular human insulin, insulin lispro was found not to be cost-effective compared to regular human insulin *(2)*.

For DPP-4 inhibitors versus sylphonylureas as second-line treatment of type 2 diabetes, industry studies from Germany and Sweden found saxagliptin plus metformin to be cost-effective compared to sulfonylurea plus metformin *(4,5).* Another from Spain found saxagliptin plus metformin plus sulfonylurea to be cost-effective compared to basal insulin plus metformin plus sulfonylurea *(6).* Another from the UK found alogliptin plus metformin to be more cost-effective than metformin plus sulfonylurea *(7).* The one independent study in this category *(8)* found that amongst several different second-line hypoglycaemic agents (in combination with metformin) none came close to being as cost-effective as the sulfonylurea plus metformin combination. For SGLT-2 inhibitors versus sylphonylureas as second line treatment of type 2 diabetes, industry studies from several European countries found dapaglifloxin plus metformin to be cost-effective compared to sulfonylurea plus metformin *(9,10)*. No independent studies comparing these treatments were identified.

For thiazolidinediones (TZD) versus sylphonylureas as second-line treatment for type 2 diabetes, industry studies from Spain, Germany and the UK found rosiglitazone plus metformin to be more cost-effective than sulfonylurea plus metformin *(11,12,13)*. A study based in Germany found pioglitazone plus metformin and pioglitazone plus sulfonylurea to be more cost-effective than sulfonylurea plus metformin *(14).* No independent studies comparing these treatments were identified. For DPP4- inhibitors versus insulin as second- or third-line treatment, an industry study from Poland found saxagliptin plus metformin to be more cost-effective than insulin plus metformin and saxagliptin plus sulfonylurea to be more cost-effective than insulin plus sulfonylurea *(15).* For SGLT-2 inhibitors versus insulin as second- or third-line treatment and TZD versus insulin as second- or third-line treatment, no evidence was identified.

In sum, with very few exceptions, industry-funded studies find newer diabetes drugs to be good value for money compared to the older drugs in wealthy country settings, whereas independently conducted studies do not come to this conclusion.

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Appendix 8. Reviews of patient treatment preferences

Review 1. Treatment preferences in patients with type 2 diabetes: oral hypoglycaemic agents or insulin initiation for treatment intensification – a narrative review

Introduction

Type 2 diabetes is a disease involving advancing β-cell dysfunction *(1)* and treatment often needs to be intensified with disease duration. Guidelines recommend initial management with lifestyle modifications (dietary changes and weight loss) *(2)*. If blood glucose targets are not met, oral hypoglycaemic agents (OHAs) are recommended, with agents added as required *(2)*. Many patients eventually require insulin for adequate control *(2)*.

The current World Health Organization Model List of Essential Medicines for diabetes includes metformin, gliclazide, and short- and intermediate-acting human or animal insulin *(3)*. In recent years, the options for OHAs have increased. Aside from metformin and sulfonylureas, DPP4 inhibitors, SGLT-2 inhibitors, and TZDs are now available and recommended for treatment augmentation in various high-income settings. However, these new OHAs are quite expensive and often cost more than human insulin, which could be an alternative option for treatment augmentation. When choosing a treatment, clinical goals need to be balanced with patient preferences and well-being.

This review had two objectives:

1. To determine patient preferences in the treatment of type 2 diabetes and to review treatment satisfaction in patients receiving treatment intensification with OHAs compared to insulin;
2. To ascertain what factors contribute to treatment satisfaction.

Methods

A PubMed search was performed using terms related to and variants of “type 2 diabetes”, “treatment”, “insulin”, “satisfaction”, “stated preference” and “decision analysis”:

("diabetes mellitus, type 2"[mh] OR diabet*[tiab] OR"non-insulin dependent"[tiab] OR type- 2[tiab] OR "type II"[tiab] OR "type 2"[tiab]“Ketosis-Resistant Diabetes Mellitus”[tw] OR“Non- Insulin-Dependent Diabetes Mellitus”[tw] OR “Type 2 Diabetes Mellitus”[tw] OR “Stable Diabetes Mellitus”[tw] OR “Maturity-Onset Diabetes Mellitus” [tw] OR “Maturity Onset Diabetes Mellitus”[tw] OR “MODY”[tw] OR “NIDDM”[tw] OR“Adult-Onset Diabetes Mellitus”[tw]) AND (Treatment[tiab] OR management[tiab] OR pharmaceutical[tiab] OR “drug therapy”[mesh] OR medication[tiab] OR insulin [mesh] OR insulin[tiab]) AND ("conjoint analysis" OR "satisfaction" OR "choice model" OR "stated preference" OR "discrete choice" OR DCE OR "decision analysis" OR preferences OR "multi-criteria decision analysis" OR MCDA OR "multi-attribute utility" OR "analytic hierarchy process" OR "trade off" OR "self- explicated" OR "best-worst scaling" OR utilities OR "preference weight" OR “willingness to pay” OR WTP OR “willingness to accept” OR “contingent valuation” OR priorities[tiab] OR valuation[tiab])

Results

The initial search returned 1193 citations. Studies were excluded if there was no English language text, if no full text was available, and if they involved non-insulin injectable anti-diabetic medications (i.e. GLP-1 agonist). A total of nine studies were included in this review, five for objective one, and four for objective two. Of the five studies included for objective one, three were trials *(4–7)* and two

were single-arm intervention studies investigating the effect of insulin initiation in treatment satisfaction *(8–10).* All three included randomized controlled trials were conducted in North America (Table 1). A variety of tools were used to evaluate treatment satisfaction and well-being *(11–16)*.

