EFFICACY AND SAFETY OF SWITCHING AMONG HUMAN INSULINS, INSULIN ANALOGUES, AND THEIR BIOSIMILARS IN PATIENTS WITH DIABETES: A SYSTEMATIC REVIEW

REPORT NOVEMBER 2020

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Review questions 1

INSULIN ANALOGUES

In people of all ages under active treatment for diabetes mellitus, either type 1 (T1DM) or type 2 (T2DM), does the switch from one insulin analogue to another and from one insulin analogue to its biosimilar safely compare to non-switching?

The question is extended to the switch from one biosimilar to another.

Evidence on the switch between insulin originators and biosimilars derived from three completed randomised trials, all focused on IGla. Switching from the originators to their biosimilars does not affect safety and efficacy of the treatment. However, these findings are supported by studies with methodological issues (i.e., small sample size, post hoc analysis) that affect our ability to draw firm conclusions.

We are unable to draw any conclusion about the switch between insulin analogues, as we only retrieved one small, randomised trial.

Data in paediatric population is very scarce. Moreover, methodological concerns, small sample size and lack of generalizability (i.e. most studies conducted in Asian patients) make it difficult to assess the efficacy and safety of switching.

If the switch from the insulin originator to its biosimilar, or from one analogue to another, still is a relevant clinical question, larger studies with longer follow-up may be useful to dispel any concern about interchangeability.

Review questions 2

INSULIN ANALOGUES – HUMAN INSULIN

In people of all ages under active treatment for diabetes mellitus, either type 1 (T1DM) or type 2 (T2DM), does the switch from insulin analogues to human insulin or vice versa safely compare to non-switching?

The question is extended to the switch from one biosimilar to another.

Evidence from one randomised and two cohort studies in T2DM patients from low-income settings suggested that the switch back to human insulin from IGla may result in a small increase in the risk of hypoglycaemia events and HbA1c levels. The clinical impact of these findings is uncertain and should be considered in the light of a possible increase in patients' access to less costly interventions.

We are unable to draw any conclusion about the switch from human insulin (NPH) to analogues as only retrieved one small, randomised trial and one historically controlled cohort study.

Data in paediatric population is very scarce. Moreover, methodological concerns, small sample size and lack of generalizability (i.e. most studies conducted in Asian patients) make it difficult to assess the efficacy and safety of switching.

A possible explanation of this scarce number of studies could be that this switch is normally done in clinical practice and does not represent a research priority. If the switch from analogue to human, or vice versa, still is a relevant clinical question, larger studies with longer follow-up may be useful to dispel any concern about interchangeability.

List of abbreviations

A-H: analogue to human insulin

ACCORD: Action to Control Cardiovascular Risk in Diabetes

AE: Adverse Event

DTSQ: Diabetes Treatment Satisfaction Questionnaire

EDS: exception drug status

EMA: European Medicines Agency

EML: Essential Medicines List

FDA: Food and Drug Administration

FUP: follow-up

GRADE: Grades of Recommendation, Assessment, Development and Evaluation Working Group

H-A: human to analogue

HbA1c: Glycated Haemoglobin

HRQL: Health-Related Quality of Life

HTA: Health Technology Assessment

IDeg: Insulin Degludec

IDet: Insulin Detemir

IGla: Glargine Insulins

ILisp: Insulin Lispro

ITR-QoL: Insulin Therapy-Related Quality of Life

LMIC: low-income and middle-income countries

MMAS: Morisky Medication Adherence Scale

MOOD: absolute means of daily differences

NPH: Neutral Protamine Hagedorn

OR: Odds Ratio

PROs: Patient Reported Outcomes

QoL: Quality of Life

RCT: Randomized Clinical Trial

SAE: Serious Adverse Event

SD: Standard Deviation

SE: Standard Error

SMBG: self-monitored blood glucose

SWING: resource utilisation and patient satisfaction associated with SWItchiNG Insulin

T1DM: type 1 diabetes mellitus

T2DM: type 2 diabetes mellitus

TEAE: Treatment Emergent Adverse Event

TEAR: Treatment Emergent Antibody Response

WED: Well-being Enquiry for Diabetes

WHO: World Health Organization

Introduction

Access to insulin a challenge in many countries

Over 70% of global deaths are due to non-communicable diseases, including diabetes, cardiovascular disease, cancer, and respiratory disease.

Diabetes is the seventh leading cause of death and a major cause of costly and debilitating complications such as heart attacks, stroke, kidney failure, blindness and lower limb amputations (WHO 2019). On average, diabetes reduces life expectancy in people aged 40–60 years by 4–10 years and independently increases the risk of death (Chan 2020).
Diabetes prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries. In 2019, 463 million people had diabetes worldwide, with 80% from LMICs.

People with T1DM need insulin to survive and maintain their blood glucose at low enough levels to reduce the risk of common complications such as blindness and kidney failure. People with T2DM need insulin for controlling blood glucose levels to avoid complications when oral medicines become less effective as the illness progresses (WHO Diabetes 2020 and Chan 2020).

Insulins can be broadly classified into conventional and analogues. Conventional insulins - NPH, regular human insulin - are generally less expensive than many types of analogues, but do not mimic the pattern of basal and postprandial endogenous secretion of insulin in the human body (Horvath 2007). Analyses of the body of evidence comparing conventional insulins to analogues suggest small differences in terms of blood glucose control both in T1DM and T2DM. Most of the studies comparing either IDet or IGla to NPH showed no significant difference in HbA1c levels. When a difference in HbA1c between analogues and conventional insulin was observed, its magnitude was smaller than the minimally required difference to establish clinical significance. Analogues appear to perform better than conventional insulins in preventing severe and nocturnal hypoglycaemic events (Wirtz 2016).

The several types of insulin available are also categorized by how quickly they work, when they peak, and how long they last. Action of insulin varies from rapid acting insulins which can start to work almost immediately after being injected, through to long acting insulins which can keep working for up to a day and some can last even longer. In between, there are regular (or short-acting) and intermediate insulins. Mixed or combination insulins contains a pre-mixed combination of either very rapid-acting or short-acting insulin, together with intermediating-acting insulin. Premixed insulins mean less injections and helping to make dosages simpler. In patients with T1DM, basal–bolus insulin regimens (i.e., therapy involving multiple injections a day of long-acting or intermediate-acting insulin and short-acting or rapid-acting insulin at each meal) appear to offer better glycaemic control than twice daily regimens, especially if accompanied by the appropriate education and blood glucose self-monitoring (American Diabetes Association).

Analogues of human or animal insulins (e.g., bovine and porcine sources) are now widely used in many countries, given their usefulness in basal–bolus regimens and effect in minimising the risk of nocturnal hypoglycaemia (Fullerton 2016 and Pedersen-Bjergaard 2014). Nevertheless, human and biosimilar insulins are more affordable insulins in LMICs than insulin analogues. An analysis of the availability, price and affordability of different insulin types in 15 LMICs estimated a median government procurement price of five dollars for human insulins and 33 dollars for long-acting analogues (Ewen 2019). Data collected by the WHO in 2016-2019 from 24 countries in four continents showed that human insulin was available only in 61% of health facilities and analogue insulins in 13%. The data showed that a monthly supply of insulin would cost a worker in Accra, Ghana, the equivalent of 5.5 days of pay per month or 22% of his/her earnings (WHO Diabetes 2020).

Biosimilars of insulin analogues are currently available in several world's regions. The first biosimilar of insulin analogues was authorized in Europe by the EMA in 2017, and in USA by the FDA in 2015 (Allocati 2020). However, compared with the development of other therapeutic biologics, the entry of insulin biosimilars seems to have promoted no large pricing competition. Over 90% of the global insulin volume in 2018 was supplied by three branded insulin manufacturers (Aideed 2019). In the US, biosimilars of insulins were licensed as "follow-on" — a regulatory term that the FDA uses to define non-innovator insulins referencing to originator brands. A new draft guidance from the FDA could facilitate the development of insulin biosimilars, potentially allowing for cheaper near-identical versions of these biologic drugs to be interchanged with their originators (FDA 2019).

In several countries, insulins are provided to patients in public outpatient clinics and bought through national tenders. There is no automated substitution of originator with biosimilars, but there is an increasing interest by national authorities to provide treatment recommendations that include a series of switches. This includes: switching to a biosimilar those patients who are already satisfactorily treated with the originator (non-medical switch, also called substitution, occurring at the point of dispensing by a pharmacist providing a generic/biosimilar medication in place of the prescribed drug) and, in some humanitarian contexts, switching to a human insulin those patients who were treated with an analogue or alternating insulin originator and biosimilar for diabetes following the patent expiration of the analogue originator.

As for other biologic drug classes, the mistrust in efficacy and safety of biosimilars may affect the adoption of biosimilars for the treatment of diabetes, discouraging competition and contributing to a limited reduction of drug prices (Tricco unpublished).

General purpose

The general scope of this report is to collect evidence that reduces uncertainties about the use of biosimilars possibly showing that analogues may replace human insulin and price differences are justified.

This report aims to inform the WHO EML Expert Committee in charge of issuing recommendations on switching from human insulin to insulin analogues and vice versa, as well as interchangeability of insulin analogues and their biosimilar products. Guidance provided by WHO and its Expert Committee will support countries in making evidence-based, timely and informed choices when considering the inclusion of insulin analogues and biosimilar medicines (both human and analogues) on their national lists.

Objective

With an eye to those medicines and indications that were considered by the Expert Committee of Essential Medicines List (WHO EML 2019), this analysis reports a comprehensive review of studies that assessed the efficacy and safety of switching between human insulin and insulin analogues, and vice versa. It is aimed to figure out whether insulin analogues should be listed in the Essential Medicines List, alongside human insulins. In addition, this report is aimed to determine whether biosimilar insulin products should be listed as a replacement for reference products (including originator insulin analogues) when the latter products are not available due to cost or supply issues.

The general framework of the review questions is the following:

Review question 1: In people of all ages under active treatment for diabetes mellitus, either type 1 (T1DM) or type 2 (T2DM), does the switch from one insulin analogue to another and from insulin analogue to its biosimilar safely compare to non-switching?

Review question 2: In people of all ages under active treatment for diabetes mellitus, either type 1 (T1DM) or type 2 (T2DM), does the switch from insulin analogues to human insulin or vice versa safely compare to non-switching?

Both questions are extended to the switch from one biosimilar to another.

Methodology

The methodological approach is defined below. Evidence was collected across patients with T1DM or T2DM and considering both pre-marketing trials and post-marketing drug-utilization data.

The review questions are detailed in the following PICOS:

POPULATION:	People of all ages under active treatment for all insulin dependents
INTERVENTIONs	switch from insulin analogues to human insulin OR switch from human insulin to insulin analogues (both insulin analogues and human insulin can be originator or their biosimilars)
INTERVENTION	switch to another insulin analogue or its biosimilar or switch form biosimilar X to biosimilar Y of the same biologic medicine
COMPARISON	non-switching
MAIN OUTCOMES	reduced HbA1c (efficacy), number of (severe) hypoglycaemia incidences (safety), patient compliance, patient reported outcomes, switch impact cost-effectiveness
STUDY DESIGN	Systematic reviews, RCTs, prospective cohort studies (+retrospective and uncontrolled studies only for paediatric population)

Eligibility criteria

Primary literature

We included RCTs and prospective controlled cohort studies evaluating safety, and/or efficacy of switching from human insulin to insulin analogues and vice versa and switching from insulin originator to its biosimilars and vice versa, or from different biosimilars of the same biologics.

In addition, as we expected to find very few studies including children, we included uncontrolled studies, e.g. single-arm trials and prospective and retrospective cohort studies for both the adult and the paediatric settings.

Secondary and tertiary literature

We included up-to-date systematic reviews and other types of evidence syntheses (e.g., HTA reports, clinical guidelines if developed following a systematic approach) evaluating safety, and/or efficacy of switching from human insulin to insulin analogues and vice versa, and switching from insulin originator to its biosimilars and vice versa, or from different biosimilars of the same biologics. We considered as “up-to-date” those evidence syntheses in which the last date of literature search was not older than two years from the preparation of this report (September 2020). The reference lists of those evidence syntheses that were considered not up to date where also checked to identify possible additional studies.

Search strategies

To retrieve the evidence, we searched MedLine, EMBASE, and The Cochrane Library adapting the search strategies reported in the Appendix 1. We checked the reference lists of the eligible reviews (included and excluded at the full text screening stage). To retrieve information on ongoing or unpublished studies, we searched the main trial registries and the International Clinical Trials Registry Platform. Finally, we searched the main HTA official websites (Appendix 1).

Study selection

Two reviewers independently screened titles and abstracts of the retrieved records to exclude any clearly irrelevant records. The full publications of possibly eligible records were retrieved and checked by two reviewers to confirm eligibility. Any discrepancies were resolved by discussion with a third reviewer.