Table 1: Study characteristics

Study (Year)	Country/Region	Study Type	Patient Characteristics	Interventions Assessed
Randomised Controlled Trials				
Aljabri et al. (2004) (4)	Canada	RCT	Pioglitazone group **Sex**: 60% male, 40% female **Age (years):** 59 ± 9 **BMI**: 26 ± 9 **HbA1c (%):** 9.7 ± 1.5 **Duration of DM (years)**: 9 ± 6 Insulin group **Sex**: 61% male, 39% female **Age (years):** 57 ± 14 **BMI**: 25 ± 6 **HbA1c (%):** 10.1 ± 1.4 **Duration of DM (years)**: 11 ± 8	Pioglitazone and usual OHAs Bedtime NPH and usual OHAs
Gerstein et al (2006) (5) & Houlden et al. (2007) (6)*	Canada	RCT	Oral OHA (intensified) **Sex**: 30% male, 70% female **Age (years):** 56.8 ± 10.1 **BMI**: 31.5 ± 4.6 **HbA1c (%):** 8.5 ± 1 **Duration of DM (years)**: 8.2 ± 6.5 Insulin glargine + OHA **Sex**: 32% male, 68% female **Age (years):** 56.3 ± 9.4 **BMI**: 31.1 ± 4.4 **HbA1c (%):** 8.6 ± 1 **Duration of DM (years)**: 7.6 ± 5.4	Oral OHA (intensified) – combination of metformin, insulin secretagogues or rosiglitazone Addition of insulin glargine to existing OHA
Vinik et al. (2007) (7)	USA	RCT	Rosiglitazone group **Sex**: 58% male, 42% female **Age (years):** 55.3 ± 11.4 **BMI**: 33.6 ± 6.3 **HbA1c (%):** 8.7 ± 1.0 **Duration of DM (years)**: 8.1 ± 5.1 Insulin group **Sex**: 45% male, 55% female **Age (years):** 55.9 ± 10.5 **BMI**: 34.6 ± 7.0 **HbA1c (%):** 8.8 ± 1.0 **Duration of DM (years)**: 8.5 ± 5.8	Addition of insulin glargine to sulfonylurea and metformin Addition of rosiglitazone to sulfonylurea and metformin
Single-Arm Trials				
Tsukube et al (2015) (8)	Japan	Single-arm trial	**Sex****: 61% male, 39% female **Age (years):** 62.3 **BMI**: 24.9 **HbA1c (%):** 9.4 **Duration of DM (years)**: <5 years (15%), 5-<10 years (18%) 10+ years (45%), unknown (22%)	Addition of insulin glargine to existing OHA
Wilson et al. (2004) (9)	New Zealand	Single-arm trial	**Sex**: 60% male, 40% female **Age (years):** 60.5 **BMI**: 30.9 ± 6.0 **HbA1c (%):** 9.69 ± 1.61 **Duration of DM (years)**: *unknown*	Addition of insulin to OHA

* Both trials were part of the INSIGHT study and were included as one trial

** Patient characteristic information taken from original ALOHA2 study as this study was a sub-analysis *(10)*

Trial results

The first RCT found an improvement in treatment satisfaction with the addition of insulin glargine to existing OHA regimens compared to optimization of OHA alone *(5, 6)* (Table 2). At baseline, both groups had high levels of perceived hyperglycaemia, low levels of perceived hypoglycaemia, and similar treatment satisfaction and quality of life. Both groups experienced significant increases in treatment satisfaction, but the increase was significantly larger in the glargine group. It is possible that this was related to better glycaemic control, as those in the glargine group were 1.68 times as likely to achieve two consecutive HbA1c results of </= 6.5%, the clinical end goal of the trial. However, the authors also suggested that a greater sense of empowerment may have accounted for at least part of the larger increase, as patients were trained to titrate their insulin dose based on their blood glucose readings *(5, 6)*. There was no difference between groups in frequency of hypoglycaemia, and those in the glargine group had a 1.9 kg greater increase in weight than the oral OHA group **–** a significant difference *(5, 6)*.

The second RCT examined the addition of rosiglitazone compared to insulin glargine to existing treatment with metformin and a sulfonylurea. Both groups experienced an increase in health-related quality of life, with significantly greater improvement in the glargine group *(7)*. The glargine group also experienced significant improvements in symptom distress scores and perception in general health. More specifically, patients in the glargine group experienced significantly greater improvements in mood symptoms, ophthalmologic symptoms, ophthalmologic distress, and fatigue distress *(7)*. HbA1c decline was similar between the two groups, but those with higher baseline levels (≥ 9.5%) experienced greater declines on insulin as compared to rosiglitazone *(7)*. This suggests that those with higher HbA1c levels benefit even more from a treatment regimen involving insulin than one with OHAs alone.

The third RCT found no difference in satisfaction between groups when comparing the addition of pioglitazone to usual OHAs compared to the addition of bedtime NPH insulin, with high levels of satisfaction in both groups *(4)* (Table 2). Although there were no statistically significant differences in any of the satisfaction domains, those in the insulin group rated their satisfaction with understanding diabetes and the convenience of treatment higher, and they reported feeling less frequent hypoglycaemia. Both groups were very similar in their satisfaction with continuing current treatment, and with the likelihood of recommending the treatment to others *(4)*.

Participants in both single-arm studies reported increased treatment satisfaction when insulin was added to their existing OHA compared to when they were using OHAs alone *(8, 9)*. However, in one study, satisfaction was related to glycaemic control, with those achieving HbA1c of less than 7% being more satisfied *(8)* (Table 2).

Table 2: Summary of results

Study (Year)	N	Assessment Method (Preferences)	Treatment Preference
Alijabri et al. (2004) (4)	62	WHO Diabetes Treatment Satisfaction Questionnaire (Status) (DTSQs)	**No difference between groups** **DTSQs**: High levels of satisfaction in both groups
Gerstein et al. (2006) (5) & Houlden et al. (2007) (6)*	405 + 366	Audit of Diabetes Dependent Quality of Life (ADDQoL) WHO Diabetes Treatment Satisfaction Questionnaire (Status) (DTSQs)	**Glargine + existing OHA** **DTSQs**: Treatment satisfaction improved in both groups but significantly more in glargine + OHA group No between group differences in perceived hypoglycaemia **ADDQoL**: Quality of life improved in both groups but significantly higher in glargine + OHA group
Tsukube et al. (2015) (8)	1251	WHO Diabetes Treatment Satisfaction Questionnaire (Change) (DTSQc) WHO Diabetes Treatment Satisfaction Questionnaire (Status) (DTSQs) EuroQol 5 Dimension (EQ-5D)	**DTSQ**: Treatment satisfaction improved with addition of insulin- improvement was greater in patients who achieved HbA1c target (<7%) **EQ-5D**: significant improvement in overall score in all participants regardless of whether or not HbA1c target was reached
Vinik et al. (2007) (7)	217	Diabetes Symptom Checklist Revised (DSC-R) Medical Outcomes Study Short-Form Health Survey (SF-36)	**DSC-R:** Significantly greater improvement in glargine group in symptom distress score (indicating less distress) **SF-36:** Significantly better perception of general health in glargine group Both groups achieved similar levels of glycaemic control and both groups reported improved health-related quality of life
Wilson et al. (2004) (9)	50	WHO Diabetes Treatment Satisfaction Questionnaire (Change) (DTSQc) Well Being Questionnaire	**Insulin + OHA** Improvement in overall satisfaction and all domains of satisfaction except frequency of unacceptably high or low glucose readings in DTSQc

*Both trials were part of the INSIGHT study and are included as one trial

Treatment attributes contributing to patient preference

Of the four studies included for objective two, three discrete-choice experiments looked at which attributes were considered by patients to be the most important in treatment decisions and one cross-sectional study examined treatment attributes associated with greatest treatment satisfaction.

Within the discrete choice experiments, treatment characteristics that patients valued most when choosing between regimens were route of administration *(17–19)*, avoiding or reducing the number of injections *(17, 18)*, side effects *(19)*, avoidance (specifically) of nausea *(17, 18)*, glycaemic control (blood glucose level maintenance or reduction of HbA1c) *(17–19),* the risk of (or avoiding) hypoglycaemia *(17–19)*, avoidance of weight gain or experiencing weight loss *(17, 18)*, reduction of CVD risk *(17)*, and reduction in frequency of blood glucose monitoring *(17)*. These are the same characteristics previously found to be valued most by patients taking oral medications for diabetes management *(20)*. These are summarised in Table 3.

From the cross-sectional study, treatment satisfaction was highest in patients using diet control only, followed by those using OHAs, and then by those using insulin *(21)*. This may be because patients using insulin may perceive that their health has deteriorated, or because they are more likely to have diabetes-related micro- or macro-vascular complications (retinopathy, neuropathy,

nephropathy or foot ulcer) *(21)*. Treatment satisfaction, regardless of treatment regimen, was associated with being negatively affected by diabetic complications *(6)*, which may be a confounding factor in assessment of overall satisfaction by treatment type as diabetic patients with more diabetes-related complications are more likely to be using insulin.

Table 3: Treatment attributes most valued by patients

Study (Year) & Country/Region	Study Type (N)	Study Question	Attributes
Casciano et al. (2011) (19) 18 countries (Africa/Middle East, Asia, Eastern Europe, Latin America)	Discrete choice modelling (14033)	What product attributes are most important in determining drug selection and use amongst patients with type 2 diabetes?	Route of administration (significance diminishes in patients with previous or current exposure to insulin) Side effects of treatment Maintenance of blood glucose Risk of hypoglycaemia
Morillas et al. (2015) (17) Spain & Portugal	Discrete choice experiment (330)	What do patients (and physicians) value in treatments for type 2 diabetes?	Avoidance of weight gain Avoidance of hypoglycaemia Reduction of cardiovascular risk Reduction of nausea Reduction of HbA1c by 1% Reduction in number of injections Route of administration Reduction in frequency of blood glucose monitoring
Bogelund et al. (2011) (18) Denmark	Discrete choice experiment	What treatment attributes are important to patients with type 2 diabetes?	Avoiding weight gain/experiencing weight loss Avoidance of hypoglycaemia Avoidance of injections Avoidance of nausea
Biderman et al. (2009) (21) Israel	Cross-sectional study	What factors contribute to treatment satisfaction in diabetes patients?	Diet alone was preferred to OHA which was preferred to insulin Treatment in primary care was preferred to diabetes clinics Lower treatment satisfaction associated with micro- or macro-vascular diabetic complications

Discussion

Overall, four of the five trials found that patients experienced improvements in treatment satisfaction with initiation of insulin.

However, studies have found that initiation of insulin is often delayed by 3-5 years despite recognition of inadequate glycaemic control *(22, 23)*. In the DAWN study, investigators found that despite local guidelines recommending insulin be started at an HbA1c of 8.4%, insulin was actually initiated at an HbA1c of 9.6% *(23)*. Recognition of a problem in patient management with a failure to act is known as clinical inertia *(23)*.

Resistance to insulin initiation from both patients and physicians contribute to clinical inertia. Common myths and misconceptions about insulin therapy and patient-identified barriers to insulin initiation are shown in Table 4.