Data extraction and synthesis

The key features of each review or study were summarised in a tabular format by one reviewer and checked by two other reviewers. Data extracted for each study comprised the following predefined items: (1) author name and year of publication, (2) journal reference, (3) other publications, (4) study design, (5) population, (5) country/es involved in the study, (6) study duration and (7) follow up, (8) sample size, (9) switch from one insulin to another and (10) which is the control and (11) which is the intervention, (12) outcome measure(s), (13) main results and (14) main conclusions, (15) limitation of each study,(16) comments, (17) risk of bias/quality assessment. Data were collected in a predefined spreadsheet (Excel). The effect of switching on drug efficacy and/or safety, was noted for each published study. We planned to extract numeric information on the results and perform meta-analysis, using OR with 95% confidence intervals (95% CIs). However, the data we retrieved could not be pooled in meaningful meta-analysis. Thus, we reported a narrative description of the included studies and their results.

Risk of bias assessment

We assessed the risk of bias of included primary studies by using the criteria of The Cochrane Collaboration: Risk of bias tool for RCT (Higgins 2011) and ROBINS-I for cohort studies (Sterne 2016). Two review authors independently assessed the risk of bias of each study and resolved disagreements by discussion with a third reviewer to reach consensus.

We did not evaluate the certainty of evidence (inconsistency, indirectness, imprecision and publication bias) as defined by the GRADE methodology (GRADE 2019) as planned, given the small number of studies retrieved for each comparison.

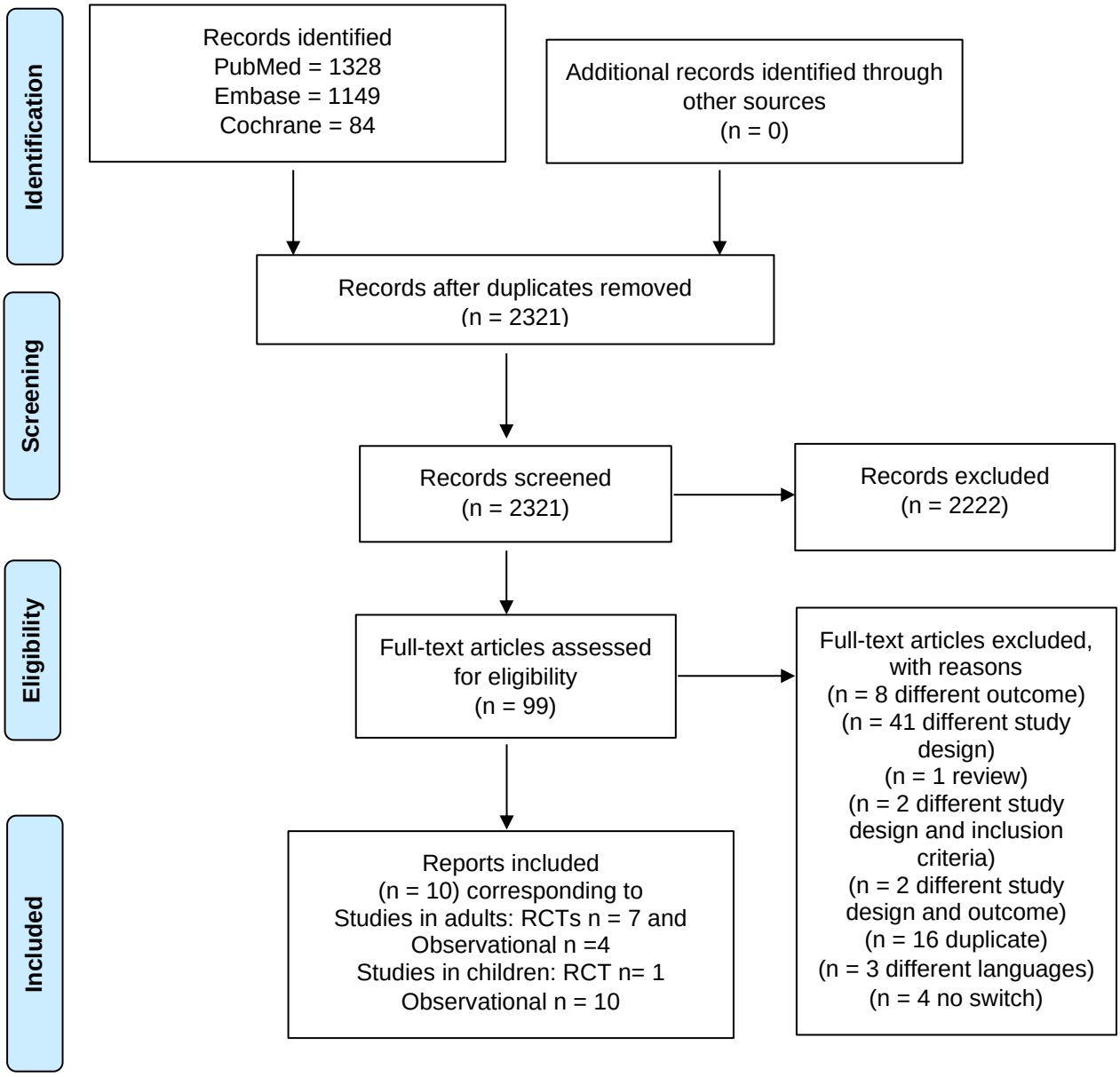
Results

The systematic searches launched in April 2020 resulted in 2321 records, after duplicates were discarded. As shown in Figure 1, 99 records were selected for the full text reading. Appendix 2 reports the list of excluded studies with reasons for exclusion. Overall, we included 22 studies.

From the HTA reports/guideline search (November 2020) did not provide information specific for our review questions.

We reported separately the studies involving adults and paediatric populations.

Figure 1: Flow chart (RCT)



Data on Adults

We identified 10 studies including adults: six RCTs with results (reported in five publications) (Yamada 2007, Berard 2015, Blevins 2020, Yamada 2014, Hadjiyianni 2016), one ongoing with no results (Jprn, Umin 2018) and four cohort studies (Curington 2017, Reaney 2012, Luo 2019, Manini 2007).

Appendix 3 reports the risk of bias assessment of the included studies.

Review question 1: SWITCH BETWEEN INSULIN ANALOGUES

Overall, we found five RCTs with results and one ongoing study exploring the switch between insulin analogues. Four studies - INSTRIDE 3 (Blevins 2020), the post hoc analyses of ELEMENT 1 and 2 trials (Hadjiyianni 2016), and an ongoing Japanese study (Jprn, Umin 2018) - focused on the switch from an insulin analogue originator to its biosimilar (Table 1). One RCT (Yamada 2014) focused on the switch between IDeg and IGla (Table 2).

From insulin analogue originator to biosimilar

Table 1: RCTs exploring the switch from an insulin analogue originator to its biosimilar

1st author (year); reference	Design, setting	Study duration (and follow up)	Population	Total random	Switch	Intervention	Control (non-switchers)	Main outcomes
Blevins, 2020 Diabetes Obes Metab (INSTRIDE 3)	RCT, open-label, USA	36 weeks (safety FUP at week 40)	T1DM	127	Originator to biosimilar (IGla to MYL-1501D)	MYL-1501D (N= 64) Weeks 0-12: MYL-1501D Weeks 12-24: Weeks 24-36: MYL-1501D	IGla US-Lantus (N= 63)	HbA1c; hypoglycaemic events; nocturnal hypoglycaemic events; immunogenicity TEAEs
Hadjiyianni, 2016 (2) Diabetes Obes Metab ELEMENT 2 (NCT01421459)	Randomized, 2-arm; post hoc analysis; Europe, Japan, USA	52 weeks (24 weeks primary efficacy outcomes)	T2DM (subgroup of ELEMENT 2, participants who had prestudy IGla)	298	Originator to biosimilar	Biosimilar IGla (N= 154)	Originator IGla (N= 144)	HbA1c; hypoglycaemia incidence; SAEs, TEAEs, AEs, TEAR
Hadjiyianni, 2016 (1) Diabetes Obes Metab ELEMENT 1 (NCT01421147)	Randomized, 2-arm; post hoc analysis; Europe, Japan, USA	52 weeks (24 weeks primary efficacy outcomes)	T1DM (subgroup of ELEMENT 1, participants who had prestudy IGla)	452	Originator to biosimilar	Biosimilar IGla (N= 218)	Originator IGla (N= 234)	HbA1c; hypoglycaemia incidence; SAEs, TEAEs, AEs, TEAR
Jprn, Umin, 2018	Randomized parallel group study; Japan	6 months (6 months)	T2DM adults aged between 20 and 80 years	Recruiting – target sample size: 100	Originator to biosimilar	Biosimilar IGla	Gla U-300	QoL; hypoglycaemia

Blevins 2020 reported a phase III, multicentre, open-label, randomised, parallel-group study (INSTRIDE 3). The completers of 52-week reference IGla treatment in the INSTRIDE 1 study, were randomised to continue the treatment with the reference insulin originator (n=63) or to switch to its biosimilar (MYL-1501D, n= 64). Participants in the switching arm received MYL-1501D between weeks 0 to 12, then switched again to the reference IGla at weeks 12 to 24 and again to the biosimilar from weeks 24 to 36. The study outcomes were HbA1c changes (defined as mean, SE) and hypoglycaemic events (defined as SMBG $\geq$ 3.9 mmol/l). The study met its primary objective by demonstrating that the change in HbA1c from baseline to week 36 in participants switching between MYL-1501D and reference IGla was statistically equivalent to that observed in patients receiving reference IGla over the 36-week period. Change in HbA1c (Mean, SE) switching group: −0.05 (0.032); reference IGla: −0.06 (0.034) mean difference: 0.01 (95%CI, -0,085 to -0,101. The overall incidence of any hypoglycaemic event was similar between the switching arm and reference IGla arm, with no statistically significant differences overall or at any visit. Both treatment sequences were well tolerated, with no meaningful differences in immunogenicity.
This study demonstrated that participants switching multiple times between reference IGla e and its biosimilar MYL-1501D achieved similar glucose control, with a similar safety profile. The study findings may be limited due to the small sample size and short follow up. Another possible limitation was the open-label design, although the assessment of critical endpoints (HbA1c and immunogenicity) was blinded.

The research letter published by **Hadjiyianni 2016** reported on two post hoc analyses of the ELEMENT-1 and ELEMENT-2 studies, two RCTs comparing IGla biosimilar (LY IGla) to originator (IGla) in patients with TD1M and TD2M respectively (Blevins 2015 and Rosenstock 2015). These analyses included only those participants who have had prior use of IGla or other basal insulin (ELEMENT-1, n=452) or were either insulin naïve or prior users of IGla (ELEMENT-2, n=298). At randomisation, patients transitioned from their pre-study IGla to equivalent doses of LY IGla or IGla. In both studies, the main outcomes included change in HbA1c (%) at 24 weeks, hypoglycaemia and adverse events.
In the ELEMENT-1 post-hoc analysis the HbA1c % was -0.315 (LY IGla) vs -0.419 (IGla) and the least-squares mean difference (last observation carried forward) was -0.104 (95% CI -0.016 to 0.224) at 24 weeks. At 52 weeks, HbA1c % was -0.275 (LY IGla) vs -0.256 (IGla) and the least-squares mean difference was -0.018 (95% CI -0.149 to 0.112). The incidence of total, documented symptomatic, nocturnal hypoglycaemias were similar for both groups, as well as that of severe hypoglycaemias (LY IGla: 5% and IGla: 4%, p=0.816). The median insulin antibody levels were also similar and low (<5%). A small, but statistically significant treatment difference was observed for weight change (mean difference least squares mean percentage change from baseline (<2%); LY IGla: 1.81±0.42; IGla: 0.41±0.39; p=0.035).

In the ELEMENT-2 post-hoc analysis the HbA1c % was -1.017 (LY IGla) vs -1.013 (IGla) and the least-squares mean difference was 0.004 (95% CI -0.193 to 0.185) at 24 weeks. The incidence of total documented symptomatic and nocturnal hypoglycaemias was similar for both groups during the 24-week. No patients reported severe hypoglycaemia. The overall proportion of detectable antibodies TD2M patients in LY IGla group was statistically significantly higher than in IGla-treated patients. The study authors suggested that this had happened because more patients with detectable antibodies had been randomly assigned to the LY IGla group at baseline. However, the median insulin antibody levels were low (<5% binding antibodies) and similar between the two groups at the 24-week-endpoint.

Overall, both analyses suggested that patients who had pre-study IGla treatment, were randomized to LY IGla or continued the originator had similar efficacy and safety outcomes. However, post hoc analyses should be interpreted with caution, as neither study was designed to

prospectively to compare biosimilar and reference glargine. So that, the study results should be not considered sufficient to support interchangeability.