Table 4: Common barriers to insulin initiation and strategies to overcome them

Patient identified barrier	Strategies to address barrier
Fear of injection pain (22, 24, 25)	Demonstration of available tools and needle sizes (22) Adequate practice and support of injections to overcome fear (25)
Fear of weight gain (22, 24)	Dietary control and adequate exercise can minimise weight gain while also improving glycaemic control (25)
Fear of inability to manage insulin regimen (22)	Education and support (19) Simplification of regimen and use of simple self-titration tools (i.e. TITRATE™ 303 algorithm) (22)
Fear of hypoglycaemia (22, 25)	Use of long-acting formulas to reduce hypoglycaemia risk (22) Education on recognition, management and avoidance of hypoglycaemia (22) Reassurance that incidence of serious hypoglycaemia is rare (22)
Fear that diabetes has gotten worse or has become 'end stage' (22,24,25)	Introduction of insulin as a diabetes management tool early in course of T2DM (24, 25) Reassurance that insulin requirement is an inevitable part of the disease course (22)
Decreased lifestyle flexibility (22, 24)	Explanation of different insulin regimens and injection schedules (24)
Social stigma associated with injecting (22,24,25)	Introduction of tools such as insulin pens to make injecting simpler and more discreet (22)
Insulin is not beneficial or can harm health (22, 24, 26)	Adequate education (26)

Once barriers are overcome and insulin has been initiated, patients report higher treatment satisfaction *(5–9)*. Interestingly, the number of injections required per day has no impact on treatment satisfaction *(27, 28),* nor does the formulation of insulin used (biphasic, prandial or basal) *(28).* Although type 2 diabetes patients state that route of administration is a very important factor in determining treatment satisfaction, the significance is diminished in patients who have previous or current exposure to insulin *(19)*. In one study, patients using insulin reported more issues with pain and problems with social functioning than patients using OHA, but despite this, patients in the insulin group reported higher overall satisfaction with treatment *(7)*. There is some evidence that the initial benefits of initiating insulin may wear off or be forgotten over time, as treatment satisfaction in patients using insulin was reported to be lower at 4 years than at baseline in one study *(29)*. This may be avoided or mitigated with continued education and support.

One of the limitations of this review is that the majority of studies were performed in high-resource settings. However, there is no evidence thus far that preference for insulin compared to oral medications would differ based on culture or resources. Another limitation is that many studies (three of the five trials included) were funded by pharmaceutical companies that manufacture insulin, creating a potential conflict of interest as reducing barriers to insulin initiation would increase profits. Of the four trials that measured treatment satisfaction using the WHO DTSQ, only two used the DTSQc, which specifically measures change in satisfaction from previous treatment. The DTSQ measures only the current level of satisfaction, and has been criticized for not being effective at evaluating change in satisfaction, particularly when baseline level of satisfaction is high *(24)*. A final limitation is that trials only considered TZD, and there are currently no trials that have compared treatment intensification with DPP-4 inhibitors or SGLT-2 inhibitors and insulin.

Conclusion

Due to the progressive nature of type 2 diabetes, insulin often has an important role in maintaining adequate glycaemic control to delay or avoid complications. There are, perhaps unsurprisingly, a number of barriers to insulin initiation. If these can be overcome, there is evidence that treatment satisfaction improves along with the likelihood of reaching glycaemic targets. Many of these barriers

can be overcome through adequate patient education and early introduction of insulin as an important tool in diabetes management.

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Review 2. Patient preferences for type of insulin for type 1 diabetes – a narrative review

Introduction

Diabetes is a chronic disease that has both short-term and long-term impacts on health *(1)*. Poorly controlled glucose levels contribute to accelerated development of diabetic complications, including nephropathy, retinopathy, neuropathy and vascular disease *(2, 3)*. Adherence to treatment is improved when decisions are made together with the patient, with consideration of the patient's preferences and concerns. This, in turn, improves prognosis and quality of life *(4)*. This is particularly important for insulin treatment, where there are multiple barriers to adherence, including embarrassment about injecting in public, and injections interfering with daily activities *(5)*.

Systematic reviews of randomized clinical trials comparing clinical outcomes in patients using analogue and human insulin have been performed. Long-acting insulin analogues have been found to result in statistically significant decreases in HbA1c, and reduced risk of nocturnal and severe hypoglycaemia compared to human insulin *(6)*. Short-acting insulin analogues were compared to human insulin in a recent Cochrane Review which found a minor benefit to short-acting insulin analogues on glucose control in those with type 1 diabetes *(7)*. Patient preferences and treatment satisfaction are increasingly recognized as important treatment goals, and a number of validated measures have been developed to assess these goals *(8).* However, a systematic review of patient preferences has not yet been performed.

This review aims to elicit the differences in adult patient preferences between conventional human insulin and insulin analogues in people with type 1 diabetes.

Methods

A PubMed search was performed using terms related to and variants of "type 1 diabetes", "insulin", "satisfaction", "stated preference", and "decision analysis":

("diabetes mellitus, type 1"[mh] OR "diabetes mellitus, brittle" [tw] OR "brittle diabetes mellitus" [tw] OR "diabetes mellitus, insulin-dependent" [tw] OR "diabetes mellitus, insulin dependent" [tw] OR "insulin-dependent diabetes mellitus" [tw] OR "diabetes mellitus, juvenile onset" [tw] OR "diabetes mellitus, juvenile-onset" [tw] OR "juvenile-onset diabetes mellitus" [tw] OR "diabetes mellitus, ketosis prone" [tw] OR "diabetes mellitus, ketosis-prone" [tw] OR "ketosis-prone diabetes mellitus" [tw] OR "juvenile-onset diabetes" [tw] OR "diabetes, juvenile-onset" [tw] OR "juvenile onset diabetes" [tw] OR "diabetes mellitus, sudden onset" [tw] OR "diabetes mellitus, sudden-onset" [tw] OR "mellitus, sudden-onset diabetes" [tw] OR "sudden-onset diabetes mellitus" [tw] OR "type 1 diabetes mellitus" [tw] OR "Diabetes Mellitus, Insulin-Dependent, 1" [tw] OR "Insulin-Dependent Diabetes Mellitus 1" [tw] OR "Insulin Dependent Diabetes Mellitus 1" [tw] OR "Type 1 Diabetes" [tw] OR "Diabetes, Type 1" [tw] OR "IDDM" [tw] OR "Diabetes, Autoimmune" [tw] OR "Autoimmune Diabetes" [tw] OR "type-1" [tiab] OR "type I" [tiab] OR "insulin dependent" [tiab])))) AND (Treatment[tiab] OR management[tiab] OR pharmaceutical[tiab] OR “drug therapy”[mesh] OR medication[tiab] OR insulin [mesh] OR insulin[tiab])AND ("conjoint analysis" OR "satisfaction" OR "choice model" OR "stated preference" OR "discrete choice" OR DCE OR "decision analysis" OR preferences OR "multi-criteria decision analysis" OR MCDA OR "multi-attribute utility" OR "analytic hierarchy process" OR "trade off" OR "self- explicated" OR "best-worst scaling" OR utilities OR "preference weight" OR “willingness to pay” OR WTP OR “willingness to accept” OR “contingent valuation” OR priorities[tiab] OR valuation[tiab])