From one insulin analogue to another

Table 2: RCT exploring the switch one insulin analogue to another

1st author (year); reference	Design, setting	Study duration (and follow up)	Population	Total random	Switch	Intervention	Control (non-switchers)	Main outcomes
Yamada, 2014 Diabetology International	Randomized cross-over study; Japan	4 weeks (4 weeks)	T1DM	21	Analogue to analogue Dosage of IDeg equal to the dosage of IGla	IGla-IGla-IDeg (N= 10)	IGla-IDeg-IGla (N= 11)	Steady-state MOOD[1]

[1]Steady-state MOOD: absolute means of daily differences – measures the day-to-day variability of glucose

We retrieved only one RCT that evaluated the switch from one insulin analogue to another, focused on IDeg and insulin glargine.

Yamada 2014 reported a small, 4-week, cross-over study aimed to assess switching from IGla to insulin degludec. The study included 21 Japanese patients with T1DM all treated with IGla at baseline as basal insulin combined with mealtime bolus insulin therapy. Eleven patients in the intervention group switched to IGla treatment and after two weeks switched back to IGla for other two weeks (IGla-IDeg-IGla). The 10 patients in the control group remained under IGla treatment for the first two weeks of the study and then switched to insulin degludec (IGla-IGla-IDeg). The main outcomes of the study were pre-prandial glucose levels, dosage of IGla and degludec, and symptoms, including hypoglycaemia. Day-to-day variability of glucose was evaluated by absolute means of daily differences (MODD). Steady-state MODD was 59.8 ± 39.1 and 46.9 ± 31.6 mg/dl during IGla treatment and IDeg treatment, respectively (p = 0.25). No severe hypoglycaemia occurred during the study period. Data from this study suggested that in T1DM, IGla reduces glucose levels before lunch more effectively than insulin glargine. Results also suggested that the initial dose of IGla should be equal to or lower than the dose of IGla. Dose reduction by 20% or more may be appropriate for patients treated with twice-daily injections of IGla. The potential risk of hypoglycaemia before lunch may be reduced by lowering the morning dose of bolus insulin when switching from IGla to IDeg. Conclusions from this study are highly limited by the small sample size of the trial and the short follow-up.

Review question 2: SWITCH FROM INSULIN ANALOGUES to HUMAN INSULIN (and vice versa)

Overall, two RCTs (Berard 2015, Yamada 2007), and four cohort studies (Luo 2019, Curington 2017, Yamada 2007, Manini 2007) reported data on this review question.

From insulin analogue to human insulin

Three studies analysed the switch from IGla to human insulin, one RCT (Berard 2015, Table 3) and two cohort studies (Lou 2019 and Curington 2017, Table 4). All included T2DM patients in low-income settings, i.e. indigent patients and/or the ones who were not covered by any insurance.

RCT

Table 3: RCT exploring the switch from insulin analogue to human insulin

1st author (year);	Design, setting	Study duration (and follow up)	Population	Total randomised	Switch	Intervention	Control (non-switchers)	Main outcomes
Berard, 2015 (ACCORD)	RCT, open-label, single site; Canada	6 months	T2DM Adults aged between 40 and 79 years (from ACCORD study)	66	Analogues to human (IGla to NPH)	NPH (N= 34)	IGla (N= 32)	Hypoglycaemic events, HbA1c; DTSQ[1]

[1]ITR-QoL: Insulin Therapy-Related Quality of Life; DTSQ: Diabetes Treatment Satisfaction Questionnaire

Berard 2015 reported a single-site, open-label, randomised, 6-month comparative study of 66 patients enrolled in a Canadian site of the ACCORD trial (ACCORD 2008). After the ACCORD study completion participants were referred to their standard diabetes management but, in the province of Manitoba, IGla is available only through private medical insurance coverage or provincial EDS application.
Thus, it was considered important to collect evidence on patient safety when replacing IGla with NPH insulin. Patients who were treated with IGla in the ACCORD trial and were ineligible for financial reimbursement for IGla or unable to afford to pay for this drug were randomised to continue once-daily IGla (n=32) or switch to once-daily NPH (n=34). Data about blood glucose control, hypoglycaemia episodes, and patient satisfaction (DTSQ) were recorded during the 6-month study.
The IGla group showed a significant decrease in HbA1c compared with the NPH group (mean $\pm$ SE, IGla: -0.34%$\pm$0.11; NPH: -0.01%$\pm$0.10), even though neither group achieved the HbA1c target of $\leq$7.0% as recommended by the Canadian Diabetes Association Clinical Practice Guidelines. The authors suggested that the failure to reach this goal may be due to the characteristics of the trial population itself which consisted of individuals between 40 and 79 years of age with A1c > 7.5%. Therefore, given the older ages of the subjects, combined with their previous poor glycaemic control, the study population might have had difficulty in reaching HbA1c target.

The rates of symptomatic (IGla: 37.5 ± 2.2; NPH: 31.1 ± 2.1) and nocturnal (IGla: 4.2$\pm$0.7; NPH 4.4$\pm$0.8) hypoglycaemia did not differ significantly between groups. Conversely, the rates of severe hypoglycaemia showed a meaningful difference. Patients treated with NPH insulin had higher frequencies of severe hypoglycaemia (6.1±0.9) compared to 2.7±0.6 for the IGla group.

The study authors reported that these findings are consistent with that of a meta-analysis which determined that patients treated with IGla had a 46% reduction in severe hypoglycaemic events compared to those treated with NPH insulin (Rosenstock 2005). From a pharmacological point of view the effect may be due to the smooth action profile of IGla compared with NPH insulin that causes a peak in insulin concentration. The consistent delivery of IGla over a long period of time facilitates glycaemic control and decreases the frequency of hypoglycaemia events.
Finally, based on the test scores of the DTSQ, the study found a greater treatment satisfaction in patients treated with IGla compared to those in the NPH insulin arm.
In conclusion, this study suggested that switching from IGla to NPH insulin could double the rate of severe hypoglycaemia and reduce metabolic control, which results in greater treatment satisfaction with IGla. However, the overall risk of bias for this study - judged as high - and the small sample size may hamper these conclusions. The specific setting of the study may affect the generalisability to different contexts.

Cohort studies

Table 4: Cohort studies exploring the switch from insulin analogue to human insulin

1st author (year)	Design &setting	Study duration (and follow up)	Population	Total randomised	Switch	Intervention	Control (non-switchers)	Main outcomes
Luo, 2019	Retrospective cohort study; USA	3 years: Jan 1 2014 to Dec 31, 2016 (729 days)	T2DM	1966	Analogues to human	Human insulin (N= 983)	Insulin analogues (N= 983)	HbA1c; serious hypoglycaemia; hyperglycaemia; cost and utilization outcome
Curington, 2017	Prospective cohort pilot study; USA	24 weeks	T2DM; underserved and financially disadvantaged; adults aged ≥18 years	29	Analogues to human (IGla to NPH)	NPH (N= 14)	Glargine (N= 15)	HbA1c; hypoglycaemic events; MMAS scores[1]

[1]MMAS: Morisky Medication Adherence Scale

Luo 2019 reported a retrospective cohort study using population-level interrupted times series analysis of members participating in a Medicare Advantage and prescription drug plan operating in four US states. The study was aimed to demonstrate that a health plan program that encourages patients to switch from analogue to human insulin could lead to a better change in glycaemic control and avoid the Medicare Part D coverage gap (out-of-pocket prescription drug program). Indeed, the objective of the study was to evaluate the association between implementation of a health plan-based intervention of switching patients from analogue to human insulin and glycaemic control in routine clinical care.

The authors compared Medicare's patients who switched from analogue insulin to human insulin with patients who continued taking insulin analogues. The study assessed overall glycaemic control (HbA1c mean %), serious hypoglycaemia or hyperglycaemia (event rate per 1000 person-years at risk). The author used a closed cohort for this analysis, excluding members (1) who did not have continuous enrolment; (2) whose first prescription claim was for human insulin; (3) who switched back to analogue insulin after switching to human insulin; and (4) who did not have at least 365 days between the first analogue and first human insulin prescription. To control for measured baseline differences between participants who did and who did not switch from analogue to human insulin, a propensity score was developed, adjusting for demographic,

geographic, economic, and clinical measures, including diabetes type, year of first analogue insulin prescription fill, severity of disease, clinical comorbidities, other prescription medicines, and most recent mean HbA1c.

The post-hoc analysis of the study included 983 patients per arm (1966 overall) with insulin prescription between January 1, 2014 and December 31, 2016 with a median follow-up of 729 days.
At the end of the study, the switch from analogue to human insulin was associated with a small increase in population-level HbA1c (switch: 0.11% (95% CI, −0.02% to 0.24%); control: −0.01% (95% CI, −0.15% to 0.13%)) with a difference between-group of 0.12% (95% CI, −0.08% to 0.32%). Moreover, the intervention was not associated with changes in rates of serious hypoglycaemia (estimated rate ratio 0.97 (95% CI, 0.14-6.88) or hyperglycaemia (estimated rate ratio 0.60 (95% CI, 0.25-1.44)).
The author concluded that the observed increase in population level HbA1c may not be clinically important because the value (0.14%) falls within the biological within-patient variation of modern HbA1c assays. Switching was not associated with changes in rates of serious hypoglycaemia or hyperglycaemia.

Curington 2017 reported a 24-week prospective pilot study to assess the clinical outcomes of 29 indigent patients with T2DM after therapy change from IGla to NPH insulin. The purpose of the study was to evaluate the switch from IGla to NPH, which, according to the authors, is a therapeutically equivalent interchange. From the pharmacy prescription database, patients who received IGla or NPH insulin were identified: those patients already using NPH were enrolled in the control group (n=14) and those using IGla were switched to the NPH regimen (n=15) and enrolled in the intervention group.
During the 24 weeks of the study, changes in HbA1c (% mmol/mol) and hypoglycaemic episodes (mg/dl) and adherence were assessed. At the end of the study, 5 patients in the control group and 7 patients in the intervention group discontinued, 9 because entered in the coverage system, 2 (intervention group) were lost at follow-up because patient or physician preferred IGla to NPH. No significant differences in glycaemic control (control: 8.0±1.9%; switch: 7.8±1.6%); hypoglycaemic episodes (control: 0.3±0.7; switch: 0.6±1.1) and adherence (control: 6.7±1.6; switch: 6.5±2.0) between NPH and IGla were reported at follow-up.
Despite the small number of patients and the high limitations in generalizability, the authors sustained that, in this setting, the cost saving of converting IGla to NPH translates in a larger supply of insulin for multiple patients. Unfortunately, cost saving data were not reported in the paper.

From human insulin to insulin analogue

Two studies analysed the switch from human insulin to analogues (IGla or ILisp): one small Japanese RCT enrolling T2DM patients (Yamada 2007, Table 5) and one Italian cohort study enrolling T1DM patients (Manini 2017, Table 6).

Table 5: RCT exploring the switch from human insulin to insulin analogue

1st author (year)	Design, setting	Study duration (and follow up)	Population	Total randomised	Switch	Intervention	Control (non-switchers)	Main outcomes
Yamada, 2007	Open-label, prospective, randomized, Japan	4 months	T2DM	30[1]	Human to analogues (premixed human to ILisp)	50/50 premixed ILisp (N=15)	70/30 premixed human (N=13) 50/50 premixed human (N=2)	HbA1c; ITR-QoL; DTSQ[1]

[1]for both groups doses adjusted every month, if needed

Yamada 2007 reported an open-label RCT aimed to evaluate the clinical effectiveness of switching from premixed human insulin to premixed ILisp. Thirty patients treated with 70/30 human insulin or 50/50 human insulin were enrolled in the study and randomized to switch to 50/50 premixed ILisp (n=15) or continue human insulin (n=15). During the period of the study, if needed, the doses were adjusted every month. The mean dose of insulin required in the analogue group did not change over 4 months. The main outcome of the study was changes in Hb1Ac (mean %). In addition, for the intervention group, the ITR-QoL and DTSQ were used to measure patients' quality of life and satisfaction. After 4 months, there was a significant decrease in HbA1c levels in the ILisp arm (from 7.59±0.44 to 7.24±0.49), and a non-significant decrease in the premixed human insulin (from 7.33±0.58 to 7.29±0.65). However, the two groups (intervention and control) did not differ. Since 50/50 premixed ILisp is known to control postprandial glucose, the improvement in HbA1c seems to be due to the reduction in postprandial glucose.
The study was judged at high risk of bias and enrolled a small number of patients for a short follow-up. Thus, firm conclusions cannot be drawn from this study.