Studies were excluded if they focused exclusively on children and adolescents, if there was no English language text, and if no full text was available. Studies investigating inhaled insulin or newer technologies such as an artificial pancreas were excluded, as they are not widely used. Comparisons of preferences between various insulin injection devices (pens, syringes) were also excluded, as both analogue and human insulin is available in vials (classic syringe) and cartridges (pen).

Results

The initial search returned 1017 citations. A total of 16 studies were included in this review (see Table 1). Eight studies compared rapid-acting analogue and short-acting human insulin; four compared long-acting insulin analogue and intermediate-acting human insulin; two compared both rapid- and long-acting analogue with short- and intermediate acting human insulin (one of which involved injections and the other of which involved a continuous subcutaneous insulin infusion); and two compared biphasic human and analogue insulin (one of which involved injections and the other of which involved continuous subcutaneous insulin infusion).

Table 1: Summary of study characteristics*

Study (Year)	Country/Region	Study Type	Insulin Assessed	Blinding (Y/N)
Rapid acting analogue vs. short acting human insulin				
Bott et al. (2003)	German-speaking countries	Randomised, open-label trial	Rapid acting analogue Short acting human	N
DeVries et al. (2003)	Oceania, Europe and South Africa	Randomised, open-label trial	Rapid acting analogue Short acting human	N
Gale et al. (2000)	**United Kingdom**	**Randomised, crossover trial**	**Rapid acting analogue Short acting human**	**Y**
Home et al. (2000)	Europe	Randomised, open-label trial	Rapid acting analogue Short acting human	N
Kotsanos et al. (1997)	Canada, France, Germany, USA	Randomised, crossover trial	Rapid acting analogue Short acting human	N
Melki et al. (1998)	France	Randomised, crossover trial	Rapid acting analogue Short acting human	N
Renner et al. (1999)	Germany	Randomised, crossover trial	Rapid acting analogue Short acting human	N
Tamas et al. (2001)	Belgium, Croatia, Czech Republic, France, Hungary, Israel, Macedonia, Poland, Russian Federation, Slovenia, Spain	Randomised, open-label trial	Rapid acting analogue Short acting human	N
Long acting analogue vs. intermediate acting human insulin				
Chatterjee et al. (2007)	United Kingdom	Randomised, crossover trial	Long acting analogue Intermediate acting human	N

Gallen & Carter (2004)	United Kingdom	Audit	Long acting analogue Intermediate acting human	N
Manini et al. (2007)	Italy	Prospective Cohort	Long acting analogue Intermediate acting human	N
Witthaus et al. (2001)	Europe	Randomised, controlled trial	Long acting analogue Intermediate acting human	N
Biphasic analogue insulin vs. biphasic human insulin, or basal-bolus regimen				
Ashwell et al. (2008)	United Kingdom	Randomised, crossover trial	Rapid acting analogue + long acting analogue Short acting human + intermediate acting human	N
Clements et al. (2008)	Europe	Randomised, open-label trial	Biphasic analogue insulin Biphasic human insulin	N
Machado-Alba et al. (2016)	Colombia	Cross-sectional	Rapid acting analogue + long acting analogue Short acting human + intermediate acting human	N
McNally et al. (2007)	**United Kingdom**	**Randomised, Two-period crossover**	**Biphasic analogue insulin Biphasic human insulin**	**Y**

*Blinded studies are bold

Of the studies comparing rapid-acting analogue and short-acting human insulin, two found no difference in satisfaction scores between groups *(9, 10)*, six found significantly higher satisfaction scores with analogue insulin *(3, 11–15)*, and no studies found higher satisfaction with human insulin (Table 2). Of the studies comparing long-acting analogue and intermediate-acting human insulin, all four found significantly higher satisfaction with analogue insulin (Table 2) *(2, 16–18)*. Of the studies comparing both rapid- and long-acting analogue and both short- and intermediate-acting human insulin, one study found patients preferred the analogue insulin *(19),* and one study found no difference between groups (Table 2) *(20)*.

Table 2: Summary of results*

Study (Year)	N	Assessment Method	Insulin Preferred
Rapid acting analogue vs. short acting human insulin			
Bott et al. (2003)	424	DTSQ Diabetes-Specific Quality of Life Scale (DSQOLS)	Analogue
DeVries et al. (2003)	368	DTSQ	Analogue
Gale et al. (2000)	**93**	**DTSQ Well-Being Questionnaire (W-BQ28) Global Impression Questionnaire**	**No difference**
Home et al. (2000)	1070	DTSQ	Analogue
Kotsanos et al. (1997)	468	Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ)	Analogue
Melki et al. (1998)	39	DTSQ Questionnaire on Stress in Patients with Diabetes (QSD)	Analogue
Renner et al. (1999)	113	DTSQ	Analogue
Tamas et al. (2001)	426	DTSQ Diabetes Health Profile (DHP)	No difference
Long acting analogue vs. intermediate acting human insulin			
Chatterjee et al. (2007)	60	DTSQ ADDQOL	Analogue
Gallen & Carter (2004)	85	DTSQ W-BQ28	Analogue
Manini et al. (2007)	47	Well-Being Enquiry for Diabetics (WED)	Analogue
Witthaus et al. (2001)	517	DTSQ W-BQ28	Analogue
Biphasic analogue insulin vs. biphasic human insulin, or basal-bolus regimen			
Ashwell et al. (2008)	54	WHO Diabetes Treatment Satisfaction Questionnaire (DTSQ) Audit of Diabetes Dependent Quality of Life Questionnaire (ADDQOL)	Analogue
Clements et al. (2008)	667	DTSQ	No difference
Machado-Alba et al. (2016)	238	Diabetes 39 Quality of Life Survey (D-39) European Quality of Life – 5 Dimensions (EQ-5D)	No difference
McNally et al. (2007)	**160**	**DTSQ**	**No difference**