Observational studies

Table 5: RCT exploring the switch from human insulin to insulin analogue

1st author (year)	Design &setting	Study duration (and follow up)	Population	Total randomised	Switch	Intervention	Control (non-switchers)	Main outcomes
Manini, 2007	Cohort study, historically controlled; Italy	6-8 months	T1DM (at least 1 year duration)	87	Human to analogue (NPH to IGla)	IGla (N= 47)	NPH (N= 40)	WED[1]; QoL[2]

[1]WED: Well-being Enquiry for Diabetes
[2]QoL: in this specific case, questionnaire derived from the Diabetes-specific QoL Scale and Diabetes QoL Measure

Manini 2007 reported a national cohort study, with an historical control arm, aimed to assess the beneficial effects of IGla on disease specific HRQL. Forty-seven T1DM patients treated with NPH were switched to IGla. The control was a group of unselected T1DM patients on intensive insulin treatment, previously enrolled on a longitudinal survey of HRQL. The main study outcome was HRQL, measured with the WED, an Italian scale which, according to the authors, addresses the issue of psychological well-being in patient with diabetes and has been extensively validated. The study showed that switching from NPH to IGla improved HRQL, reducing the burden of disease on everyday life. HbA1c levels decreased in the intervention group (mean HbA1c% 0.7%) and did not change in the control group.

Switch in either direction

Reaney 2012 reported the SWING study. This is the only study we retrieved that assessed the switch of patients from human to insulin analogue or from analogue to human insulin (Table 6). This prospective, 12-month, multicentre observational study conducted in nine European countries primarily assessed direct treatment costs when switching from short-acting human insulins to rapid-acting insulin analogues (H-A) or vice versa (A-H) in patients with T2DM. The primary objective of the study was to estimate insulin direct costs (including T2DM medications, treatments or interventions diagnostic tests, self-monitoring blood glucose; contacts with healthcare professionals and diabetes specialists, referral to hospital due to T2DM complications and time

spent in hospitals or outpatient clinics) within the first year following the switch. We report here the clinical outcomes that were also collected and analysed.

Table 6: Details on SWING study

1st author (year)	Design &setting	Study duration (and follow up)	Population	Total randomised	Switch	Intervention	Control (non-switchers)	Main outcomes
Reaney, 2012	Prospective, multicentre, observational, 9 European countries	4 years (12 months)	T2DM; adults aged ≥18 years	2389	Human to analogues Analogues to human	H-A 2203 A-H[1] 186	n.a.	Mean (SD) direct diabetes related costs; HbA1c; hypoglycaemia

[1]H: human insulin; A: insulin analogue; both prescribed in accordance with usual clinical practice; control and intervention formulation are branded

This study was designed on the assumption that most switches would occur from A-H, owing to the contemporary limitations on the reimbursement of insulin analogues. However, among the eligible patients, 2203 underwent H-A switch and 186 A-H.

During the 12 months of follow up, the proportion of patients at or below HbA1c levels of 7% (n/N%) was H-A: 533/1855 (28.7%); A-H: 42/161 (26.1%). The hypoglycaemic events (n/N%) were: H-A: 529/1855 (28.5%); A-H: 46/161 (28.6%).

A small decline in hypoglycaemia occurred over time, but there were no clinically meaningful changes in mean PROs.

In patients switching in either direction between short-acting human insulin analogues, resulted only small changes in mean direct cost (following adjustment for time interval) mean (SD) direct diabetes-related costs (pro-rated to account for variable visit schedules) 6–12 months following switch: H-A 568.6 (590.7); A-H 461.6 (335.0).

However, switches from H-A insulin in this study outnumbered A-H switches by a ratio of 12:1. The authors underlined that regardless of the cause, the difference in the sizes of the H-A and A-H groups should be taken into account when interpreting the data.

Data on Paediatric Population

We identified 11 studies including paediatric populations: one cross-over RCT (Urakami 2017), four prospective cohort studies (Kosteria 2017, Urakami 2015, Elbarbary 2017, Dündar 2009), five retrospective cohort studies (Jinno, 2012, Bosco 2016, Päivärinta 2008, Braun 2008, Predieri 2018 and one single arm study in which it was unclear if the data collection was prospective or retrospective (Xatzipsalti 2017). All studies included patients with T1DM, the majority of the studies assessed the switch between insulin analogues.

The risk of bias of the included RCT (Urakami 2017) is reported in the Appendix 3. All the cohort studies were judged at high risk of bias given their uncontrolled design. Overall, the absence of well-designed RCTs and the methodological flaws of cohort studies (e.g., lack of control arm, small sample size and short follow-up) highly affects the possibility to draw conclusions in the paediatric population.

Review question 1: SWITCH BETWEEN INSULIN ANALOGUES

We found only one cross-over RCT (Urakami 2017) evaluating the efficacy and safety of switching from IGla to IDeg in 18 children (11 males, 7 females; age 11.0 ± 0.5 years). All subjects had been previously treated with IGla once daily at bedtime. After the switch but before the cross over, levels of HbA1c were similar between the two groups. Results from this study suggested that IDeg, injected once at bedtime, may provide similar glycaemic control as IGla while better reducing the risk of nocturnal hypoglycaemia in children with T1DM.

Kosteria 2017 reported a study assessing the switch to IDeg from IDet or IGla. Thirty-three consecutive patients (22 males and 11 females, mean age 11.7 (SD=3.8), range 5-18 years old) with a history of diabetes of 5.5 (SD=2.2), range 1-10 years were included. They were treated with 1 or 2 injections daily injections of IDet or 1 injection of IGla along with short acting analogues and were switched to IDeg without changes in the type of short-acting analogues used. No statistically significant difference was found in terms of HbA1c before and after switching as well as regarding the daily requirement of long-acting insulin.

Urakami 2015 investigated the efficacy and safety of switching to insulin glulisine from other rapid-acting insulin analogues (aspart or lispro) in 26 Japanese children (11 boys and 15 girls, aged 12.5 ± 5.5 years). They were treated with multiple daily injections of insulin or continuous subcutaneous insulin infusion. After the switch, the mean HbA1c decreased as well as the mean frequency of hypoglycaemia, while insulin doses and obesity degree were stable.

Elbarbary 2017 enrolled 43 patients (11.8±1.3 years of age, duration of diabetes 4.6±1.9 years) who started IDeg once daily as basal insulin after at least 1 year on IDet twice daily. Both HbA1c and fasting plasma glucose levels decreased significantly from baseline to 6 months. The authors concluded that switch from IDet to insulin was safe and seemed to improve metabolic control, while reducing the frequency of hypoglycaemia episodes in young people with T1DM.

Xatzipsalti 2017 reported a single arm study aimed to assess the switch from IGla to IDeg in 63 children (30 females, mean age 14.3 (SD=5.0) years; disease duration 7.0 (SD=4.70) years. These patients were treated with multiple injection regimens of IGla U100 as basal insulin and switched to IDeg with the same bolus regimen. HbA1c was similar for the overall study period, i.e., during the 3 month periods before and after switching to IDeg. The authors concluded that the glycaemic control is similar comparing the period before and after-switch, with less hypoglycaemic episodes.

Two retrospective studies provided additional - very poor - evidence on the switch from IGla to IDeg (Predieri 2018, 37 patients mean age 11.7 (SD=4.22)) and from IGla to IDeg (Bosco 2018, 58 patients).

Review question 2: SWITCH FROM INSULIN ANALOGUES to HUMAN INSULIN (and vice versa)

We retrieved only one prospective cohort study assessing the switch from human insulin (NPH) to insulin analogues.

Dundar 2009 included 34 children and adolescents (19 females and 15 males) who had regular controls at Pediatric Endocrinology Department for at least one year. The mean age of the patients and the mean duration of disease were 12.7 ± 3.4 and 5.4 ± 3.0 years, respectively. All patients were under intensive insulin therapy with three doses of insulin aspartate and one dose of NPH for at least six months. At onset of study, patients under NPH treatment were switched to IGla (Group 1, n=19) or IDet (Group 2, n=15) once daily without any change in the rapid acting insulin therapy. At 6 months of treatment, no significant differences were observed between the glargine- and IDet-treated groups with respect to HbA1c. Daily insulin requirements, mean fasting blood glucose levels and frequency of severe hypoglycaemia before and after treatment with IGla and IDet were not significantly different. Both IGla and IDet proved to be safe and well tolerated in children and adolescents.

Two retrospective studies provided additional - very poor - evidence on the switch between NPH and IDet (Braun 2008, 105 patients, age: <12 mean 8.4+2.6; >12 mean 14+1.6) and IGla (Päivärinta 2008, 76 patients, mean age (SD) 12.7 (2.8) year; range 5.1–17.5).

Finally, Jinno 2012 reported a multicentre study on 90 Japanese patients (mean age (SD): 11.9 (3.8) years) previously treated with IGla or NPH who switched to IDet.

Summary of the main findings

We reported a systematic review aimed to evaluate the potential effects of switching among insulins (i.e., originator to its biosimilar, from one analogue to another and from human insulins to insulin analogues and vice versa).

Main Findings
Overall, we were able to retrieve few studies addressing our review questions, and, particularly, a very small number of RCTs. Problems in the methodology (risk of bias, small number of patients) and issues in the generalizability of the results (studies conducted in specific population, short follow-up period) affect our ability to draw firm conclusions. Large studies such as ACCORD, A_1CHIEVE, SWITCH 1 and SWITCH 2, IMPROVE, PREDICTIVE, ELEMENT 1 and ELEMENT 2, REFLECT (Appendix 2), were excluded because not focused on switch, or because their study design or outcome did not meet our inclusion criteria.

Evidence on the switch between insulin originators and biosimilars derived from three completed RCTs, all focused on IGla. All these studies demonstrated equivalent efficacy and similar safety and immunogenicity when switching participants from originator to biosimilar IGla.
However, these findings are supported by studies with a small size (Blevins 2020) and post-hoc analysis (Hadjiyianni 2016). Larger studies with longer follow-up may be useful to dispel any concern about interchangeability.
Data on switching between different analogues are close to zero. We found only one small Japanese RCT that demonstrated that switching from IGla to IDeg decreased blood glucose levels in both T1DM and T2DM and reduced the risk of hypoglycaemia (Yamada 2014). However, these findings should be carefully interpreted due to the small sample size and the possible low generalisability of data in Asian population with diabetes.

We found one RCTs (Berard 2015) and two cohort studies (Lou 2019 and Curington 2017) assessing the switch between insulin analogues to human insulin. All the studies assessed the switch from IGla to NPH and were conducted in North America in low-income settings, including indigent patients and/or the ones who were not covered by any insurance. Also, the study by Reaney 2012 - which was aimed to increase evidence on the clinical and economic implications of switching between human insulin and insulin analogues - found that switches from human insulin to analogue outnumbered the switches from analogues to human insulin in a 12:1.

The economic burden is the main reason justifying the rationale of these studies. Consumption of analogue insulin products increased in all market segments. These products are more expensive than human insulin, thus health expenditures have increased globally, resulting in higher tax burden, insurance premiums or individual household expenditures (Wirtz 2016).

The included studies suggested that the switch back to human insulin may result in a small increase in the risk of hypoglycaemia events and HbA1c levels. For instance, Berard 2015 found that switching from IGla to NPH doubled the rate of severe hypoglycaemia and led to decreased metabolic control. Although limited by a small sample size, these findings are somehow in line with the body of evidence suggesting that the pharmacokinetic profile of IGla results in a decreased frequency of nocturnal hypoglycaemia compared to NPH. For instance, Luo 2019 observed an increase in population-level HbA1c of 0.14%, which falls within the biological within-patient variation of modern HbA1c assays. Moreover, this large cohort study did not show any changes in rates of serious hypoglycaemia or hyperglycaemia.
The shift towards less costly interventions such as human insulin may help increasing the patients' coverage, reaching unserved population in both high-income countries and LMICs. The consistent supply of insulin for multiple patients represents an intervention which is far more cost-effective

than untreated diabetes. So, in some settings, the switch to human insulin may avoid costs due to the progression of the disease or hospitalisation and have an impact not only on the total expenditure but also on the diabetes management at a population level.
To note, these studies were conducted before the introduction of biosimilars of insulin analogues in the US market.

Quite surprisingly, we found only two small studies assessing the switch from human insulin to analogues (IGla or ILisp). Both studies had some important limitations that preclude any firm conclusions on the efficacy and safety of this switch. Moreover, they were published in 2007 and no further studies are available. A possible explanation of this scarce number of studies could be that this switch is normally done in clinical practice and does not represent a research priority.
For instance, the NICE guideline for the management of T2DM reports a recommendation about switching from NPH to IDet or IGlar when hypoglycaemia (dependent or not to HbA1c) occurs and when the patient has difficulties in NPH injections (cannot use the device or need healthcare professional to administer the injection) (NICE 2019) This recommendation is extended to any current and future biosimilar product(s) of insulin glargine that have an appropriate marketing authorisation that allows the use of the biosimilar(s) in the same indication.

Data in paediatric population is very scarce. Moreover, methodological concerns, small sample size and lack of generalizability (i.e. most studies conducted in Asian patients) make it difficult to assess the efficacy and safety of switching.

Concluding remarks

The main question arisen at the end of this review is why we were not able to find more studies that evaluate the switch between insulins. Is this a relevant clinical question or not? Do clinicians switch from the insulin originator to its biosimilar, or from one analogue to another, or from analogue to human, so regularly and confidently that they do not feel the need for equivalence studies providing evidence that supports their practice?

References

ACCORD 2008. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008 Jun 12;358(24):2545-59.

Aideed 2019. Aideed H. Will Biosimilars Solve The Insulin Cost-Conundrum In The U.S.? Available at https://www.biosimilardevelopment.com/doc/will-biosimilars-solve-the-insulin-cost-conundrum-in-the-u-s-0001 Accessed November 2020.

Allocati 2020. Allocati E, Bertele' V, Gerardi C, Garattini S, Banzi R. Clinical evidence supporting the marketing authorisation of biosimilars in Europe. Eur J Clin Pharm. 2020;76, 557–566.

American Diabetes Association Insulin Basics Available at https://www.diabetes.org/diabetes/medication-management/insulin-other-injectables/insulin-basics Accessed October 2020

AMSTAR-2 2017. The new and improved AMSTAR. Available at: https://amstar.ca/Amstar-2.php Accessed October 2020.

Berard 2015. Berard, L. and Cameron, B. and Woo, V. and Stewart, J. Replacing Insulin Glargine with Neutral Protamine Hagedorn (NPH) Insulin in a Subpopulation of Study Subjects in the Action to Control Cardiovascular Risk in Diabetes (ACCORD): Effects on Blood Glucose Levels, hypoglycemia and Patient Satisfaction. Can J Diabetes 39 (2015) 296e301.

Blevins 2015. Blevins TC, Dahl D, Rosenstock J, Ilag LL, Huster WJ, Zielonka JS, et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus®) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT 1 study. Diabetes, Obesity and Metabolism 2015;17: 726–733.

Blevins 2020. Blevins TC, Barve A, Raiter Y, Aubonnet P, Athalye S, Sun B, et al. Efficacy and safety of MYL-1501D versus insulin glargine in people with type 1 diabetes mellitus: Results of the INSTRIDE 3 phase 3 switch study. Diabetes Obes Metab. 2020;22:365–372.

Bosco 2016. Bosco A, Cardani R, Moretti A, Trettene A, Salvatoni A. Ultra long-acting degludec versus long-acting insulin glargine in children and teenagers with type 1 diabetes. Pediatric Diabetes October 2016; 17 (Suppl. 24): 36–164.

Braun 2008. Braun D, Konrad D, Lang-Muritano M, Schoenle E. Improved glycemic control and lower frequency of severe hypoglycaemia with insulin detemir; long-term experience in 105 children and adolescents with type 1 diabetes. Pediatric Diabetes 2008: 9(Part II): 382–387.

Chan 2020. Chan JCN, Lim LL, Wareham NJ, Shaw JE, Orchard TJ, Zhang P, et al. The Lancet Commission on diabetes: using data to transform diabetes care and patient lives. Lancet. 2020; S0140-6736(20)32374-6.

Curington 2017. Curington R, Espel M, Heaton PC, Luder H, Brown B. Clinical outcomes of switching from insulin glargine to NPH insulin in indigent patients at a charitable pharmacy: The Charitable Insulin NPH: Care for the Indigent study. Journal of the American Pharmacists Association 57 2017;S229eS235.

Dündar 2009. Dündar BN, Dündar N, Eren E. Comparison of the efficacy and safety of insulin glargine and insulin detemir with NPH insulin in children and adolescents with type 1 diabetes mellitus receiving intensive insulin therapy. J Clin Res Ped Endo 2009;1(4):181-187.

Elbarbary 2017. Elbarbary NS. Efficacy and safety of switching from insulin detemir to insulin degludec with mealtime insulin aspart in pediatric patients with type 1 diabetes. An observational prospective study. Horm Res Paediatr 2017;88(suppl 1):1–628.

Ewen M 2019. Ewen M, Joosse HJ, Beran D, Laing R. Insulin prices, availability and affordability in 13 LMICs. BMJ Glob Health 2019; 4: e001410.

FDA 2019 Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-immunogenicity-considerations-biosimilar-and-interchangeable-insulin-products Accessed November 2020.

Fullerton 2016. Fullerton B, Siebenhofer A, Jeitler K, et al. Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus. Cochrane Database Syst Rev 2016; 2016: CD012161

GRADE 2019 The GRADE working group. Available at: https://www.gradeworkinggroup.org/ Accessed October 2020.

Hadjiyianni 2016. Hadjiyianni I, Dahl D, Lacaya, LB, Pollom RK, Chang CL, Ilag LL. Efficacy and safety of LY2963016 insulin glargine in patients with type 1 and type 2 diabetes previously treated with insulin glargine. Diabetes, Obesity and Metabolism 18: 425–429, 2016.

Higgins 2011 Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials BMJ 2011;343:d5928.

Horvath 2007. Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J, Kaiser T, Pieber TR, Siebenhofer A. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD005613.

Jinno 2012. Jinno K, Urakami T, Horikawa R, Kawamura T, Kikuchi N, Kikuchi T, et al. Usefulness of insulin detemir in Japanese children with type 1 diabetes. Pediatrics International 2012; 54, 773–779.

Jprn, Umin, 2018. Available at: http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000031415. Accessed September 2020.

Kosteria 2017. Kosteria I, Arkoumani M, Paschou SA, Chrousos GP, Kanaka-Gantenbein C. Efficacy of insulin degludec after switching from insulin detemir or glargine in children with type 1 diabetes. Pediatr Diabetes 2017; 18 (Suppl. 25): 47–137.

Luo 2019. Luo J, Khan N, Manetti T, Rose J, Kaloghlian A, Gadhe B. et al. The clinical and economic effects of switching US Medicare beneficiaries with type 2 diabetes from analog to human insulin. JAMA. 2019;321(4):374-384.

Manini 2007. Manini R, Forlani G, Moscatiello S, Zannoni C, Marzocchi R, Marchesini G. Insulin glargine improves glycemic control and health-related quality of life in type 1 diabetes. Nutrition, Metabolism & Cardiovascular Diseases 2007;17, 493e498.

NICE 2019. NICE Type 2 diabetes in adults: management 2015. Updated 2019. Available at: https://www.nice.org.uk/guidance/ng28 Accessed November 2020.

Päivärinta 2008. Päivärinta, M.; Tapanainen, P.; Veijola, R. Basal insulin switch from NPH to glargine in children and adolescents with type 1 diabetes. Pediatric Diabetes 2008: 9 (Part II): 83–90.

Pedersen-Bjergaard 2014 Pedersen-Bjergaard U, Kristensen PL, Beck-Nielsen H, et al. Effect of insulin analogues on risk of severe hypoglycaemia in patients with type 1 diabetes prone to recurrent severe hypoglycaemia (HypoAna trial): a prospective, randomised, open-label, blinded-endpoint crossover trial. Lancet Diabetes Endocrinol 2014; 2: 553–61.

Predieri 2018. Predieri B, Suprani T, Maltoni G, Graziani V, Bruzzi P, Zucchini S and Iughetti L (2018) Switching From Glargine to Degludec: The Effect on Metabolic Control and Safety During 1-Year of Real Clinical Practice in Children and Adolescents With Type 1 Diabetes. Front. Endocrinol. 9:462.

Reaney 2012. Reaney M, Cypryk K, Tentolouris N, Jecht M, Cleall S, Petzinger U, et al. Resource utilisation and clinical data before and after switching between short-acting human insulin and rapid-acting insulin analogues in patients with type 2 diabetes: the SWING study. Diabetes research and clinical practice 2012; 97:231–241.

Rosenstock 2005. Rosenstock J, Dailey G, Massi-Benedetti M, et al. Reduced hypoglycaemia risk with insulin glargine: A meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005;28:950e5.

Rosenstock 2015 Rosenstock P, Hollander A, Bhargava LL, Ilag, RK, Pollom JS, Zielonka WJ, et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus®) in patients with type 2 diabetes

who were insulin-naïve or previously treated with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). Diabetes, Obesity and Metabolism 2015; 17:734–741.

Sterne 2016 Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355; i4919.

Tricco unpublished. Tricco A, Ashoor HM, Antony J, Bouck Z, Rodrigues M, Pham B, et al. Comparative efficacy and safety of ultra-long-acting, long-acting, intermediate-acting, and biosimilar insulins for type 1 diabetes mellitus: A systematic review and network meta-analysis unpublished

Urakami 2015. Urakami T, Kuwabara R, Habu M, Okuno M, Suzuki J, Takahashi S. Efficacy and safety of switching to insulin glulisine from other rapid-acting insulin analogs in children with type 1 diabetes. J Diabetes Invest 2015; 6: 87–90.

Urakami 2017. Urakami T, Mine Y, Aoki M, Okuno M, Suzuki J. A randomized crossover study of the efficacy and safety of switching from insulin glargine to insulin degludec in children with type 1 diabetes. Endocr J. 2017;64 133-140.

WHO Diabetes 2020 Available at https://www.who.int/news-room/fact-sheets/detail/diabetes/ Accessed October 2020.

WHO 2019 WHO launches first-ever insulin prequalification programme to expand access to life-saving treatment for diabetes. Available at https://www.who.int/news/item/13-11-2019-who-launches-first-ever-insulin-prequalification-programme-to-expand-access-to-life-saving-treatment-for-diabetes/ Accessed October 2020.

WHO EML 2019 WHO Model Lists of Essential Medicines Available at: https://www.who.int/medicines/publications/essentialmedicines/en/ Accessed October 2020.

Wirtz 2016 Wirtz VJ, Knox R, Cao C, Mehrtash H, Posner NW, McClenatha J. Insulin Market Profile. Health Action International. Available at http://haiweb.org/wp-content/uploads/2016/04/ACCISS_Insulin-Market-Profile_FINAL.pdf.

Xatzipsalti 2017. Xatzipsalti M, Mentesidou L, Kouloufakou-Gratsia K, Stamoyannou L, Delis D, Vazeou A. Experience of insulin Degludec in everyday clinical practice in children and adolescents with type 1 diabetes (T1D). Pediatr Diabetes October 2017; 18 (Suppl. 25): 47–137.

Yamada 2007. Yamada S, Watanabe M, Kitaoka A, Shiono K, Atsuda K, Tsukamoto Y, et al. Switching from premixed human insulin to premixed insulin lispro: a prospective study comparing the effects on glucose control and quality of life. DOI:10.2169/internalmedicine.46.0236.

Yamada 2014. Yamada K, Nakayama H, Sato S, Tajiri Y, Kaku H, Tokubuchi I, et al. A randomized crossover study of the efficacy and safety of switching from insulin glargine to insulin degludec among patients with type 1 diabetes. Diabetol Int 2014;5:74–77.