*Blinded studies are bold

Neither of the two studies comparing biphasic human and analogue insulin found a difference in patient satisfaction between groups *(21, 22)*. One of these studies was a double-blind study involving patients with type 2 diabetes *(21)*. Although the focus of this review is on patients with type 1 diabetes, it has been included here given the paucity of evidence from blinded studies.

Of the studies that found a difference in treatment satisfaction between patients using human and analogue insulin, most performed further analyses to determine what treatment characteristics were associated with improved satisfaction.

Treatment or dietary flexibility *(3, 11, 13, 14, 18, 19)*, treatment convenience *(11, 14, 18, 19)*, improvement in overall or diabetes-specific quality of life or well-being *(2, 11, 13, 16, 18)*, reduction in perceived hyperglycaemia *(2, 18, 19)*, reduction in perceived hypoglycaemia *(11, 16, 18)*, improved stability or reduced variability of blood glucose *(11, 16)*, and improved energy levels or reduced fatigue *(2, 16)* were the most-cited factors in the studies seen as contributing to improved treatment satisfaction. Patients in five studies were satisfied to continue with analogue insulin or recommend the treatment to others *(3, 11, 14, 18, 19)*.

Other reported reasons for improved treatment satisfaction were increased physical strength *(11)*, increased protection from long-term complications *(11),* feeling better *(3)*, making daily activities easier *(3),* more balanced glucose control *(3)*, decreased worry and improved emotional status *(16)* , and reduced impact of diabetes on life (on family relationships, role functioning and social network) *(16, 19)*.

Discussion

Overall, 11 of 16 included studies reported that patients preferred analogue insulin over human insulin. This was more pronounced with long- than rapid-acting analogue insulin.

These results should be interpreted with caution, however, as only two of the studies were double-blinded and there is thus a high risk of bias from patient or clinician expectations of treatment efficacy. As a group, patients who agree to participate in studies comparing novel interventions with standard ones are more likely to have a preference for the new treatment than the general population – their feelings about the group to which they have been allocated may therefore influence behaviours and appraisal of the treatment *(23).* It is important to note that neither of the double blinded studies found a significant difference in patient satisfaction between human and analogue insulin.

There is a reluctance to perform double-blinded studies because of concerns about the different recommendations regarding pre-meal injection time for analogue and human insulin. However, multiple studies have found that patients inject at a similar time regardless of the type of insulin used *(11, 24)*. Only 18% of patients in one study reported following the recommended injection interval for human insulin, with the remainder injecting between 0 and 20 minutes before a meal *(24)*. However, blinded studies are not without drawbacks, and do not allow consideration of treatment flexibility and convenience to count towards treatment satisfaction *(19)*.

Only one study considered patient preference and treatment satisfaction as a primary outcome *(11),* with all other studies focusing on clinical end points, with satisfaction as a secondary outcome. This makes it difficult to distinguish between satisfaction arising from characteristics of the treatment

itself, compared to satisfaction with change or improvement in clinical end points such as HbA1c. Two studies found that treatment satisfaction was associated with decline in HbA1c *(11, 13)*, and one study found that patients were more likely to prefer analogue insulin if their baseline HbA1c was above the median in the study population *(16).*

Conclusion

Most studies indicate that patients prefer analogue insulin compared to human insulin. Almost all studies focused on clinical endpoints, with treatment satisfaction as a secondary outcome. Greater focus needs to be placed on the patient experience, as this affects both the perceived burden of diabetes and the likelihood of adherence to recommended treatments and achievement of optimal glycaemic control. Given the high risk of bias in almost all the included studies, higher quality evidence is required before conclusions can be formed. Future studies may consider a number of study designs that are based on the framework of a randomized control trial, but take into account patient preferences to reduce bias based on these expectations, reduce the number of drop outs, and maximise patient motivation to adhere to study protocols *(23).*

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Appendix 9. Hypoglycaemic agents for third-line treatment in type 2 diabetes

Table 1: HbA1c (mean difference in change from baseline with 95% confidence interval)

TZD	0.23 ⊕OOO[2 3] (-0.62, 1.08)	0.12 ⊕OOO[2 3] (-1.12, 1.35)	-0.00 ⊕OOO[2 3] (-0.61, 0.61)	**0.86 ⊕OOO[1 3] (0.25, 1.48)**
	DPP-4 inhibitors	-0.12 ⊕OOO[2 3] (-1.52, 1.29)	-0.23 ⊕OOO[2 3] (-1.03, 0.56)	0.63 ⊕OOO[2 3] (-0.29, 1.55)
		SGLT-2 inhibitors	-0.12 ⊕OOO[2 3] (-1.39, 1.15)	0.75 ⊕OOO[2 3] (-0.32, 1.82)
			Basal insulin	**0.86 ⊕OOO[1 3] (0.18, 1.55)**
				Placebo

[1] Study limitations/risk of bias
[2] Imprecision
[3] Inconsistency (heterogeneity and incoherence)

Table 2: Body weight in kg (mean difference in change from baseline with 95% confidence interval)

TZD	**-0.23 ⊕⊕⊕O[1] (-0.46, 0.00)**	**-0.33 ⊕⊕⊕O[1] (-0.59,-0.07)**	0.16 ⊕⊕OO[1 2] (-0.36,0.68)	**-0.28 ⊕⊕⊕O[1] (-0.48,-0.08)**
	DPP-4 i	-0.09 ⊕⊕⊕O[2] (-0.40,0.91)	0.40 ⊕⊕OO[1 2] (-0.12,0.91)	-0.05 ⊕⊕⊕O[1] (-0.11,0.21)
		SGLT-2 inhibitor	0.49 ⊕⊕OO[1 2] (-0.08,1.06)	0.05 ⊕⊕⊕⊕ (-0.11,0.21)
			Basal insulin	-0.44 ⊕⊕OO[1 2] (-0.99,0.10)
				Placebo

[1] Study limitations/risk of bias
[2] Imprecision

Table 3: CVD mortality (odds ratio with 95% confidence interval)*

TZD	0.73 (0.00,136.2)	3.69 (0.05,257. 8)	2.13 (0.04,108.3)	2.42 (0.15,39.1)
	DPP-4 inhibitors	5.03 (0.24,105.1)	2.90 (0.01,1071)	3.30 (0.04,273.2)
		SGLT-2 inhibitors	0.58 (0.00,91.8)	0.66 (0.03,16.17)
			Basal insulin	1.14 (0.02,57.8)
				Placebo

*Quality not graded due to very high level of imprecision

Summary of judgments

	Favours insulin	Probably favours insulin	Choose either insulin or DPP-4 I, SGLT-2 inhibitors, or glitazones	Probably favours DPP-4 I, SGLT-2 inhibitors, or glitazones	Favours DPP-4 inhibitors, SGLT-2 inhibitors, or glitazones
Problem	☐	☐	X	☐	☐
Desirable effects	☐	☐	X	☐	☐
Undesirable effects	☐	☐	X	☐	☐
Certainty of the evidence of effects	☐	☐	X	☐	☐
Values	☐	☐	☐	X	☐
Resource use	☐	X	☐	☐	☐
Cost-effectiveness	☐	X	☐	☐	☐
Equity	☐	X	☐	☐	☐
Acceptability	☐	☐	X	☐	☐
Feasibility	☐	☐	X	☐	☐
	We recommend insulin over DPP-4 I, SGLT-2 inhibitors, or glitazones	We suggest using insulin over DPP-4 I, SGLT-2 inhibitors, or glitazones	We suggest using either insulin or DPP-4 I, SGLT-2 inhibitors, or glitazones	We suggest using DPP-4 I, SGLT-2 inhibitors, or glitazones over insulin	We recommend DPP-4 I, SGLT-2 inhibitors, or glitazones over insulin
Type of recommendation	X	☐	☐	☐	☐

Appendix 10. Long-acting insulin analogues – summary of findings tables for critical outcomes

Table 1: Summary of findings – HbA1c

Number of participants (number of studies)	Rx vs. Ctrl	Risk of bias	Inconsis-tency[a]	Indirect-ness[b]	Imprecision[c]	Overall quality of evidence	Importance[d]	Rx: % (# events/# n)	Ctrl: % (# events/ # n)	MD (95% CI)[d]
2040 (8 RCT)	Detemir[od/bid] vs. NPH[od/bid]	Serious[e]	Not Serious	Not Serious	Not Serious	Moderate ⊕⊕⊕O	Critical	NA	NA	-0.04 (-0.12,0.03)
1682 (7 RCT)	Glargine[od] vs. NPH[od/bid]	Very serious[f]	Serious[1]	Not Serious	Not Serious	Very Low ⊕OOO	Critical	NA	NA	-0.08 (-0.19,0.02)

[a] Significance level from the Q-test for heterogeneity.
[b] All treatment comparisons and included studies were direct evidence
[c] If CI crossed all three cut-off points -0.25 (appreciable harm), 0.00 (absolute effect), and 0.25 (appreciable benefit), then it was downgraded to 'Very serious' if the number of patients was fewer than 400, otherwise it was classified as 'Serious'. If CI only crossed two of the cut-off points, then it was downgraded to 'Serious'.
[d] HbA1c was classified as a critical outcome.
[e] Study scored unclear risk for allocation concealment and/or selective reporting.
[f] Study scored high risk for allocation concealment and/or selective reporting.

Table 2: Summary of findings – All-cause mortality

Number of participants (Number of studies)	Rx vs. Ctrl	Risk of bias	Inconsis-tency[a]	Indirect-ness[b]	Imprecision[c]	Overall quality of evidence	Impor-tance[d]	Rx: % (# events /# n)	Ctrl: % (# events /# n)	OR (95% CI)
530	Determir[od/bid] vs NPH[od/bid]	Serious[e]	Not Serious	Not Serious	Serious[f]	Low ⊕⊕OO	Critical	1/198 (0.5%)	1/193 (0.5%)	0.97 (0.10–9.44)

[a] Significance level from the Q-test for heterogeneity.

[b] All treatment comparisons and included studies were direct evidence.

[c] If CI crossed all three cut-off points 0.75 (appreciable harm), 1.00 (absolute effect), and 1.25 (appreciable benefit), then it was downgraded as 'Very serious' if the event count was less than 300, otherwise it was classified as 'Serious'. If CI only crossed two of the cut-off points, then it was downgraded to 'Serious'.

[d] Mortality was classified as an important outcome.

[e] Study scored unclear risk for allocation concealment and/or selective reporting.

[f] Wide confidence interval including appreciable benefit and harm.