Appendix 1: search strategy insulins

PubMed 23.04.20

N= 1326

"insulin diabet*"[tiab] OR "insulin dependent"[tiab] OR "diabetes mellitus"[tiab] OR “type 1 diabetes mellitus”[tiab] OR “type 2 diabetes mellitus”[tiab] OR hyperglycemi*[tiab] OR "gestational diabetes"[tiab] OR "Diabetes Mellitus"[Mesh] OR "Hyperglycemia"[Mesh] OR "Diabetes, Gestational”[Mesh]

AND

“Drug Substitution”[Mesh] OR Switch[tiab] OR switching[tiab] OR switched[tiab] OR switches[tiab] OR interchange*[tiab] OR interchanging[tiab] OR interchangeability[tiab] OR “inter change*”[tiab] OR “inter changing”[tiab] OR switchability[tiab] OR “Biosimilar pharmaceuticals"[Mesh] OR biosimilar*[tiab] OR "similar biological medicine*"[tiab] OR "similar biological medicinal product*"[tiab] OR “follow on biologic”[tiab] OR “subsequent entry biologic*”[tiab] OR “subsequent entry biological*”[tiab]

AND

“insulin glargine” OR “insulin detemir” OR “insulin degludec” OR "long acting insulin"[tiab] OR “insulin lispro” OR “insulin aspart” OR “insulin glulisine” OR "rapid acting insulin"[tiab] OR "regular insulin"[tiab] OR "isophane insulin" OR "short acting human insulin"[tiab] OR “nph insulin” OR "intermediate insulin"[tiab] OR "biphasic insulin"[tiab] OR "human insulin" OR “insulin analogue*” OR "Insulin/analogs and derivatives"[Mesh] OR "Insulin Detemir"[Mesh] OR "insulin degludec" [Supplementary Concept] OR "Insulin, Long-Acting"[Mesh] OR "Insulin, Short-Acting"[Mesh] OR "Insulin, Regular, Human"[Mesh] OR "Insulin, Isophane"[Mesh] OR "Insulin Glargine"[Mesh] OR "Insulin Lispro"[Mesh]) OR "Insulin Aspart"[Mesh] OR "insulin glulisine" [Supplementary Concept] OR "Isophane Insulin, Human"[Mesh] OR "Biphasic Insulins”[Mesh]

EMBASE 28.04.2020

N= 1144

('diabetes mellitus'/exp/mj OR 'diabetes mellitus' OR 'insulin dependent diabetes mellitus'/exp/mj OR 'insulin dependent diabetes mellitus' OR 'insulin dependent diabetes mellitus':ti,ab OR 'diabetes mellitus':ti,ab OR 'non insulin dependent diabetes mellitus':ti,ab OR 'non insulin dependent diabetes mellitus'/exp/mj OR 'non insulin dependent diabetes mellitus' OR 'hyperglycemia':ti,ab OR 'hyperglycemia'/exp/mj OR 'hyperglycemia' OR 'pregnancy diabetes mellitus':ti,ab OR 'pregnancy diabetes mellitus'/exp/mj OR 'pregnancy diabetes mellitus’)

AND ('drug substitution':ti,ab OR 'drug substitution'/exp/mj OR 'switch':ti,ab OR 'switch'/exp OR 'switching'/exp OR 'switching':ti,ab OR 'interchangeability':ti,ab OR 'biosimilar drug' OR 'biosimilar agent' OR 'biosimilar agent’/exp/mj)

AND ('long acting insulin'/exp/mj OR 'long acting insulin':ti,ab OR 'short acting insulin'/exp/mj OR 'short acting insulin':ti,ab OR 'insulin glargine'/exp/mj OR 'insulin glargine':ti,ab OR 'insulin detemir'/exp/mj OR 'insulin detemir':ti,ab OR 'insulin degludec'/exp/mj OR 'insulin degludec':ti,ab OR 'insulin lispro'/exp/mj OR 'insulin lispro':ti,ab OR 'insulin aspart'/exp/mj OR 'insulin aspart':ti,ab OR 'insulin glulisine'/exp/mj OR 'insulin glulisine':ti,ab OR 'pig insulin'/exp/mj OR 'pig insulin':ti,ab OR 'isophane insulin'/exp/mj OR 'isophane insulin':ti,ab OR 'biphasic insulin'/exp/mj OR 'biphasic insulin':ti,ab OR 'human insulin'/exp/mj OR 'human insulin':ti,ab OR 'insulin derivative'/exp/mj OR 'insulin derivative':ti,ab) AND [embase]/lim

Cochrane Library 28.04.2020

N= 84

#1 (“Drug Substitution” OR “Switch” OR “switching” OR “switched” OR “switches” OR “substitute” OR “substitutes” OR “substitution” OR “substituted” OR “substituting” OR “interchange” OR “interchanges” OR “interchanged” OR “interchanging” OR “interchangeability” OR “interchangeable” OR “inter-change” OR “inter-changes” OR “inter-changed” OR “inter-changing” OR “inter-changeability” OR “inter-changeable” OR “inter change” OR “inter changes” OR “inter changed” OR “inter changing” OR “inter changeability” OR “inter changeable” OR “switchability”)

#2 MeSH descriptor: [Drug Substitution] explode all trees

#3 #1 OR #2

#4 (“Biosimilar pharmaceuticals" OR "biosimilar" OR "biosimilars" OR “biosimilarity” OR "similar biological medicine" OR "similar biological medicines" OR "similar biological medicinal product" OR "similar biological medicinal products" OR “follow on biologic" OR “follow on biologics” OR “Subsequent entry biological” OR “Subsequent-entry biological” OR “Subsequent entry biologicals” OR “Subsequent-entry biologicals”)

#5 MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees

#6 #4 OR #5

#7 #3 OR #5

#8 "diabetes mellitus"

#9 MeSH descriptor: [Diabetes Mellitus] this term only

#10 "type 1 diabetes mellitus"

#11 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees

#12 "type 2 diabetes mellitus"

#13 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees

#14 hyperglycaemia

#15 MeSH descriptor: [Hyperglycemia] this term only

#16 "gestational diabetes"

#17 MeSH descriptor: [Diabetes, Gestational] this term only

#18 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#19 "insulin glargine"

#20 "insulin detemir"

#21 "insulin degludec"

#22 "insulin long acting"

#23 MeSH descriptor: [Insulin, Long-Acting] explode all trees

#24 "insulin lispro"

#25 "insulin aspart"

#26 "insulin glulisine"

#27 "rapid acting insulin"

#28 "short acting insulin"

#29 MeSH descriptor: [Insulin, Short-Acting] this term only

#30 "regular insulin"

#31 "isophane insulin"

#32 "short acting human insulin"

#33 "nph insulin"

#34 "intermediate insulin"

#35 "biphasic insulin"

#36 MeSH descriptor: [Insulin, Isophane] this term only

#37 "human insulin"

#38 "insulin analogue"

#39 #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38

#40 #7 AND #18 AND #39

#41 "accession number" near pubmed

#42 "accession number" near EMBASE

#43 #41 OR #42

#44 #40 NOT #43

HTA reports search (November 2020)

https://www.ahrq.gov/;

https://www.cadth.ca;

https://eunethta.eu/rapid-reas/;

https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance;

https://www1.health.gov.au/internet/hta/publishing.nsf/Content/commonwealth-1; looking at the last five years.

Keywords: biosimilar insulin, human insulin, insulin analogue, switch, switch insulin.

Appendix 2: list of excluded studies

N	Reference	Reason for exclusion
1	**Lane 2017** Lane, W. and Bailey, T. S. and Gerety, G. and Gumprecht, J. and Philis-Tsimikas, A. and Hansen, C. T. and Nielsen, T. S. S. and Warren, M. Effect of Insulin Degludec vs Insulin Glargine U100 on hypoglycaemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. Jama. 2017;318 33-44.	different outcome
2	**Galasso 2016** Galasso S. and Facchinetti, A. and Bonora, B. M. and Mariano, V. and Boscari, F. and Cipponeri, E. and Maran, A. and Avogaro, A. and Fadini, G. P. and Bruttomesso, D. Switching from twice-daily glargine or detemir to once-daily degludec improves glucose control in type 1 diabetes. An observational study. Nutrition, Metabolism & Cardiovascular Diseases. 2016:26 1112-1119.	different study design
3	**Shimoda 2016** Shimoda, S. and Sato, M. and Sekigami, T. and Motoshima, H. and Yoshimura, R. and Fukuda, K. and Matsuo, Y. and Noda, H. and Okubo, M. and Ichimori, S. and Fujisawa, K. and Fukunaga, M. and Araki, E. A 1-year, prospective, observational study of Japanese outpatients with type 1 and type 2 diabetes switching from insulin glargine or detemir to insulin degludec in basal-bolus insulin therapy (Kumamoto Insulin Degludec Observational study). J Diabetes Investig 2016; 7: 703–710.	different study design
4	**El Naggar 2016** El Naggar N. and Kalra, S. Switching from Biphasic Human Insulin to Premix Insulin Analogs: A Review of the Evidence Regarding Quality of Life and Adherence to Medication in Type 2 Diabetes Mellitus. Adv Ther (2016) 33:2091–2109.	Review – no studies that could be included
5	**Hussein 2013** Hussein Z. and Lim-Abrahan, M. A. and Jain, A. B. and Goh, S. Y. and Soewondo, P. Switching from biphasic human insulin to biphasic insulin aspart 30 in type 2 diabetes: results from the ASEAN subgroup of the A_1chieve study. Diabetes research and clinical practice 100S1 (2013) S24−S29 S25.	different study design
6	**Akturk 2018** Akturk, H. K. and Shah, V. N. Severe hypoglycaemia in Adults With Type 1 Diabetes After Switching to Insulin Degludec. Journal of Diabetes Science and Technology 2018, Vol. 12(3) 733–734.	different study design
7	**Wang 2014** Wang, Y. B. and Wang, S. and Bai, R. and Du, J. L. and Xing, Q. and Ba, Y. and Yang, Y. and Zhang, X. Y. and Shi, C. H. and Yao, J. J. Efficacy of switching from premixed insulin to insulin glargine regimen in Type 2 diabetes mellitus patients with different islet functions. Mol Med Rep 10: 1096-1102, 2014.	No switch
8	**Bohn 2017** Bohn, B. and Zimmermann, A. and Wagner, C. and Merger, S. and Dunstheimer, D. and Kopp, F. and Gollisch, K. and Zindel, V. and Holl, R. W. Real-life experience of patients starting insulin degludec. A multicenter analysis of 1064 subjects from the German/Austrian DPV registry. diabetes research and clinical practice 129(2017)52 –58.	different study design
9	**Schiel 2008** Schiel, R. and Müller, U. A. Efficacy and treatment satisfaction of once-daily insulin glargine plus one or two oral antidiabetic agents versus continuing premixed human insulin in patients with type 2 diabetes previously on long-term conventional insulin therapy: the Switch pilot study. Exp Clin Endocrinol Diabetes 2008; 116: 58 – 64.	different study outcomes
10	**Valensi 2009** Valensi, P. and Benroubi, M. and Borzi, V. and Gumprecht, J. and Kawamori, R. and Shaban, J. and Shah, S. and Shestakova, M. and Wenying, Y. Initiating insulin therapy with, or switching existing insulin therapy to, biphasic insulin aspart 30/70 (NovoMix 30) in routine care: safety and effectiveness in patients with type 2 diabetes in the IMPROVE observational study. Int J Clin Pract, March 2009, 63, 3, 522–531.	different study design
11	**Yenigun 2009** Yenigun, M. and Honka, M. Switching patients from insulin glargine-based basal-bolus regimens to a once daily insulin detemir-based basal-bolus regimen: results from a subgroup of the PREDICTIVE study. Int J Clin Pract, March 2009, 63, 3, 425–432.	different inclusion criteria different study design
12	**Hamasaki 2014** Hamasaki, H. and Yanai, H. Switching from insulin glargine to insulin degludec reduced HbA1c, daily insulin doses and anti-insulin antibody in anti-insulin antibody-positive subjects with type 1 diabetes. Diabetes & Metabolism 40 (2014) 481–482.	different study design

13	**Hermansen 2009** Hermansen, K. and Dornhorst, A. and Sreenan, S. Observational, open-label study of type 1 and type 2 diabetes patients switching from human insulin to insulin analogue basal-bolus regimens: insights from the PREDICTIVE study. Current Medical Research & Opinion Vol. 25, No. 11, 2009, 2601–2608.	different inclusion criteria different study design
14	**Bolli 2009** Bolli, G. B. and Songini, M. and Trovati, M. and Del Prato, S. and Ghirlanda, G. and Cordera, R. and Trevisan, R. and Riccardi, G. and Noacco, C. Lower fasting blood glucose, glucose variability and nocturnal hypoglycaemia with glargine vs NPH basal insulin in subjects with Type 1 diabetes. Nutrition, Metabolism & Cardiovascular Diseases (2009) 19, 571e579.	No switch
15	**Campbell 1998** Campbell, R. K. and Sclar, D. A. and Robison, L. M. and Stowers, J. K. and Ferguson, J. C. and Trippe, B. S. and Kayne, D. M. Impact on clinical status and quality of life of switching from regular insulin to insulin lispro among patients using insulin pumps. The Diabetes Educator Jan/Feb 1998. Vol 24, No 1.	different study design
16	**Kusunoki 2013** Kusunoki, Y. and Katsuno, T. and Miyakoshi, K. and Ikawa, T. and Nakae, R. and Ochi, F. and Tokuda, M. and Akagami, T. and Murai, K. and Miuchi, M. and Hamaguchi, T. and Miyagawa, J. and Namba, M. Effects of switching from insulin glargine or detemir to insulin degludec in patients with type 1 diabetes mellitus. Diabetes Ther (2013) 4:461–472.	different study design
17	**Cho 2019** Cho, K. Y. and Nakamura, A. and Oba-Yamamoto, C. and Tsuchida, K. and Yanagiya, S. and Manda, N. and Kurihara, Y. and Aoki, S. and Atsumi, T. and Miyoshi, H. Switching to Once-Daily Insulin Degludec/Insulin Aspart from Basal Insulin Improves Postprandial Glycemia in Patients with Type 2 Diabetes Mellitus: Randomized Controlled Trial. Diabetes Metab J 2019.	different study outcomes
18	**Wolnik 2020** Wolnik, B. and Wiza, D. and Szczepanik, T. and Syta, A. and Klupa, T. Switching from Neutral Protamine Hagedorn Insulin to Insulin Glargine 300 U/mL Improves Glycaemic Control and Reduces Hypoglycaemia Risk: Results of a Multicentre, Prospective, Observational Study. Journal of Diabetes Research Volume 2020, Article ID 8751348, 8 pages.	different study design different study outcome
19	**Okada 2015** Okada, M. and Nishigami, J. and Yamaaki, N. and Furukawa, K. and Ohyama, K. and Shimada, T. and Sai, Y. Effect of switching basal insulin regimen to degludec on quality of life in Japanese patients with type 1 and type 2 diabetes mellitus. Okada et al. Journal of Pharmaceutical Health Care and Sciences (2015) 1:26.	different study design
20	**Testa 2012** Testa, M. A. and Gill, J. and Su, M. and Turner, R. R. and Blonde, L. and Simonson, D. C. Comparative effectiveness of basal-bolus versus premix analog insulin on glycemic variability and patient-centered outcomes during insulin intensification in type 1 and type 2 diabetes: a randomized, controlled, crossover trial. J Clin Endocrinol Metab, October 2012, 97(10):3504–3514.	different study design
21	**Takeishi 2020** Takeishi, S. and Tsuboi, H. Comparison of effects when switching long-acting insulin: Randomised crossover study. DIABETES TECHNOLOGY & THERAPEUTICS Volume 22, Supplement 1, 2020 281/Abstract ID 54.	different study design
22	**Gourdy 2020** Gourdy, P. and Bahloul, A. and Boultif, Z. and Gouet, D. and Guerci, B. Efficacy and Safety of Switching Patients Inadequately Controlled on Basal Insulin to Insulin Glargine 300 U/mL: The TRANSITION 2 Study. Diabetes Ther (2020) 11:147–159.	different study design
23	**Jendle 2019** Jendle, J. and Thunander, M. and Ekman, B. and Sjöberg, S. and Ericsson, Å and da Rocha Fernandes, J. and Mårdby, A. C. and Malkin, S. J. P. and Hunt, B. PDB23 Switching to insulin degludec is a cost-saving therapy for patients with type 1 and type 2 diabetes in the Swedish based on real world data. Value in Health – November 2019 S575.	different study design
24	**Sahay 2019** Sahay, R. and De Valk, H. W. and Feher, M. and Hansen, T. K. and Jendle, J. and Merchante, Á and Koefoed, M. M. and Rizi, E. P. and Zimmermann, E. and Fadini, G. P. Switching to insulin degludec from other basal insulins reduces rates of hypoglycaemia across patient subgroups in routine clinical care: The ReFLeCT study. Indian Journal of Endocrinology and Metabolism 2019 23:7 Supplement (S12 - S13).	different study design
25	**Heller 2019** Heller, S. R. and DeVries, J. H. and Wysham, C. and Hansen, C. T. and Hansen, M. V. and Frier, B. M. Lower rates of hypoglycaemia in older individuals with type 2 diabetes using insulin degludec versus insulin glargine U100: Results from SWITCH 2. Diabetes Obes Metab. 2019;21:1634–1641.	different study design
26	**De Valk 2019** De Valk, H. W. and Feher, M. and Hansen, T. K. and Jendle, J. H. and Merchante, Á and Koefoed, M. M. and Rizi, E. P. and Zimmermann, E. and Fadini, G. P. Switching to insulin degludec from other basal insulins reduces rates of hypoglycaemia across patient subgroups in routine clinical care: The reflect study. VALUE IN HEALTH - NOVEMBER 2019.	duplicate

27	**Fadini 2019** Fadini, G. P. and Feher, M. and Hansen, T. K. and De Valk, H. W. and Koefoed, M. M. and Wolden, M. and Zimmermann, E. and Jendle, J. Reduced rates of overall hypoglycaemia in patients with type 1 diabetes after switching to insulin degludec: A european, multinational, multicentre, prospective, observational study (ReFLeCT). J Clin Endocrinol Metab, December 2019, 104(12):5977–5990.	different study design
28	**Bosnyak 2018** Bosnyak, Z. and Meneghini, L. and Zhou, F. L. and Berria, R. and Jimenez, J. and Bailey, T. hypoglycaemia risk associated with basal insulin use in type 2 diabetes (T2DM): The LIGHTNING study. ATTD, February 14–17, 2018Vienna, AustriaScan.	different study outcome different study design
29	**Langer 2019** Langer, J. and Wolden, M. L. and Shimoda, S. and Sato, M. and Araki, E. Short-term cost-effectiveness of switching to insulin degludec in Japanese patients with type 2 diabetes receiving basal-bolus therapy. Diabetes Ther (2019) 10:1347–1356.	different study design
30	**Escalada 2018** Escalada, J**.** and Bonnet, F. and Wu, J. and Bonnemaire, M. and Gupta, S. and Cambron-Mellot, M. J. and Nicholls, C. and Müller-Wieland, D. Chart review analysis of insulin glargine 300 and insulin glargine 100 use in France, Spain, and Germany. Value in Heath (2018) S1eS481.	different study design
31	**Freemantle 2018** Freemantle, N. and Gourdy, P. and Mauricio, D. and Müller-Wieland, D. and Bonadonna, R. C. and Pedrazzini, L. and Bigot, G. and Mauquoi, C. and Bonnemaire, M. Exploring clinical outcomes in diverse populations with uncontrolled type 2 diabetes switching to insulin Gla-300: First-stage analysis of the pooled European Gla-300 studies (REALI). Diabetologia (2018) 61 (Suppl 1):S1–S620.	different study design
32	**Pedersen-Bjergaard 2020.** Pedersen-Bjergaard, U, and Philis-Tsimikas, A. and Lane, W. and Wysham, C. H. and Bardtrum, L. and Østoft, S. H. and Heller, S. Relationship between A1C and hypoglycaemia risk in individual patients comparing insulin degludec with insulin glargine U100. Diabetes 2020;22:779–787.	duplicate
33	**Guarnotta.** Guarnotta, V. and Di Bella, G. and Pillitteri, G. and Ciresi, A. and Giordano, C. Improved cardiovascular and cardiometabolic risk in patients with type 1 diabetes and autoimmune polyglandular syndrome switched from glargine to degludec due to hypoglycaemic variability. Front. Endocrinol. 9:428.	different study design
34	**Luo 2018** Luo, J. and Khan, N. F. and Manetti, T. and Rose, J. J. and Kaloghlian, A. and Gadhe, B. and Jain, S. H. and Gagne, J. and Kesselheim, A. The clinical and economic effects of switching medicare beneficiaries with type 2 diabetes from analogue to human insulin. 2018 Diabetes	duplicate
35	**Heller 2018** Heller, S. R. and Devries, J. H. and Wysham, C. H. and Hansen, C. T. and Hansen, M. V. and Frier, B. M. Insulin degludec has lower hypoglycaemia risk than insulin glargine U100 in older people with type 2 diabetes. 2018 Diabetes	duplicate
36	**Philis-Tsimikas 2020** Philis-Tsimikas, A. and Lane, W. and Pedersen-Bjergaard, U. and Wysham, C. H. and Bardtrum, L. and Østoft, S. H. and Heller, S. Relationship between A1C and hypoglycaemia risk in individual patients comparing insulin degludec with insulin glargine U100. Diabetes Obes Metab. 2020;22:779–787.	different study outcome
37	**Pscherer 2018** Pscherer, S. and Fritsche, A. and Anderten, H. and Pegelow, K. and Seufert, J. and Pfohl, M. Switching to insulin glargine 300 u/ml (GLA-300) after failure of advanced insulin therapy (IT) with other basal insulins (BI) in patients (PTS) with type 2 diabetes (T2DM) improved glycemic control. Diabetes 2018 67 Supplement 1 (A597-).	different study design
38	**Bonabello 2018** Bonabello, L. A. and Maggi, D. and Fiorini, S. and Tozzo, V. and Cordera, R. Switching from Glargine to Degludec is not associated with an overt change in glucose control in a cohort of patients with type 1 diabetes: a CGM analysis. Acta Diabetologica (2018) 55:637–639.	different study design
39	**Lane 2018** Lane, W. and Bailey, T. S. and Gerety, G. and Gumprecht, J. and Philis-Tsimikas, A. and Hansen, C. T. and Nielsen, T. S. S. and Warren, M. L. and Fulcher, G. R. SWITCH 1: reduced risk of hypoglycaemia with insulin degludec vs insulin glargine U100 in patients with type 1 diabetes – a randomized, double-blind, crossover trial. 2018 Clinical Endocrinology	duplicate
40	**Nagai 2018** Nagai, Y. and Nishine, A. and Hashimoto, E. and Nakayama, T. and Sasaki, Y. and Murakami, M. and Ishii, S. and Kato, H. and Tanaka, Y. Efficacy and safety of switching from basal insulin to once-daily insulin degludec/insulin aspart in Japanese patients with inadequately	different study design