Table 3: Summary of findings - CVD mortality*

Number of participants (Number of studies)	Rx vs. Ctrl	Importance	Rx: % (# events/# n)	Ctrl: % (# events/# n)	Relative risk (95% CI)
534 (1)	Glargine[od] vs NPH[bid]	Critical	1/270 (0.4%)	0/264 (0%)	0.34 (0.01–8.33)
130 (1)	Detemir[bid] vs NPH[bid]	Critical	0/66 (0%)	1/64 (1.6%)	4.47 (0.24–82.58)

* Quality not graded due to very high level of imprecision

Table 4: Summary of findings – Severe hypoglycaemia

Number of participants (Number of studies)	Rx vs. Ctrl	Risk of bias	Inconsis-tency[a]	Indirect-ness[b]	Imprecision[c]	Overall quality of evidence	Impor-tance[d]	Rx: % (# events /# n)	Ctrl: % (# events /# n)	OR (95% CI)
1876 (6 RCT)	Detemir[od/bid] vs. NPH[od/bid]	Serious[e]	Not Serious	Not Serious	Not Serious	Moderate ⊕⊕⊕O	Critical	127/1086 (11.7%)	132/790 (16.7%)	0.68 (0.52, 0.89)
1415 (4 RCT)	Glargine[od] vs. NPH[od/bid]	Very serious[f]	Not Serious	Not Serious	Serious[i]	Low ⊕⊕OO	Critical	28/702 (4.0%)	70/714 (9.8%)	0.48 (0.21, 1.10)

a Significance level from the Q-test for heterogeneity.
b All treatment comparisons and included studies were direct evidence
c If CI crossed all three cut-off points 0.75 (appreciable harm), 1.00 (absolute effect), and 1.25 (appreciable benefit), then it was downgraded as 'Very serious' if the event count was less than 300, otherwise it was classified as 'Serious'. If CI only crossed two of the cut-off points, then it was downgraded to 'Serious'.
d Severe hypoglycaemia was classified as a critical outcome.
e Study scored unclear risk for allocation concealment and/or selective reporting.
f Study scored high risk for allocation concealment and/or selective reporting
g Study includes absolute effect and appreciable benefit.
h Wide confidence interval including appreciable benefit and harm.
i Study includes absolute effect and appreciable harm and/or benefit.

Table 5: Summary of findings - Visual impairment

Author, Year	Number of participants (Number of studies)	Rx vs. Ctrl	Impor-tance	Rx: % (# events/# n)	Ctrl: % (# events/# n)	OR (95% CI)
Standl (2004)	289 (1 RCT)	Detemir[bid] vs. NPH[bid]	Critical	11% (17/154)	11.2% (15/134)	0.98 (0.47–2.06)

Table 6: Summary of findings – Other critical outcomes

Quality assessment									Summary of findings		
Reference	Number of participants (Number of studies)	Rx vs. Ctrl	Risk of bias	Inconsis-tency	Indirect-ness	Impreci-sion	Overall quality of evidence	Impor-tance	Rx: % (# events/# n)	Ctrl: % (# events/# n)	OR (95% CI)
Progression of nephropathy											
No data								critical			
End-stage renal disease											
No data								critical			
Lower limb amputation											
No data								critical			
Ketoacidosis											
No data								critical			

Appendix 11. Short-acting insulin analogues – summary of findings tables for critical outcomes

(Adapted from Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A, et al. Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus. The Cochrane Library. 2016.)

Outcomes	Regular human insulin	Short-acting insulin analogues	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
HbA1c at end of follow-up (%) Follow-up: 24–52 weeks	The mean HbA1c ranged across control groups from 6.3% to 9.3%	The mean HbA1c in the intervention groups was 0.15% lower (0.2 to 0.1 lower)	-	2608 (9)	⊕⊕OO low[a]	-
All-cause mortality Follow-up: 24–52 weeks	See comment	See comment	See comment	See comment	See comment	Mortality was not a primary outcome in any of the included trials. Overall, there was only one death in six trials that reported on deaths as an adverse event.
Severe hypoglycaemic episodes (heterogeneous definitions of severe hypoglycaemia) Follow-up: 24–52 weeks	166 per 1000	150 per 1000 (124 to 182)	OR 0.89 (0.71 to 1.12)	2459 (7)	⊕OOO very low[b]	
Health-related quality of life Follow-up: 24–52 weeks	See comment	See comment	See comment	See comment	See comment	Health-related quality of life was either only assessed in subpopulations of three trials or insufficiently reported. Overall, there was no clear evidence for a substantial effect of short-acting insulin analogues on this outcome.
Progression of nephropathy	See comment	See comment	See comment	See comment	See comment	Not reported
Visual impairment	See comment	See comment	See comment	See comment	See comment	Not reported
End-stage renal disease	See comment	See comment	See comment	See comment	See comment	Not reported
Lower limb amputation	See comment	See comment	See comment	See comment	See comment	Not reported
Ketoacidosis	See comment	See comment	See comment	See comment	See comment	Not reported

CI: confidence interval; **HbA1c**: glycated haemoglobin A1c; **OR**: odds ratio

[a] Downgraded by two levels because of inconsistencies in reporting of the results and indirectness (HbA1c as a surrogate outcome measure).[b] Downgraded by three levels because of high risk for performance bias, pooling of different outcome definitions and participant populations, and wide confidence intervals being compatible with both beneficial and harmful effects.

Summary of judgments

	Favours human insulin	Probably favours human insulin	Choose either human insulin or insulin analogues	Probably favours insulin analogues	Favours insulin analogues
Problem	☐	X	☐	☐	☐
Desirable effects	☐	☐	X	☐	☐
Undesirable effects	☐	☐	☐	X	☐
Certainty of the evidence of effects	☐	☐	X	☐	☐
Values	☐	☐	X	☐	☐
Resource use	X	☐	☐	☐	☐
Cost-effectiveness	☐	X	☐	☐	☐
Equity	X	☐	☐	☐	☐
Acceptability	☐	☐	X	☐	☐
Feasibility	☐	☐	X	☐	☐
	We recommend human insulin over insulin analogues	We suggest using human insulin over insulin analogues	We suggest using either human insulin or insulin analogues	We suggest using insulin analogues over human insulin	We recommend insulin analogues over human insulin
Type of recommendation	X	☐	☐	☐	☐


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