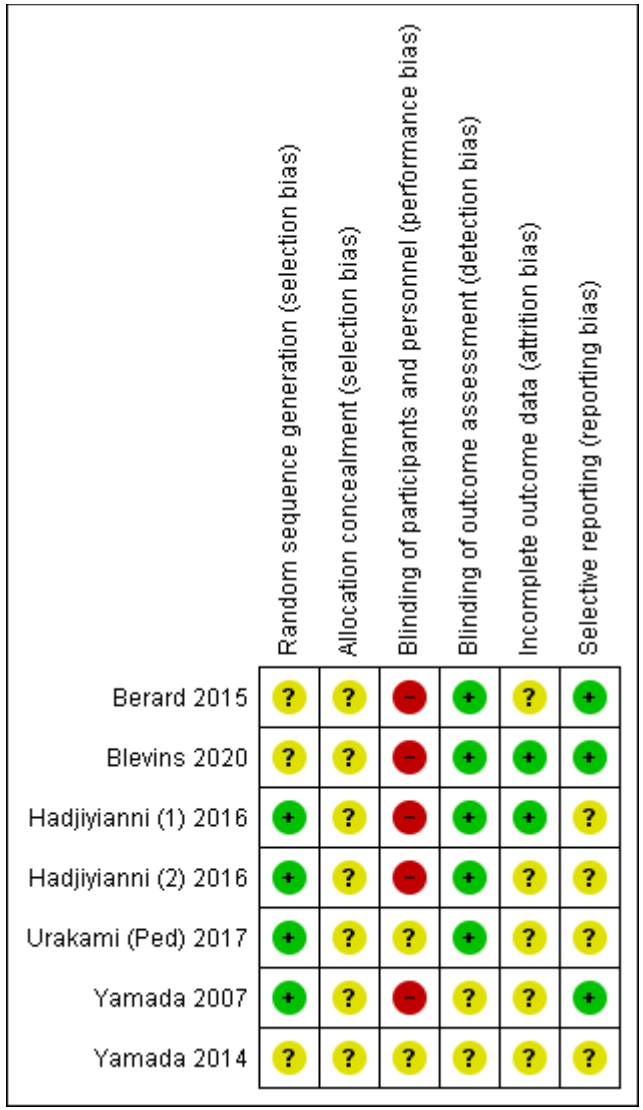
	controlled type 2 diabetes: A 4-week, randomized, open-label, treat-to-target study. J Diabetes Investig 2018; 9: 567–572.	
41	**Grassi 2018** Grassi, G. and Wysham, C. and Gumprecht, J. and Lane, W. and Troelsen, L. N. and Tutkunkardas, D. and Salvi, L. and Heller, S. Insulin degludec shows consistent risk reductions across hypoglycaemia definitions vs insulin glargine U100 in the SWITCH 1 and 2 trials. Italian Journal of Medicine 2018; 12(s2).	different study outcome
42	**Heller 2018** Heller S., Gumprecht J., Lane W., Nørgard Troelsen L., Tutkunkardas D., Wysham C.H. Insulin degludec (IDeg) shows consistent risk reductions across hypoglycaemia definitions vs insulin glargine U100 (IGlar U100) in the SWITCH 1 and SWITCH 2 trials. Diabetic Medicine 2018 35 Supplement 1 (145-)	duplicate
43	**Martinez 2018** Martinez, D. B. and Ponce, M. H. and Romero, A. C. and Villamarin, X. D. and Gomez, P. N. and Romero, R. M. and Fajardo, C. D. Insulin degludec in clinical practice: Type 1 diabetes patients switched from their basal insulin to insulin degludec. Int J Clin Pharm (2018) 40:203–317.	different study design
44	**Wysham 2018** Wysham, C. and Gumprecht, J. and Lane, W. S. and Troelsen, L. N. and Tutkunkardas, D. and Heller, S. Insulin degludec (Ideg) shows consistent risk reductions across hypoglycaemia definitions vs insulin glargine U100 (Iglar) in the Switch 1 and Switch 2. Diabetology and Metabolic Syndrome 2018 10 Supplement 1	duplicate
45	**Ramirez De Arellano Serna 2017** Ramirez De Arellano Serna A., Darba J., Tikkanen C., Conde V. Cost-effectiveness analysis of insulin degludec versus insulin glargine u100 in type 1 and type 2 diabetes patients from the Portuguese national healthcare system perspective: Evidence from the switch 1&2 trials. Value in Health 2017 20:9 (A481-)	different study outcome
46	**Danne 2016** Danne, T. and Thalange, N. and Tutkunkardas, D. and Nørgård Troelsen, L. and Lane, W. Randomised, double-blind, crossover trial comparing the safety and efficacy of insulin degludec (IDeg) and insulin glargine U100 (IGlar.U100) in young adults with type 1 diabetes (T1D): SWITCH 1 subgroup analysis. Pediatric Diabetes October 2016; 18 (Suppl. 25): 18–46.	different study outcome
47	**Didangelos 2017** Didangelos, T. and Tziomalos, K. and Mourouglakis, A. and Karlafti, E. and Stogianou, D. and Alkayiet, S. and Sofogianni, A. and Hatzitolios, A. Safety and efficacy of insulin degludec in patients with type 1 diabetes mellitus after one year treatment. Diabetes Technology and Therapeutics 2017 19 Supplement 1 (A115-A116)	different study design
48	**van Brunt 2016** van Brunt, K. and Curtis, B. and Ivanyi, T. and Balogh, E. and Chalkiadaki, C. and MacLachlan, S. and Neasham, D. and Raluy-Callado, M. Basal-bolus therapy in patients with type 2 diabetes mellitus in UK: patients characteristics, treatment patterns and the effect of switching to premixed insulin. Diabetes Therapy 2016 7:4 (793-807)	different study design
49	**Shimoda 2016** Shimoda, S. and Sato, M. and Sekigami, T. and Motoshima, H. and Yoshimura, R. and Fukuda, K. and Matsuo, Y. and Noda, H. and Okubo, M. and Ichimori, S. and Fujisawa, K. and Fukunaga, M. and Araki, E. and Nishikawa, T. and Furukawa, N. and Matsumura, T. and Kondo, T. and Kawashima, J. and Senokuchi, T. and Igata, M. and Nishida, K. and Yano, T. and Taguchi, T. and Matsuda, H. and Tsuruzoe, K. and Hirashima, Y. and Kaneko, K. and Kitanao, S. and Hazekawa, I. and Ebihara, K. and Murata, Y. and Watanabe, E. and Ishii, N. and Nishioka, H. and Horio, K. and Furusho, M. and Ikema, M. and Otsu, K. and Yano, T. and Shirao, T. and Matsuyama, R. and Nishiyama, T. and Matsuyoshi, A. and Takeda, H. and Kasho, M. and Tsutsumi, E. and Ono, K. 2016 Journal of Diabetes Investigation	duplicate
50	**Lane 2016** Lane, W. and Bailey, T. S. and Gerety, G. and Gumprecht, J. and Philis-Tsimikas, A. and Hansen, C. T. and Nielsen, T. S. S. and Warren, M. L. SWITCH 1: Reduced risk of hypoglycaemia with insulin degludec vs insulin glargine U100 in patients with type 1 diabetes: A randomised, double-blind, crossover trial. 2016 Diabetologia	duplicate
51	**Wysham 2016** Wysham, C. and Bhargava, A. and Chaykin, L. B. and De La Rosa, R. and Handelsman, Y. and Troelsen, L. N. and Kvist, K. and Norwood, P. SWITCH 2: Reduced risk of hypoglycaemia with insulin degludec vs insulin glargine U100 in a type 2 diabetes population on basal insulin: A randomised, double-blind, crossover trial. Diabetologia 2016 59:1 Supplement 1 (S43-S44)	different study outcome
52	**Fujii 2016** Fujii, H. and Ito, S. and Kanno, K. and Kato, M. and Kato, N. and Kondo, H. and Yoshida, N. and Morita, M. and Sato, R. and Takamura, H. and Ueki, A. and Takesue, M. and Kodani, E. and Daikoku, H. and Nogawa, M. and Watanabe, Y. and Kawagoe, Y. and Miyakawa,	Different study design

	T. and Kitaoka, T. Once daily insulin degludec injection has achieved non-inferior glycemic control with less dosege among intensive insulin therapy of type 1 diabetes patients who are splitting basal insulin twice in Japan: Therapeutics of diabetes. J Diabetes Investig Volume 7 Suppl. 2 May 2016.	
53	**Yamada 2016** Yamada, S. and Komuro, M. and Inoue, G. and Tabata, M. and Matsubara, H. and Irie, J. Insulin degludec provides similar glycemic control with insulin glargine in patients with type 2 diabetes. Diabetes 2016 65 Supplement 1 (A250-A251)	No switch
54	**Roussel 2015** Roussel, R. and D'Emden, M. C. and Fisher, M. and Ampudia-Blasco, F. J. and Stella, P. and Grisoni, M. L. and Cali, A. M. G. and Wysham, C. H. Switching from twice-daily basal insulin to once-daily new insulin glargine 300 U/mL (GLA-300): An analysis in people with T2DM (Edition 1 and 2). Diabetes 2015 64 SUPPL. 1 (A261-)	different study design
55	**Dieuzeide 2014** Dieuzeide, G. and Latif, Z. A. and Chen, J. W. and Slim, I. and Soewondo, P. The safety and effectiveness of switching from basal insulin to once-,twice-,or three-times daily biphasic insulin aspart 30 in the A1chieve study. Diabetes 2014 63 SUPPL. 1 (A231-)	different study design
56	**Curington, R 2014** Curington, R Clinical outcomes of switching from insulin glargine to NPH insulin in indigent patients at a charitable pharmacy: The cinci study. 2014 Journal of the American Pharmacists Association	duplicate
57	**Hamasaki, H. and Yanai, H. 2014** Hamasaki, H. and Yanai, H. Switching from insulin glargine to insulin deglidec reduced HbA1c, daily doses and anti-insulin antibody in anti-insulin antibody-positive subjects with type 1 diabetes. 2014 Diabetes and Metabolism	duplicate
58	**Dieuzeide 2013** Dieuzeide, G. and Marcucci, G. and Grossman, C. and Zambón, F. and Issa, C. and Katz, S. and Pugnaloni, N. and Berghella, A. M. and Marín, M. and Litwak, L. The A1chieve study – an observational non-interventional study of patients with type 2 diabetes initiationg or changing to insulin analogue therapy: data from the Argentinean population. Revista Argentina de Endocrinologia y Metabolismo 2013 50:4 (219-232)	different language (spanish)
59	**Home 2013** Home, P. D. and Malek, R. and Gálvez, G. G. and Hammerby, E. and Nikolajsen, A. and Henriksen, O. and Andersen, M. F. B. Short and long-term cost effectiveness of switching therapy from insulin glargine to insulin detemir in people with type 2 diabetes. 2013 Value in Health	duplicate
60	**Malek 2013** Malek, R. and Gálvez, G. G. and Hammerby, E. and Nikolajsen, A. and Henriksen, O. and Andersen, M. F. B. Short and long-term cost effectiveness of switching therapy from insulin glargine to insulin detemir in people with type 2 diabetes. Value in Health 2013 16:7 (A690-)	Different study design
61	**Baser 2012** Baser, O. and Miao, R. and Wei, W. and Xie, L. Real world outcomes of adding rapid acting insulin vs switching to analog premix insulin among patients with type 2 diabetes treated with insulin glargine. Diabetes 2012 61 SUPPL. 1 (A618-)	Different study design
62	**Prázný, 2011** Prázný, M. Human insulin vs insulin analogue: results of a prospective, multi-center, open labelled, non-interventional study in type 2 diabetics taking NovoRapid®, NovoMix® or Levemir® Interni Medicina pro Praxi 2011	different language (ceco)
63	**Cleall 2011** Cleall, S. and Reaney, M. and Tentolouris, N. and Cypryk, K. and Petzinger, U. and Koivisto, V. and Jecht, M. Direct costs of care and clinical outcomes in patients with type 2 diabetes switching between short acting human insulin and rapid-acting insulin analogues. 2011 Diabetologica	duplicate
64	**Berard, L. D. 2011** Berard, L. D. and Woo, V. C. Safety and efficacy of NPH after switching from insulin glargine in Canadian patients 2011 Diabetologica	duplicate
65	**Kvapil, M.** and Krivska, B. and Avý, Z. R. Switching from an NPH insulin to insulin glargine basal-bolus regimen improves glycemic control in diabetic patients: the Linda study. Diabetes 2011 60 SUPPL. 1 (A621-)	different study design

66	**Jermendy, G.** Switching from human basal insulin to once daily insulin detemir in type 2 diabetic patients treated by MDI regimen. Results from the LEONCET 2, an observational, prospective, multicenter study. Diabetes 2010	different study design
67	**Ligthelm, R.** and Christensen, T. E. and Thomsen, T. L. and Yang, W. Long-term outcomes of switching patients with type 2 diabetes from biphasic insulin to biphasic insulin aspart 30/70: An improve study subgroup analysis. Value in Health 2009 12:7 (A402-)	different study design
68	**Brod M,** Valensi P, Shaban JA, Bushnell DM, Christensen TL. Patient treatment satisfaction after switching to NovoMix® 30 (BIAsp 30) in the IMPROVE™ study: an analysis of the influence of prior and current treatment factors. Qual Life Res. 2010 Nov;19(9):1285-93.	different study design
69	**Hajos, T.** and Pouwer, F. and De Grooth, R. and Holleman, F. and Diamant, M. and Snoek, F. J. Switching from NPH to insulin glargine positively impacts on glycemic control and psychological well-being in suboptimally controlled type 2 diabetes patients. An observational study. Diabetes 2009 58 SUPPL. 1A	different study design
70	**Sreenan S,** Virkamäki A, Zhang K, Hansen JB; PREDICTIVE study group. Switching from NPH insulin to once-daily insulin detemir in basal-bolus-treated patients with diabetes mellitus: data from the European cohort of the PREDICTIVE study. Int J Clin Pract. 2008 Dec;62(12):1971-80.	different study design
71	Comparison of NN1250 versus insulin detemir, both combined with insulin aspart in subjects with type 1 diabetes Nct 2009 Available at: https://clinicaltrials.gov/show/NCT00841087	No switch
72	Investigating the effectiveness of Tresiba® (insulin degludec) after switching basal insulin in a population with type 1 or type 2 diabetes mellitus Ntc 2015 Available at: https://clinicaltrials.gov/show/NCT02662114	Different study design
73	An open-label randomized controlled trial on the efficacy of switching from insulin glargine U100 to insulin glargine U300 or insulin degludec in type 2 diabetes mellitus. Jprn, Umin 2017. Available at: http://www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000025122	Different study design
74	Urakami, T. and Kuwabara, R. and Mine, Y. and Aoki, M. and Okuno, M. and Suzuki, J. A randomized crossover study of efficacy and safety of switching from insulin glargine to insulin degludec in children with Type 1 diabetes: Pediatric endocrinology Journal of Diabetes Investigation 2016	duplicate
75	Urakami, T. and Mine, Y. and Kuwabara, R. and Aoki, M. and Okuno, M. and Suzuki, J. A randomized crossover study of the efficacy and safety of switching from insulin glargine to insulin degludec in children with type 1 diabetes Diabetes 2015	duplicate
76	Urakami, T. and Kuwabara, R. and Habu, M. and Okuno, M. and Suzuki, J.Efficacy of insulin degludec after switching from insulin glargine or insulin detemir in young persons with type 1 diabetes. Diabetes Research and Clinical Practice 2014	different study design
77	Sumník, Z.; Venhácová, J.; Brázdová, L.; Skvor, J. Long-term improvement of fasting glycaemia after switching basal insulin from NPH to determir in children with type 1 diabetes: a 1-year multicentre study Cas Lek Cesk 2008	different language (ceco)

Appendix 3: Risk of bias assessment of included studies

RCTs (ROB Cochrane 2011)



Non RCTs (ROBINS-I)

Authors, year	Outcome	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
Curington, 2017	Hba1c	Serious	Moderate	Low	Low	Serious	Low	Moderate	Serious
Luo, 2019	HbA1c; hypoglycaemia, costs	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Manini, 2007	HbA1c	Critical	Serious	Moderate	NI	NI	Low	Moderate	Critical
	QoL						Moderate		
Reaney, 2012	Costs	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
	QoL						Moderate		